Negative dynamics of the hepatic artery resistive index as a predictor of early arterial thrombosis after deceased donor liver transplantation

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Abstract

Aim. The study aim was to assess the negative dynamics of the hepatic artery resistive index as a reliable predictor of early thrombosis in liver transplant recipients from a postmortem donor, to determine risk factors and to identify a group of patients with an increased risk of this complication.

Material and methods. From July 2018 to August 2021, 92 orthotopic liver transplants from a deceased donor were performed at the Surgical Clinic of the City Clinical Hospital n.a. S.P. Botkin. All liver grafts were taken from donors with brain death. Control Doppler ultrasound

examination of hepatic blood flow in all patients was performed on days 1, 3, 5, 7, if necessary, daily. The hepatic arteries resistive index was considered normal at values from 0.55-0.79, high at 0.8-0.89, extremely high above 0.9. Depending on the resistive index value on the 1st postoperative day and its further dynamics, we divided the patients into 3 groups. In each group, we analyzed the incidence of hepatic artery thrombosis and assessed the impact of various risk factors on the resistive index elevation on the 1st day after surgery and on its growth during dynamic observation in the early postoperative period.

Results. *Of 92 liver transplants, in three cases, we recorded hepatic artery thrombosis (3.2%), which was not associated with technical difficulties of arterial reconstruction. No mortality was recorded in all three cases. In patients with a normal or high resistive index on the 1st day, without its increase during dynamic observation, the incidence of arterial thrombosis was 0%. In patients with a normal or high resistive index on the 1st day, and its increase during dynamic observation, as well as in patients with an extremely high resistive index on the 1st day, the incidence of arterial thrombosis was 18.1% and 11.1%, respectively. The risk factors of thrombosis were the age of the recipient over 50 years old in an extremely high resistive index on the 1st postoperative day (p=0.024), and the age of the donor over 50 years old in the growth of the resistive index during follow-up (p=0.04).*

Conclusion. *The lack of positive dynamics in the hepatic artery resistive index reduction may be an additional predictor of arterial thrombosis after liver transplantation. This fact makes it possible to identify a high-risk group of arterial thrombosis, to take additional preventive measures in these patients and to improve the immediate results of treatment in this group of patients.*

Keywords: liver transplantation, hepatic artery thrombosis, resistive index

ALT, alanine aminotransferase

AST, aspartate aminotransferase

CMV, cytomegalovirus

HA, hepatic artery

IR, resistive index

LT, liver transplantation

US examination, ultrasonography/ultrasound examination

Introduction

Just over half a century has passed since Thomas Starzl's first liver transplantation in 1963, during which time transplant care has extended all-over. To date, liver transplantation (LT) is a highly effective and unique radical method of treating and increasing the survival of patients with end–stage renal disease. However, being a major and traumatic operation, liver transplantation inevitably carries the risk of life-threatening complications.

The active development of surgery, immunology, and general medical science have made it possible to minimize the incidence of fatal

complications: thus, in the era of first transplants, the prevalence of arterial thrombosis among adult cadaveric liver recipients was almost 10%, and today, in the world's leading centers, it does not reach even 3% [1]. However, the severity of this complication did not decrease. It is still one of the most dangerous problems, and the cause of many-fold increase of postoperative mortality. In the absence of timely revascularization, it exceeds 50% [2], and graft loss in the absence of active surgical tactics is observed in more than 80% of cases of hepatic artery (HA) thrombosis [3]. This dictates the need to identify reliable risk factors, thorough prevention and timely diagnosis.

The overwhelming majority of authors unanimously consider technical difficulties of arterial reconstruction to be the main cause of early HA thrombosis [4, 5]. Developing HA thrombosis can be a consequence of stenosis, inflection, torsion, excessive tension of the arterial anastomosis, as well as atherosclerotic vascular damage, which is especially characteristic of older recipients and grafts from age-related donors.

Other causes and risk factors for arterial thrombosis after liver transplantation are not so obvious. In various studies, such factors as the discordance between the donor and recipient anthropometric data, the hypercoagulation state in the early postoperative period, prolonged time of cold ischemia and arterial reconstruction, the AB0 incompatibility of the donor and recipient, retransplantation, massive blood loss and blood transfusion, cytomegalovirus (CMV) infection (transplantation from a CMV-positive donor to a CMV-negative recipient), and others reach statistical significance [6-11].

Like many authors, we consider the routine use of ultrasound Dopplerography in the early postoperative period to assess blood flow in the graft to be the major monitor for possible vascular complications [12].

Ultrasound Doppler examination has all the advantages of a screening method and, despite its operator-dependent nature, it demonstrates high sensitivity to changes in arterial blood flow when used regularly in the early postoperative period. Among the Doppler characteristics of blood flow in the hepatic artery, in our opinion, the peripheral resistive index (RI) is the most informative and convenient for dynamic assessment, since, being a relative parameter, it characterizes both systolic and diastolic blood flow and can be compared between patients in a study group. In this study, we retrospectively evaluated the significance of negative dynamics of the hepatic artery resistive index as a predictor of early thrombosis in liver transplant recipients, as well as identified risk factors and an increased risk group for this complication.

Material and methods

From July 2018 to August 2021, 92 orthotopic liver transplants from a post-mortem donor were performed at the Surgical Clinic of the City Clinical Hospital named after S.P. Botkin. There were 51 males (55.4%) and 41 females (44.6%). The mean age was 48.74 ± 8.3 (24-66) years. Indications for surgery included liver cirrhosis resulting from chronic viral hepatitis (CVH) C in 48 patients (52.2%), cirrhosis resulting from autoimmune liver damage in 16 patients (17.4%), alimentary liver cirrhosis in 13 patients (14.1%), cirrhosis resulting from CVH B in 6 patients (6.5%), and other causes in 9 patients (9.7%). All liver grafts were taken from donors with confirmed brain death. Data on post-mortem donors are presented in Table 1.

Table 1. Characteristics of postmortem liver graft donors

Parameter	Mean value
Donor age, years	43.94±11.1 (21-63)
Donor ALT, U/L	38.68±3736 (5-206)
Donor AST U/L	50.13 ± 60.27 (5-346)
Donor Na, mmol/L	142.5±9.36 (127-159)
Donor bilirubin, μmol/L	11.06±7.26 (2-43)
Length of the donor hospital stay, hours	60.39±40.98 (10-216)
The liver graft steatosis,%	12.38±11.1 (0-50)

Notes: ALT, alanine aminotransferase; AST - aspartate aminotransferase

Ninety one patients (98.9%) underwent liver transplantation using the "piggy-back" technique, and 1 patient (1.1%) underwent the surgery by classical method. Arterial anastomosis was formed by continuous suture of Prolen 6-0 or 7-0. All patients received standard immunosuppressive therapy in accordance with National Clinical Guidelines, and all patients received a continuous infusion of alprostadil at a dose of 120 mcg per day for the first 5 days. Anticoagulant therapy was given in a preventive regime considering the thromboelastography data; antiplatelet therapy was administered after the platelet level in peripheral blood had increased over $50x10^9$ per liter.

The data of the surgical interventions performed are presented in Table 2.

Table 2. Characteristics of surgical interventions for liver transplantation

| Parameter	Mean value
Surgery duration, min	496.26±61.19 (360-720)
Cold ischemia time, min	333.36±74.59 (210-590)
Warm ischemia time, min	38.15±9.66 (15-70)
Blood loss, ml	1197.59±728.71 (200-3200)
Length of ICU stay, bed days	1.8±0.56 (1-7)
Total bed days	13.5±4.76 (10-39)
30-day mortality,%	2 (2.1%)
Postoperative complications (III and higher according to Clavien-Dindo)	9 (9.7%)

Note: ICU, Intensive Care Unit

Control ultrasound (US) examination in all patients was performed on the 1st, 3rd, 5th, 7th days, or daily, if necessary. At US examination, the presence/absence of free and delimited fluid in the abdominal cavity was determined; the presence and spectral characteristics of blood flows along the inferior vena cava, portal vein, the common hepatic artery trunk, right and left lobar branches were evaluated. Resistive indices were calculated for arterial blood flow. If it was impossible to visualize arterial blood flow in the liver graft, emergency computed tomography (CT) with intravenous contrast was performed to exclude vascular complications.

When determining the resistive index in the arteries of a liver graft, the values were defined as normal in the range of 0.55–0.79 (Figure 1), high at 0.8–0.89, and extremely high at above 0.9 (Figure 2).
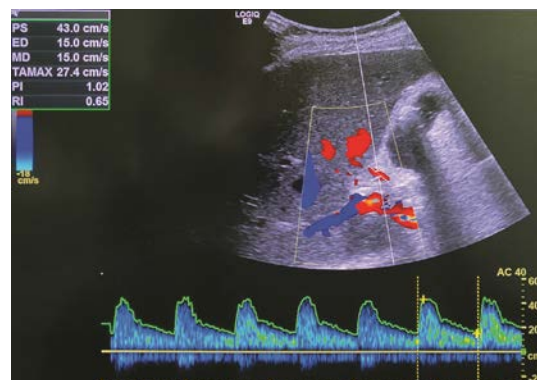
Fig. 1. Ultrasonogram of the liver graft on the 1st postoperative day. Normal resistive index in the left hepatic artery
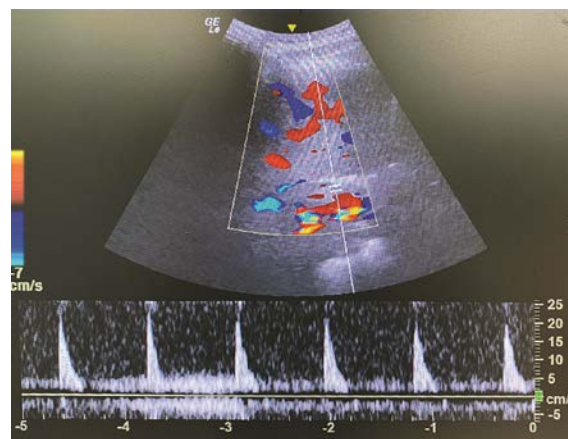
Fig. 2. Ultrasonogram of the liver graft on the 1st postoperative day. Extremely high resistive index in the left hepatic artery

With regard to the RI on the 1st postoperative day and the dynamics of its changes in the early postoperative period, we divided patients into 3 groups. Group I included 72 patients (78.2%) patients who had a normal or high RI on day 1, without its increase during dynamic observation. Group II included 11 patients (11.9%) with a normal or high RI on day 1 with negative dynamics during dynamic observation. Group III included 9 patients (9.9%) with an extremely high RI on the 1st day after surgery. In each group, we analyzed the incidence of HA thrombosis that was not related to technical problems of arterial anastomosis, and also evaluated the impact of various risk factors on the RI increase in on the 1st day after surgery and on its growth during dynamic observation in the early postoperative period.

Results

Of 92 liver transplants, 3 cases of hepatic artery thrombosis (3.2%) were recorded, which was not related to technical difficulties of arterial reconstruction. All patients were diagnosed with arterial thrombosis later than 3 postoperative days. Two patients underwent emergency liver retransplantation; in 1 case, X-ray endovascular balloon dilatation with stenting was performed. In all three cases, no deaths were recorded in the early postoperative period.

Of the three cases of arterial thrombosis non-related to technical problems, 2 patients were from Group II and 1 patient was from Group III, thus making the thrombosis incidence 0% in group I, 18.1% in group II, and 11.1% in group III. Based on the obtained data, we noted a tendency to arterial thrombosis development in the patients with negative RI dynamics in the early postoperative period and with extremely high RI on the 1st day after transplantation. Next, we analyzed the impact of

various factors on the development of a high and extremely RI at postoperative day 1 (Table 3).

Table 3. The impact of risk factors on the development of a high resistive index on the 1st postoperative day

Factor	Resistive Index		p
	Normal RI (n-71)	High/extremely high RI (n-21)	
Recipient age: <50 years > 50 years	44 27	7 14	0.024
Surgery duration: <500 minutes > 500 minutes	35 36	12 9	0.55
Donor age: <50 years > 50 years	39 32	10 11	0.11
Donor hospital length of stay: <50 hours > 50 hours	36 35	11 10	0.78
Liver steatosis: <30% > 30%	50 21	13 8	0.87
Warm ischemia time: <40 minutes > 40 minutes	34 37	9 12	0.61
Cold ischemia time: <300 minutes > 300 minutes	30 41	11 10	0.36
Blood loss: <1000 ml > 1000 ml	44 27	10 11	0.34

As can be seen from the Table, among the possible risk factors, only the recipient's age over 50 years had a statistically significant association with an increase in the resistive index on the first day after liver transplantation ($p=0.024$).

The analysis of risk factors for the resistive index increase during the dynamic observation is presented in Table 4.

Table 4. The impact of risk factors on the growth of the resistive index during follow-up

Factor	Resistive Index		p
	No negative dynamics in RI (n=81)	With negative dynamics in RI (n=11)	
Recipient age: <50 years >50 years	46 35	3 8	0.189
Surgery duration: <500 minutes > 500 minutes	43 38	6 5	0.766
Donor age: <50 years >50 years	48 33	4 7	0.04
Donor hospital length of stay: <50 hours > 50 hours	46 35	6 5	0.79
Liver steatosis: <30% >30%	55 26	8 3	0.67
Warm ischemia time: <40 minutes > 40 minutes	47 34	4 7	0.1
Cold ischemia time: <300 minutes >300 minutes	37 44	5 6	0.72
Blood loss: <1000 ml >1000 ml	47 34	6 5	0.94

Discussion

Arterial thrombosis is one of the most serious complications after orthotopic liver transplantation. Its development in most cases requires retransplantation, which leads to an increase in the waiting list for cadaveric liver transplantation.

In the development of arterial thrombosis, 3 groups of factors can be distinguished: the peculiarities of the arterial anatomy of the donor and recipient celiac trunk branches (branched type of blood supply, mismatch of vessel diameters), technical problems of arterial reconstruction (intima

dissection, torsion, kinking, excessive tension), as well as factors related to the liver graft microcirculation. As for the first two groups of factors, the experience of the surgical team can play a significant role in most cases. However, in the 3 cases of arterial thrombosis after liver transplantation in the Botkin Hospital, the operating team neither encountered any specific features of arterial anatomy nor had any problems with forming the anastomosis. The effect of the liver graft condition on the risk of arterial thrombosis has not yet been assessed. There are reports in the world literature on studying non-surgical causes and risk factors for early HA thrombosis, but we have not found reliable predictors or recommendations for the prevention of this complication. This prompted us to search for additional predictors and risk factors for early hepatic artery thrombosis.

We evaluated the state of arterial vascular resistance during the first week after surgery. The choice of this factor was based on the fact that the resistive index allows us to assess the degree of spasm of the liver graft small arteries. The spasm leads to an acute slowdown in the blood flow velocity in a diastole until almost the complete cessation at a resistive index close to 1. Slowing down the blood flow velocity together with the vascular wall damage in the anastomotic area abruptly increase the risk of thrombosis according to Virchow's triad.

The presence of normal or high RI on the first postoperative day without subsequent negative dynamics on days 3 and 5 did not lead to the development of arterial thrombosis in any case (Group I). Patients in this group, in our opinion, do not need additional preventive measures. On the other hand, patients with normal or high RI on the 1st day and with negative dynamics in the follow-up had an 18.1% risk of arterial thrombosis (Group II). Patients with extremely high RI on day 1 had an 11.1% risk of developing complications.

Analyzing the data of the world literature, we did not find any evidence-based studies to investigate the effect of arterial blood flow resistance in the graft on the development of hepatic artery thrombosis. In two retrospective single-center studies [13, 14] of the relationship between a high resistive index after LT and the development of HA thrombosis in the early postoperative period, the significance of a high RI as a predictor of this complication was not confirmed. However, none of the studies investigated the absence of positive dynamics in the reduction of RI within a few days after transplantation as a potential predictor of arterial thrombosis. Nevertheless, we are not inclined to dispute the conclusions of the authors of those studies, since in our observations, in most patients from groups I and III, high and extremely high resistive indices were also transient phenomena and had reached normal values by days 3-5. Meantime, in 1 of 9 patients in Group III (with extremely high RI on day 1), there was no positive dynamics in reducing RI, and arterial thrombosis was diagnosed on the 4th postoperative day. This was a good reason to allocate such patients to a high-risk group.

Unfortunately, the treatment of early HA thrombosis after liver transplantation is extremely complex and, to date, has uncertain results. This necessarily obliges surgeons to search for additional measures to prevent this life-threatening complication. In our opinion, patients with an extremely high RI (>0.9) on the 1st postoperative day, as well as with a negative RI dynamics on days 3-5 after surgery, have an increased risk of developing hepatic artery thrombosis and need additional preventive measures. In the absence of contraindications, we increase the anticoagulant therapy to therapeutic doses (posing the effect on the third risk factor in the Virchow's triad), and also increase the dose of hormonal pulse therapy for several days in order to reduce the liver graft edema. Ultrasound monitoring of arterial blood flow in these patients is

performed twice a day. Special attention, in our opinion, should be paid to patients over 50 years of age, as well as the recipients who underwent orthotopic liver transplantation from an age-related donor.

Conclusions

1.	The absence of positive dynamics in the reduction of the resistive index in the hepatic artery may be an additional predictor of arterial thrombosis after liver transplantation.

2.	The dynamic assessment of the resistive index in the arteries of a liver graft makes it possible to identify a high-risk group of arterial thrombosis, to take additional preventive measures in these patients, thereby reducing the risk of developing this complication and improving the immediate results of treatment in this group of patients.

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