Incidence of Vasoplegic Syndrome during Liver Transplantation and Patient Outcomes

S. González-Suárez[1, 2]*, I. M. Dammala[2], M. Grao[2], E. Camio[2]

[1]*Department of Surgery, Universitat Autònoma de Barcelona, Passeig Vall d'Hebron 119, Barcelona, Spain*
[2]*Department of Anesthesia, University Hospital Vall d'Hebron, Passeig Vall d'Hebron 119, Barcelona, Spain*

ABSTRACT

Background: The incidence of vasoplegic syndrome during liver transplantation is unknown, and it is occasionally confused with postreperfusion syndrome, which is another similar form of hemodynamic instability. In these cases, monitoring patients with the Swan-Ganz catheter may be useful for differential diagnosis.

Objective: The main outcome was the incidence of vasoplegic syndrome or postreperfusion syndrome in the patients, and the prognosis of patients with vasoplegic syndrome was the secondary outcome.

Methods: This retrospective study included 246 consecutive orthotopic liver transplantation procedures performed in patients aged >18 years who were monitored using a Swan-Ganz catheter.

Vasoplegic syndrome was defined as mean arterial pressure <50 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, central venous pressure <5 mmHg, cardiac index >2.5 L/min/m2, systemic vascular resistance <800 dyn/s/cm-5, and increased heart rate and mean pulmonary arterial pressure from the baseline (anhepatic phase). The estimated marginal means and their 95% confidence intervals were determined for the total sample.

Results: Of the 246 patients, only two (0.81%) developed vasoplegic syndrome after unclamping the portal vein. Another patient (0.40%) showed the hemodynamic features of vasoplegic syndrome but was diagnosed with septic shock due to positive blood culture. One patient with vasoplegic syndrome presented with postoperative renal failure and graft rejection, requiring another liver transplantation, and the other patient did not survive.

Conclusion: Most episodes of hemodynamic instability after liver graft reperfusion are due to postreperfusion syndrome, and the occurrence of vasoplegic syndrome is very rare and is associated with poor prognosis.

KEYWORDS: Liver transplantation; Vasoplegic syndrome; Postreperfusion Syndrome

INTRODUCTION

Vasoplegic syndrome (VS) is the most severe form of hemodynamic instability and is generally characterized by increased cardiac index (CI), decreased filling pressures and systemic vascular resistance (SVR), and a poor response to intravascular volume expansion and vasoconstrictor drugs [1, 2]. Several factors could be related to its appearance, such as surgical trauma, transfusion of blood components, liver and gastrointestinal tract ischemia-reperfusion injury, neuroendocrine disorders, and systemic inflammatory response [3-6]. The duration of VS significantly influences the outcome of patients; therefore, prompt, accurate diagnosis and aggressive management are crucial for reducing the risks of postoperative morbidity and mortality [7]. Intravenous administration of volume expanders and catecholamines,

*Correspondence: Susana González-Suárez, M.D
Department of Surgery, Universitat Autònoma de Barcelona, Department of Anesthesia, University Hospital Vall d'Hebron, Passeig Vall d'Hebron 119, Barcelona, Spain
ORCID: 0000-0001-7119-1092
Tel: +34-636-272697
E-mail: susana.gonzalez@vallhebron.cat
susana.gonzalez@uab.cat

vasopressin, methylene blue, and a high-dose hydroxocobalamin improve the prognosis [8–11]. To our knowledge, the incidence of VS among patients undergoing liver transplantation is unknown and only isolated cases have been published [12-14]. On the other hand, VS can be confused with postreperfusion syndrome (PRS) since both share common hemodynamic features, such as a decrease in SVR and mean arterial pressure (MAP) [15-18].

PRS occurs because many inflammatory mediators from the liver graft enter the systemic circulation, resulting in a sudden load of cold and acidotic blood leading to increased morbidity and mortality [19-21]. Volume expansion, correction of acid-base status, use of vasopressor and inotropic agents, and maintenance of normal body temperature improve the clinical outcomes. Its incidence ranges from 12% to 77% of patients undergoing liver transplantation [22, 23]. This variability can be attributed to not only the preoperative and intraoperative factors associated with the differences in the anesthetic-surgical practices among hospitals but also to the use of different definitions of PRS.

The lack of standard diagnostic criteria for VS and PRS makes it difficult to analyze their incidence. Nevertheless, VS causes an increase in the CI with a decrease in the filling pressures, and PRS causes a decrease in CI with an increase in filling pressures. Therefore, determining pulmonary pressures using Swan-Ganz catheter can be helpful in some cases of confusion.

This study aimed to determine the incidence of VS among patients undergoing liver transplantation, using a Swan-Ganz catheter, and to determine the morbidity and mortality associated with VS during orthotopic liver transplantation (OLT). The data reported by Ozal et al. [24] for VS and by Aggarwal et al. [22] for PRS were used as reference since they offer a clear and precise distinction to identify both syndromes.

MATERIALS AND METHODS

This single-center retrospective observational study included consecutive patients aged ≥18 years, who underwent liver transplantation from January 12, 2010, to July 21, 2022, and were monitored using a Swan-Ganz catheter. All donors were deceased. The exclusion criteria were OLT for acute liver failure, combined liver and kidney transplantation, moderate/severe vascular and valvular heart disease, moderate/severe hepatopulmonary syndrome, moderate/severe portopulmonary syndrome, and re-transplantation. Fig. 1 shows the flow diagram of the inclusion and exclusion processes.

Anesthesia Protocol

Anesthesia was administered according to the institutional protocol. After establishing non-invasive monitoring, anesthesia induction was performed with the administration of 2 $\mu g.kg^{-1}$ of fentanyl, 2 $mg.kg^{-1}$ of propofol, and 0.5 mg.kg-1 of atracurium. After tracheal intubation, mechanical ventilation was started (55–60% oxygen–air mixture) and adjusted to maintain an end-tidal carbon dioxide concentration between 33 and 38 mmHg. Anesthesia was maintained with a sevoflurane and fentanyl infusion (2 $\mu g.kg^{-1}.hour^{-1}$) and atracurium infusion (0.4 $mg.kg^{-1}.hour^{-1}$). A triple lumen Swan-Ganz introducer and pulmonary artery catheter were inserted in the right internal jugular vein to measure the intracardiac pulmonary pressures and cardiac output (CO). Standard monitoring included mean arterial pressure (MAP), mean pulmonary artery pressure (mPAP), pulmonary capillary pressure (PCP), central venous pressure (CVP), heart rate (HR), SVR, CI, mixed venous oxygen saturation, and urine output. Arterial blood gases were measured at the beginning of surgery, before unclamping of the inferior portal vein, at 1 min and 5 min after unclamping, and in the neohepatic phase after completion of the vascular anastomoses.

Electrolytes and arterial blood gases were monitored and corrected throughout the surgery. Anesthetic management during the anhepatic phase focused on the maintenance of

cardiac preload and correction of arterial blood gas and electrolyte imbalances. A base deficit greater than 10 mmol/L was treated with sodium bicarbonate. An ionized calcium level of <4 mg/dL was treated with calcium chloride, and hyperkalemia (>5 mmol/L) was treated with insulin and glucose. Noradrenaline infusion was administered when the systolic arterial blood pressure remained below 90 mmHg. Packed red blood cells were administered to maintain a hemoglobin level above 90 g/L, fresh frozen plasma was administered to treat clinically significant bleeding, and platelets were administered to maintain a platelet count above 50×10^9/L.

Surgical Technique

Liver allografts were preserved in a cold University of Wisconsin solution. Anastomosis of the liver graft was performed using the piggyback technique with or without temporary portocaval shunting. Before completing the hepatic vein anastomosis, the liver graft was perfused with albumin through the portal vein. All the patients were transported to the intensive care unit (ICU) postoperatively.

Study Outcomes

The main outcome was to determine the incidence of VS at any stage of liver transplant surgery and PRS after unclamping the portal vein. The secondary outcomes were the development of postoperative complications during the first 3 months after liver transplantation in terms of renal failure (glomerular filtration <60), need for new surgery due to bleeding or vascular or biliary complications, graft rejection, need for a new transplant, and survival.

Data Collection and Clinical Definitions

We collected the hemodynamic parameters at each stage of liver transplantation surgery: dissection phase, anhepatic phase prior to unclamping the inferior portal vein, at 1 and 5 min after graft reperfusion, and in the neohepatic phase after completion of the vascular anastomosis. The VS criteria in any phase of the liver transplant were MAP<50 mmHg, PCP≤10 mmHg, CVP<5 mmHg, CI>2.5 L/min/m^2, SVR<800 dyn/s/cm^{-5}, increased HR from the baseline, decreased mPAP from the baseline for at least 3 hours within the first 48 hours of the patient's arrival at the ICU. The PRS criteria were MAP≥30% mmHg during the first 5 min after unclamping the inferior portal vein; decrease in the CI and SVR from the baseline; and increase in PCP, CVP, and mPAP from the baseline values.

Postoperative data included graft rejection, second surgery after liver transplant, the need for re-transplantation, renal dysfunction (glomerular filtration<60), hospital stay, and survival. When the patients developed VS, we checked for any possible infections, using blood cultures, and carried out transthoracic echocardiogram and chest radiography. Postoperative data were retrospectivelly collected from the patients' medical records during hospital admission. The data on the need for a new transplant and survival were collected 3 months after surgery.

All items that could be used to identify the patient (clinical record ID number or name) were removed to protect the personal data.

Ethical Considerations

This study was approved by the Ethics Committee of Vall d'Hebron University Hospital (PR(AG)460/2017, date: March 02, 2017). The patients provided written informed consent for the recording of their clinical data and their inclusion in further studies. For the reported cases, informed consent was obtained from one patient, and from the family in the other case. The study followed the principles of Good Clinical Practice and was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed using the descriptive values of the medians and interquartile ranges. The hemodynamic variables of the total sample were expressed as estimated marginal means and their 95% confidence intervals.

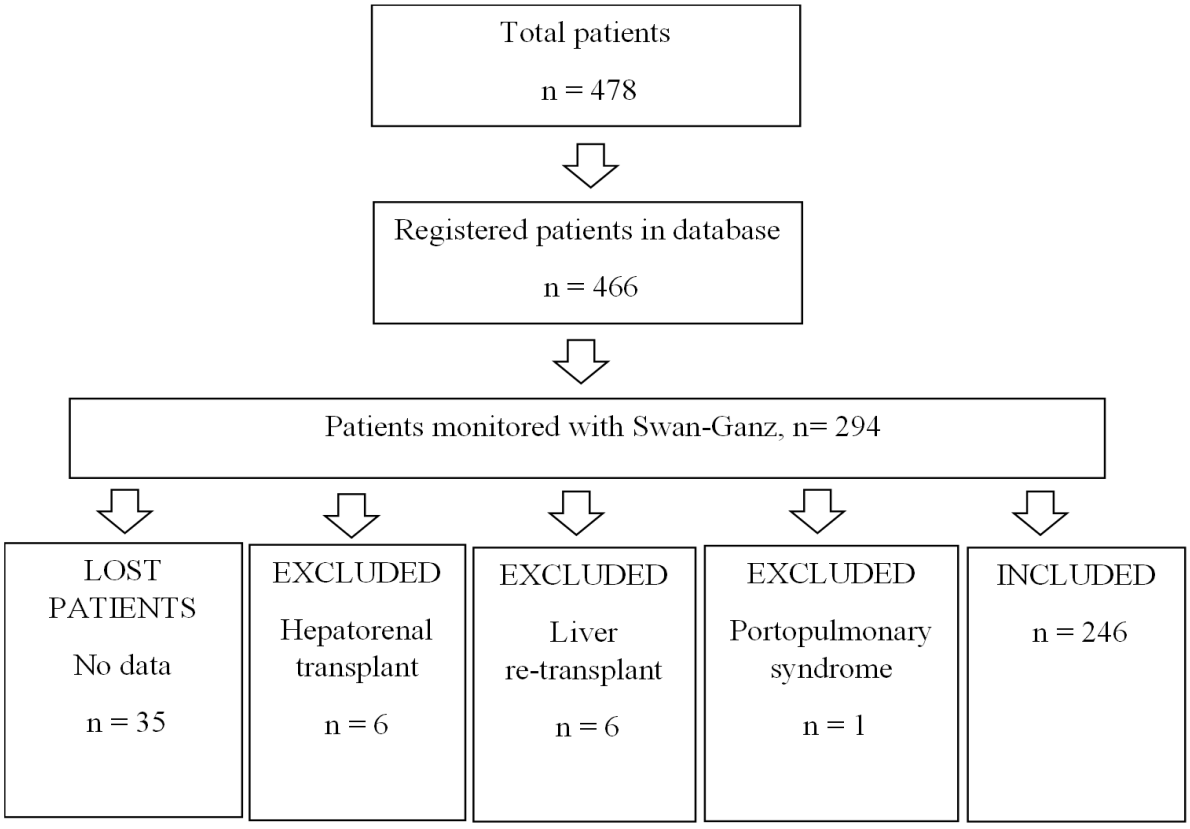

Figure 1: Flow diagram of inclusion/exclusion criteria.

RESULTS

The baseline characteristics of the total population and the patients with VS are shown in Table 1. Of the 246 patients included in the study, only 2 (0.81%) developed VS after unclamping of the portal vein, and 57 (23.17%) developed PRS. One patient (0.40%) showed the hemodynamic characteristics of VS but was diagnosed with septic shock due to Klebsiella-positive blood cultures, and Klebsiella was also found in the liver graft-preservation solution.

The patients with VS had no previous allergies and did not show any signs of ongoing infection. Postoperative transthoracic echocardiogram did not show any cardiac dysfunctions in either of the two patients with VS, and their chest radiographs showed no remarkable findings; their blood cultures yielded negative results.

The anesthetic and intraoperative data of the patients with VS are shown in Tables 1 and 2. The hemodynamic characteristics of the two patients are shown in Table 3. Arterial blood gases evaluated in patients with VS at 5 min and 60 min after unclamping the portal vein demonstrated an increase in lactic acid (serum lactate 20-25 mmol/L) accompanied by a worsening base deficit (11 mmol/L), despite increased administration of bicarbonate (125–150 mEq).

One patient with VS died on the fifth postoperative day. The patient had developed multiorgan failure and hypovolemia due to a ruptured splenic aneurysm; both aneurysm surgery and transfusion were unsuccessful.

The other patient with VS needed a noradrenaline infusion at 1 µg/kg/min dose to support arterial blood pressure over the first postoperative 6 h; later, the noradrenaline requirements decreased until discontinuation at 40 h. The patient had developed renal failure

Table 1: Basal characteristics of the total patients and for patients with vasoplegic syndrome (VS).

Parameters	Total (n= 246)	VS patient 1	VS patient 2
Recipient age	56.7±10.4	64	55
Sex, male	184 (74.8)	Male	Male
Etiology of cirrhosis			
Hepatitis B virus (HBV)	20 (8.1)	No	Yes
Hepatitis C virus (HCV)	80 (32.5)	No	No
Human immunodeficiency virus (HIV)	5 (2.0)	No	No
Enolic	119 (48.4)	Yes	Yes
NAFLD	17 (6.9)	No	No
Fulminant	4 (1.6)	No	No
Autoimmune	9 (3.7)	No	No
Primary biliary cirrhosis	15 (6.1)	No	No
Other causes	25 (10.2)	No	No
Hepatocellular carcinoma	111 (45.1)	Yes	Yes
Diabetes mellitus	78 (32.1)	No	Yes
Arterial hypertension	73 (29.8)	No	No
Hypertension treatment	58 (23.7)	No	No
Cardiopathy	21 (8.6)	No	No
Portal thrombosis	37 (15.1)	No	No
MELD	19.8 ± 13	11	19
Child-Turcotte-Pugh (CTP) score			
A	67 (27.3)	Yes	No
B	87 (35.5)	No	No
C	91 (37.1)	No	Yes

Total sample: For continuous variables, the descriptive of the mean ± SD are shown. For categorical variables, frequency and percentage are shown in parentheses. The values recorded for each patient are displayed.
NAFLD: non-alcoholic fatty liver disease, MELD: model for end-stage liver disease.

on the first postoperative day but was extubated at 48 h without complications. The patient was discharged on postoperative day 60. The cause of this prolonged hospitalization was liver graft rejection, resulting in the need for a second liver transplantation 3 months later. The postoperative data of the patients with VS and PRS are shown in Table 4.

DISCUSSION

To our knowledge, there are no studies on the incidence of VS in the population undergoing liver transplantation, and only isolated cases have been reported [12-14]. Therefore, the main finding of this study is the low incidence of VS among patients undergoing liver transplantation; only 0.81% of the patients developed VS, in contrast to 23.17% of the patients who developed PRS.

VS was initially described in cardiac surgery, and its frequency has been reported to vary between 5% and 42% [2, 25, 26]. The high incidence of VS in cardiac surgery patients is attributed to the low temperature and long duration of extracorporeal circulation [27]. However, this syndrome has multifactorial causes, such as direct surgical trauma (thoracotomy), aortic clamping, ischemia/reperfusion injury syndrome [3-6]. These factors promote the activation of inducible nitric oxide synthase (iNOS) in the vascular endothelium,

Table 2: Anesthetic-surgical parameters of the total patients and for patients with vasoplegic syndrome (VS).

Parameters	Total (n= 246)	VS patient 1	VS patient 2
Noradrenaline (mg)	10.59 ± 10.76	2	10
Adrenaline (mg)	0.34 ± 1.32	0.3	0.5
Calcium administered (g)	3.37 ± 2.70	1.5	1
Bicarbonate administered (mEq)	202.14 ± 152.43	250	170
Packed red blood cell	4.70 ± 5.59	0	4
Fresh frozen plasma (units)	4.44 ± 5.07	0	8
Platelets (pools)	0.89 ± 1.28	0	1
Bleeding (mL)	3815.04 ± 3409.88	520	3300
Urine output (mL)	673.41 ± 509.05	220	650
Hepatectomy duration (min)	170.12 ± 50.37	150	180
Anhepatic duration (min)	64.69 ± 50.26	45	45
Cold ischemia time (min)	344.93 ± 78.85	300	360
Recipient liver weight (g)	1346.04 ± 401.67	1860	1050
Donor liver weight (g)	1446.63 ± 352.43	1045	1365
Donor liver/recipient liver weight	1.16 ± 0.43	0.56	1.3
Porto-cava shunt	117 (49.20)	0	0

Total sample: For continuous variables, the descriptive of the mean ± SD are shown. For categorical variables, frequency and percentage are shown in parentheses. The values recorded for each patient are displayed.

resulting in an increase in nitric oxide, which stimulates guanylate cyclase (GC) and subsequently increases the level of cGMP, a mediator that triggers the relaxation of vascular smooth muscles [28-30]. The final step of this pathway is profound vasodilation.

The differential diagnoses of VS include septic shock, acute cardiac dysfunction, pulmonary emboli, anaphylactic shock, and postreperfusion syndrome (PRS). In our patients, hemodynamic alteration was not attributed to the existence of PRS, since the differentiation between both syndromes was made considering the predicted hemodynamic parameters described in the Methods section.

We ruled out VS in one patient who presented with similar hemodynamic characteristics (increased CI, decreased filling pressures, and SVR) in the neohepatic phase; in this patient, septic shock was confirmed by the finding of *Klebsiella* in the preservation fluid of the liver graft and blood cultures, and the patient died in the postoperative period.

The two patients with VS had excellent pump function and no valvular abnormalities; all chambers were of normal size without any signs of increased pulmonary pressure (ruling out pulmonary emboli). Cardiogenic causes of hemodynamic instability were ruled out by transthoracic echocardiogram in the immediate postoperative period. Anaphylactic shock could be ruled out because patients did not receive any blood products or new drugs for about 1 hour before the profound vasoplegia, and the transfusion required by one patient was administered 1 hour after the onset of hemodynamic instability. None of the patients with VS received ACE inhibitors 24 h prior to the procedure [31]; this medication is an established risk factor for VS, associated with an incidence of VS of 26.9% among patients undergoing cardiac surgery. Therefore, considering previous findings and that the diagnosis of VS is a diagnosis of exclusion, VS could be the most likely diagnosis of refractory vasodilation in the two patients described.

Some authors propose that VS is related to ischemia reperfusion injury of the intestine and graft liver when it occurs after liver graft

Table 3: Hemodynamic characteristics of total patients and patients with vasoplegic syndrome (VS).

		Anhepatic phase	Reperfusion (first 5 min)	Neohepatic phase
MAP (mmHg)	Total	72.60 (70.66,74.54)	54.15 (52.48,55.82)	65.37 (63.84,66.90)
	VS Patient 1	51	37	45
	VS Patient 2	69	29	49
HR (bpm)	Total	80.16 (77.48,82.83)	91.27 (87.51,95.03)	91.04 (87.98,94.09)
	VS Patient 1	93	95	92
	VS Patient 2	107	120	108
CVP (mmHg)	Total	7.25 (6.73,7.77)	8.61 (8.00,9.23)	9.81 (9.21,10.42)
	VS Patient 1	3	2	2
	VS Patient 2	3	2	0
mPAP (mmHg)	Total	16.77 (16.02,17.51)	19.23 (18.43,20.03)	20.39 (19.55,21.24)
	VS Patient 1	10	9	10
	VS Patient 2	17	13	13
PCP (mmHg)	Total	10.70 (9.96,11.44)	12.67 (11.95,13.39)	13.81 (13.11,14.51)
	VS Patient 1	4	3	5
	VS Patient 2	10	8	10
CI (L/min/m^2)	Total	3.43 (3.24,3.63)	3.64 (3.40,3.87)	5.05 (4.77,5.32)
	VS Patient 1	4.8	5	8.7
	VS Patient 2	6.4	6.7	7.5
SVR (dyn/s/cm^{-5})	Total	993.02 (915.11,1071.12)	648.90 (603.10,694.81)	553.81 (520.81,587.01)
	VS Patient 1	492	344	245
	VS Patient 2	676	264	429

For the total sample, the estimated marginal means and their 95% confidence intervals are shown in parentheses.
For patients 1 and 2 the values of each patient are displayed.
MAP: mean arterial pressure, HR: heart rate, CVP: central venous pressure, mPAP: mean pulmonary artery pressure, PCP: pulmonary capillary pressure, CI: cardiac index, SVR: systemic vascular resistance.

reperfusion [32]. One of the patients with VS experienced liver graft rejection, requiring a second liver transplantation surgery, and the other patient died without resolution of the VS. The mortality rate of patients with VS due to liver transplantation is not clear given the presence of isolated case reports [12-14]. Some authors reported high mortality rates when VS is prolonged for 36–48 h; in these cases, the mortality increases from 16% to 27% [33]. In the surviving patient in our study, the situation of VS extended up to 6 h postoperatively, and in the non-surviving patient, VS was prolonged until death on the fifth postoperative day.

Current evidence indicates that conventional vasopressors are recommended as first-line therapy. In this regard, noradrenaline is generally considered the gold standard, and vasopressin should be added to noradrenaline in case of adverse side effects related to excessive sympathetic stimulation (tachycardia, atrial fibrillation) [34]. Additionally, vasopressin can be used as an initial vasopressor [35]. Unconventional vasopressors, such as hydroxocobalamin, methylene blue, and angiotensin 2, have been used in refractory cases, but there is insufficient evidence to make definitive recommendations [36-38]. We probably did not recognize the presence of VS in these patients and limited ourselves to the administration of intravenous noradrenaline/adrenaline, but prompt recognition of VS and early and aggressive treatment should be considered important to improve prognosis.

The patients included in our study were moni-

tored with a Swan-Ganz catheter, which allowed a correct differential diagnosis between VS and PRS. However, the differences observed in the CI (high in VS and low in PRS) as well as the frequent refractoriness of hypotension to catecholamines in VS [24] could help in their differentiation.

There are limitations in our study. Due to the low incidence of patients with VS who underwent liver transplantation, we were not able to determine the possible risk factors associated with its appearance, nor to carry out a comparative analysis with those patients who had presented PRS.

In conclusion, most episodes of hemodynamic instability after liver graft reperfusion are due to PRS, and VS is very rare and seems to be associated with poor prognosis in patients undergoing liver transplantation. In addition, although very rare, it is important to rule out the presence of septic shock in patients with hemodynamic instability, since it shares the same hemodynamic characteristics as VS. Since the hemodynamic criteria for VS and PRS overlap significantly, clear and standardized definitions of both syndromes are needed to ensure early diagnosis and accurate treatment.

ACKNOWLEDGMENTS

We appreciate our colleagues, anesthesiologists and surgeons, who cooperated to perform this study.

CONFLICT OF INTEREST: None declared.

REFERENCES

1. Clinton TL, Malcolm JU, Lotto A, *et al*. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg* 2000;**69**:1198-204.
2. Argenziano M, Chen JM, Choudhri AF, *et al*. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. *J Thorac Cardiovasc Surg* 1998;**116**:973-80.
3. Orozco DM, Triana CA, Orozco AC. Vasoplegic síndrome in cardiac surgery: Definitions, pathophysiology, diagnostic approach and management. *Rev Esp Anest y Reanim* 2019;**66**:277-87.
4. Cremer J, Martin M, Redl H, *et al*. The systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 1996;**61**:1714-20.
5. Levin MA, Lin HM, Castillo JG, *et al*. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. *Circulation* 2009;**120**:1664-1671.
6. Alfirevic A, Xu M, Johnston D, Figueroa P, *et al*. Transfusion increases the risk for vasoplegia after cardiac operations. *Ann Thorac Surg* 2011;**92**:812-9.
7. Carrel T, Englberger L, Mohacsi P, *et al*. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. *J Card Surg* 2000;**15**:347-53.
8. Leyh R, Kofidis T, Strüber M, *et al*. Methylene blue: The drug of choice for catecholaminerefractory vasoplegia after cardiopulmonary bypass? *J of Thorac and Cardiovasc Surg* 2003;**125**:1426-31.
9. Augoustides J, Abrams M, Berkowitz D. Vasopressin for hemodynamic rescue in catecholamine-resistant vasoplegic shock after resection of massive pheochromocytoma. *Anesthesiology* 2004;**101**:1022-4.
10. Hosseinian L, Weiner M, Levin MA, *et al*. Methylene Blue: magic bullet for vasoplegia. *Anesth Analg* 2016;**122**:194-201.
11. McCartney SL, Duce L, Ghadimi K, *et al*. Intraoperative vasoplegia: methylene blue to the rescue!. *Curr Opin Anaesthesiol* 2018;**31**:43-49.
12. Khosravi MB, Milani S, Ghaffaripour S. Very high dose epinephrine for the treatment of vasoplegic syndrome during liver transplantation. *Int J Organ Transplant Med* 2013;**41**:32-4.
13. Cao Z, Tao G. Is it possible to distinguish between vasoplegic syndrome and postreperfusion syndrome during liver graft reperfusion? In response. *Anesth Analg* 2010;**110**:970-1.
14. Cao Z, Gao Y, Tao G. Vasoplegic syndrome during liver transplantation. *Anesth Analg* 2009;**108**:1941-3.
15. Acosta F, Sansano T, Contreras RF, *et al*. Atropine prophylaxis of the postreperfusion syndrome in liver transplantation. *Transplant Proc* 1999;**31**:2377.
16. Fayed NA, Murad WS. Goal directed preemptive ephedrine attenuates the reperfusion syndrome during adult living donor liver transplantation. *Egypt J Anaesth* 2014;**30**:187-95.
17. Ayanoglu HO, Ulukaya S, Tokat Y. Causes of postreperfusion syndrome in living or cadaveric donor liver transplantations. *Transplant Proc* 2003;**35**:1442-4.
18. Siniscalchi A, Dante A, Spedicato S, *et al*. Hyperdynamic circulation in acute liver failure: reperfusion syndrome and outcome following liver transplan-

tation. *Transplant Proc* 2010;**42**:1197-9.

19. Xu ZD, Xu HT, Yuan HB, *et al*. Postreperfusion syndrome during orthotopic liver transplantation: a single-center experience. *Hepatobiliary Pancreat Dis Int* 2012;**11**:34-39.
20. Paugam-Burtz C, Kavafyan J, Merckx P, *et al*. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl* 2009;**15**:522-9.
21. Ryu HG, Jung CW, Lee HC, *et al*. Epinephrine and phenylephrine pretreatments for preventing postreperfusion syndrome during adult liver transplantation. *Liver Transpl* 2012;**18**:1430-9.
22. Aggarwal S, Kang Y, Freeman JA, *et al*. Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. *Transplant Proc* 1987;**19**:54-5.
23. Bukowicka B, Akar RA, Olszewska A, Smoter P, Krawczyk M. The occurrence of postreperfusion syndrome in orthotopic liver transplantation and its significance in terms of complications and short-term survival. *Ann Transplant* 2011;**16**:26-30.
24. Ozal E, Kuralay E, Yildirim V, *et al*. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardíac surgery. *Annal Thorac Surg* 2005;**79**:1615-9.
25. Carrel T, Englberger L, Mohacsi P, *et al*. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. *J Card Surg* 2000;**15**:347-53.
26. Kristof AS, Magder S. Low systemic vascular resistance state in patients undergoing cardiopulmonary bypass. *Crit Care Med* 1999;**27**:1121-7.
27. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. Crit. *Care* 2020;**24**:36.
28. Sabry O, Ahmed Z, Kenneth N. Cardiac Vasoplegia Syndrome: Pathophysiology, Risk Factors and Treatment. *Am J Med Sci* 2015;**349**:80-8.
29. Archer S, Huang J, Hampl V, *et al*. Nitric oxide and cGMP cause vasorelaxation by activation of a charybdotoxin-sensitive K channel by cGMP-dependent protein kinase. *Proc Natl Acad Sci USA* 1994;**91**:7583-7.
30. Janfeshan S, Masjedi F, Karimi Z. Protective effects of limb remote ischemic per-conditioning on the heart injury induced by renal ischemic-reperfusion through the interaction of the apelin with the RAS/iNOS pathway. *Bioimpacts* 2024;**14**:27567.
31. Noubiap JJ, Nouthe B, Sia YT, Spaziano M. Effect of preoperative renin-angiotensin system blockade on vasoplegia after cardiac surgery: a systematic review with meta-analysis. *World J Cardiol* 2022:**14**:250-9.
32. Koelzow H, Gedney JA, Baumann J, *et al*. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. *Anesth Analg* 2002;**94**:824-9.
33. Colleen MN. Vasoplegic syndrome in patients undergoing cardiac surgery: a literature review. *AACN Adv Crit Care* 2021;**32**:137-45.
34. Guarracino F, Habicher M, Treskatsch S, *et al*. Vasopressor Therapy in Cardiac Surgery-An Experts' Consensus Statement. *J Cardiothorac Vasc Anesth* 2021;**35**:1018-29.
35. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, *et al*. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. *Anesthesiology* 2017;**126**:85-93.
36. Sakpal SV, Reedstrom H, Ness C, *et al*. High-dose hydroxocobalamin in end-stage liver lisease and liver transplantation. *Durgs Ther Perspect* 2019;**35**:442-6.
37. Koelzow H, Gedney JA, Baumann J, *et al*. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. *Anesth Analg* 2022:**94**:824-9.
38. Running K, Weinberg D, Trudo W, *et al*. Intraoperative use of angiotensin II for severe vasodilatory shock during liver transplantation: a case report. *A A Pract* 2021;**15**:e01402.