Post-reperfusion Syndrome and Outcome Variables after Orthotopic Liver Transplantation

M. B. Khosravi, H. Sattari, S. Ghaffaripour, M. Lahsaeae, H. Salahi, M. A. Sahmeddini, A. Bahador, S. Nikeghbalian, S. Parsa, S. Shokrizadeh, S. A. Malek-Hosseini

Shiraz Organ Transplant Center, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background: Post-reperfusion syndrome (PRS) is an important complication during liver transplantation.

Objective: We studied the occurrence and severity of PRS in patients who underwent orthotopic liver transplantation (OLT) to investigate how PRS was correlated to clinical variables and outcomes.

Methods: We retrospectively recorded intra- and peri-operative data for 184 adult patients who received cadaveric OLT during a 3-year period from 2005 to 2008. Patients were divided into two groups according to the severity of PRS: Group 1 (mild or no PRS) comprised 152 patients; and group 2 (significant PRS) consisted of 32 patients.

Results: There were no significant differences in demographic and pre-operative data between groups. Group 2 had more total blood loss than group 1 (p=0.036), especially after reperfusion (p=0.023). Group 2 required more packed red cell transfusions (p=0.005), more fresh frozen plasma (p=0.003) and more platelets (p=0.043) than group 1. Fibrinolysis was more frequent in group 2 (p=0.004). Hospital stay in group 2 was significantly longer than in group 1 (p=0.034), but the frequencies of other outcomes including infection, re-transplantation, dialysis, rejection and extended donor criteria did not differ significantly between groups.

Conclusions: Bleeding, blood transfusion and fibrinolysis occurred more often in the group of severe PRS after reperfusion. Although postoperative complications like rejection, infection and the dialysis rate were not significantly different in the two groups, hospital stay was more prolonged in the group with severe PRS.

KEYWORDS: Postreperfusion syndrome; Severity; Outcomes, Transfusion; Orthotopic liver transplantation.

INTRODUCTION

Orthotropic liver transplantation (OLT) comprises three phases: 1) dissection to detach adhesions and mobilize the liver, 2) the anhepatic phase to remove the native liver and create vascular anastomoses with the transplanted organ, and 3) the neohepatic or reperfusion phase [1]. The reperfusion phase is the most critical time for anesthesiologists. Hemodynamic and metabolic events occur during reperfusion that are known as “post-reperfusion” or “post-revascularization syndrome” (PRS) [2]. The syndrome can also appear shortly after reperfusion of an ischemic tissue or organ. This complication should not be confused with ischemic reperfusion (IR) injury, which refers to local damage of a transplanted organ in response to prolonged ischemia [3].

PRS was first reported by Starzl, et al. and was described by Aggarwal, et al., in 1987 [2] as cardiovascular collapse after reperfusion.
of the transplanted liver. They defined a syndrome of severe cardiovascular dysfunction, bradycardia, decreased mean arterial pressure (MAP) and systemic vascular resistance, with a simultaneous increase in pulmonary filling pressures. PRS was more recently defined as a decrease in MAP (<70% of the reperfused value) for a minimum of 1 min within 5 min of reperfusion [2,4]. However, Hilmi, et al., pointed out that some degree of hemodynamic instability was seen in all patients. Recently, PRS has been classified according to its duration and severity [5]. The etiology of PRS is not clearly understood, but the syndrome has been attributed to different factors including metabolic acidosis, hyperkalemia, hypothermia, hypocalcemia and the release of vasoactive substances [2,6]. The incidence of PRS is about 8%–30% in patients who receive OLT [4,7,8].

In this retrospective study we investigated PRS in patients who received OLT and looked for relationships between the severity of this syndrome and potentially problematic post-reperfusion changes, the amounts of blood loss and transfusion, short-term outcomes, and post-operative complications.

METHODS

For conducting this retrospective study, we obtained institutional approval to review the anesthesia records and peri-operative data of 184 consecutive patients >14 years old who underwent cadaveric donor OLT by the piggyback hepatectomy technique during a three-year period from 2005 to 2008. Two groups of patients were defined according to the decrease in MAP or heart rate after reperfusion in relation to the baseline value recorded 10 min before portal vein declamping and reperfusion. Group 1 comprised 152 patients with mild PRS manifested as a decrease in MAP or heart rate less than 30% of the anhepatic level that lasted ≤3 min. This group also included patients who responded to an intravenous epinephrine bolus (≤100 μg) or intravenous calcium chloride (1 g), and did not need the continuous infusion of the vasopressor or inotrope. Group 2 consisted of 32 patients with severe PRS manifested as decrease in MAP >30% of the anhepatic value and severe bradycardia requiring continued vasopressor infusion after reperfusion and prolonged fibrinolysis (>30 min) [5].

We recorded demographic characteristics and preoperative laboratory values. Intra-operative hemodynamic changes, transfusion need before and after reperfusion, vasopressor usage, incidence of fibrinolysis (assessed by thromboelastogram), short-term postoperative outcomes and complications were recorded and compared between the two groups. The extended donor criteria (EDC) for liver allograft quality were: age >65 years, serum sodium level >155 mEq/L, donor liver macrosteatosis ≥30% on biopsy, warm ischemic time >90 min and cold ischemic time >16 h.

Student’s t test for independent samples and Mann-Whitney U test were used for comparison of continuous data. For categorical variables, we used χ² or Fisher exact test when appropriate. The data are presented as the mean±SD or the median. All analyses were done with SPSS v. 15. P value <0.05 was considered statistically significant.

RESULTS

Some degree of PRS was observed in all 184 patients. Among them, 152 (82.6%) patients were classified as group 1 (mild PRS), and 32 (17.4%) patients were classified as group 2 (severe PRS). We found no significant differences between groups in demographic or pre-operative data (Table 1).

Comparison of the intra-operative variables revealed that group 2 patients had more total blood loss than those in group 1 (p=0.036)—a difference that reflected the greater post-reperfusion blood loss in group 2 (p=0.023). Before reperfusion, the amount of blood loss did not differ significantly between groups. Group 2 patients used more packed red cells (PRBC) than group 1 patients (p=0.005)—a difference that was especially marked after reperfusion (p=0.003). Group 2 patients used higher amounts of fresh frozen plasma (FFP)
The incidence of fibrinolysis in group 2 was more than in group 1 (p = 0.004). The mean cold ischemic time (CIT), warm ischemic time (WIT), the amount of sodium bicarbonate (NaHCO₃) used, and serum potassium concentration after reperfusion did not differ significantly between groups (Table 2). Donor characteristics including mean age, serum sodium concentration, and duration of stay in the intensive care unit also showed no significant differences between groups (Table 3). The post-operative data showed that hospital stay was however significantly longer in group 2 patients (p = 0.034). Post-operative outcomes including infection, retransplantation, dialysis, rejection and serum creatinine, and the EDC, did not differ significantly between groups (Table 4).

### Table 1: Characteristics of patients before orthotopic liver transplantation.

| Characteristics          | Group 1 (n=152) | Group 2 (n=32) | p value |
|--------------------------|-----------------|----------------|---------|
| Age (year)               | 34.44±13.23     | 36.88±13.59    | 0.348   |
| Male                     | 67.8%           | 62.5%          | 0.352   |
| Female                   | 32.2%           | 37.5%          | 0.352   |
| Weight (kg)              | 64.12±14.49     | 63.62±15.72    | 0.861   |
| Serum creatinine (mg/dL) | 0.98±0.47       | 0.84±0.50      | 0.128   |
| Platelet count (>1000)   | 98.48±106.10    | 85.91±63.23    | 0.519   |
| INR                      | 2.77±1.94       | 2.34±1.37      | 0.843   |
| Hematocrit               | 34.25±4.32      | 34.13±3.98     | 0.608   |
| MELD                     | 21.75±5.50      | 21.56±8.25     | 0.903   |
| AIH                      | 17.8%           | 18.8%          | 0.887   |
| HBV                      | 24.3%           | 34.3%          | 0.887   |
| HCV                      | 7.1%            | 6%             | 0.887   |
| PSC                      | 17.1%           | 15.6%          | 0.887   |
| Wilson disease           | 11.2%           | 9.4%           | 0.887   |
| Cryptogenic              | 21.7%           | 15.6%          | 0.887   |

INR: International normalized ratio, MELD: Model for end-stage liver disease, PSC: Primary sclerosing cirrhosis, AIH: Autoimmune hepatitis, HBV: Hepatitis B cirrhosis, HCV: Hepatitis C cirrhosis.

### DISCUSSION

PRS was first defined in liver transplantation by Aggarwal, et al., in 1987 [2]. It is a widely reported event that can occur after the reperfusion of an ischemic organ. In different studies, many contributing factors have been reported. Hilmi, et al. [5], found that the age of the recipients differed significantly—patients with significant PRS were older. The age difference between our two groups was not sig-

### Table 2: Intra-operative data during orthotopic liver transplantation.

| Intra-operative Data               | Group 1          | Group 2          | p value |
|------------------------------------|------------------|------------------|---------|
| CIT (hrs)                          | 10.29±6.73       | 8.93±4.08        | 0.274   |
| WIT (min)                          | 63.28±13.67      | 67.97±11.25      | 0.072   |
| PRBC before reperfusion (units)    | 1.87±1.60        | 2.78±2.69        | 0.074   |
| PRBC after reperfusion (units)     | 1.82±1.62        | 4.72±4.98        | 0.003*  |
| Total PRBC (units)                 | 3.66±2.47        | 7.50±7.18        | 0.005*  |
| FFP (units)                        | 1.11±2.33        | 4.00±5.15        | 0.003*  |
| PLTS (units)                       | 1.03±2.46        | 3.15±5.38        | 0.043*  |
| NaHCO₃ (mL)                        | 218.95±122.19    | 247.69±175.13    | 0.095   |
| [K] after reperfusion (mM)         | 4.08±0.97        | 4.24±1.04        | 0.407   |
| Fibrinolysis                       | 6.6%             | 25%              | 0.004*  |
| Blood loss before reperfusion (mL) | 1000 (100-6500)† | 1300 (100-8000)† | 0.187   |
| Blood loss after reperfusion (mL)  | 1000 (100-10,000)† | 1450 (150-24,500)† | 0.023*  |

CIT: Cold ischemic time, WIT: Warm ischemic time, PRBC: Packed red cells, FFP: Fresh frozen plasma, PLTS: Platelets, NaHCO₃: Sodium bicarbonate, [K]: serum potassium

*Significant at p < 0.05. †Median and range of blood loss.
significant, although our patients were younger. Comparison of the demographic and preoperative data between the two groups revealed no significant differences. Studies by Nanshima, et al. [9] and Ayanoglu, et al. [10] also found no significant differences between pre-operative characteristics. Nanshima and colleagues also found that WIT in the PRS group was longer which was not significant. Hilmi, et al., reported shorter WIT in the significant PRS group compared to mild PRS (p=0.010) [5]. Ayanoglu and colleagues found that longer anhepatic time was associated with decreased PRS occurrence. Longer WIT, especially >90 min, can cause severe ischemic insult and worsen the extent of injury during reperfusion [11,12]. However, in our study WIT was optimal and well within the acceptable range. Intra-operative data showed that WIT in group 2 patients (significant PRS) was longer than in group 1 although this difference was not significant (Table 2).

CIT was shorter in our group 2 patients, although the difference was not significant. Most graft insults occur during reperfusion [13,14], although the initial insult begins during CIT due to mitochondrial dysfunction and cellular membrane damage [15]. Oxidative stress at reperfusion time leads to activation of Kupffer cells and microvascular dysfunction (no-reflow), and to neutrophil activation [16]. However, ischemic reperfusion (I/R) injury may result in failure or primary nonfunction of the transplanted organ. The I/R injury may or may not be the cause of hemodynamic changes immediately after reperfusion (PRS), and the relationship between the I/R injury and PRS has yet to be clearly characterized [17].

In our study blood loss and blood product usage were significantly more in group 2, and in both groups blood loss and transfusion were greater after reperfusion than before it. The greater blood loss and transfusion need in group 2 were associated with more severe and frequent fibrinolysis in this group (Table 2). Fibrinolysis can increase after reperfusion due to increasing tissue-type plasminogen activator (tPA) activity [18]. Blood transfusion can worsen the outcome in patients and in the transplanted organ [19]. The lower incidence of rejection in the first post-operative month in group 2 was notable, and may have been due

| Table 3: Donor characteristics |
|--------------------------------|
| Donor characteristics | Group 1 | Group 2 | p value |
| Age (year) 30.19± 14.26 | 33.13± 14.25 | 0.292 |
| [Na] 147.46± 10.53 | 149.92± 13.29 | 0.291 |
| ICU stay (day) 3.01± 1.94 | 2.84± 1.96 | 0.659 |
| Male 81.5% | 18.5% | 0.552 |
| Female 85% | 15% | 0.552 |

ICU: Intensive care unit, [Na]: Serum sodium.

| Table 4: Post-operative data for patients who underwent orthotopic liver transplantation. |
|-----------------------------------------------|
| Post-operative data | Group 1 | Group 2 | p value |
| Hospital stay (day) 14.93±6.98 | 19.19±10.27 | 0.034* |
| Infection 9.9% | 3.1% | 0.313 |
| Retransplantation 0% | 3.1% | 0.174 |
| Dialysis 1st month 5.3% | 9.4% | 0.409 |
| Rejection 1st month 32.9% | 25% | 0.530 |
| [Cr] first post-operative day 0.85±0.46 | 0.85±0.48 | 0.999 |
| EDC Graft 26.8% | 37% | 0.351 |

EDC: Extended donor criteria, [Cr]: Serum creatinine. *Significant at p=0.05.
to the higher transfusion volume and greater immunosuppressant effects of blood transfusion in this group [20].

The amount of sodium bicarbonate used and serum potassium level after reperfusion did not differ significantly between groups. This finding was similar to the report of Nanshima, et al. [9]. Aggarwal and colleagues also found no significant differences between groups in terms of serum potassium level, incidence of acidosis, serum calcium concentration, core temperature, or arterial blood gas tensions except for a decrease in systemic vascular resistance [5].

Our two groups did not differ in terms of the frequency of post-reperfusion complications except for the significantly longer hospital stay in patients with severe PRS. This finding is consistent with earlier results reported by Hilmi, et al. [5], and Nanshima, et al. [9].

Compliance of the grafts that were used with EDC did not differ significantly between our two groups; the use of these grafts was unrelated to the severity of PRS. Nanshima and colleagues found that donor age >50 years was associated with the occurrence of PRS, but did not affect patient or graft outcome. However, PRS may affect patient and graft outcomes, hence, the need to prevent its associated adverse hemodynamic and metabolic effects and thus improve outcomes. Different approaches are available to reduce reperfusion injuries. Examples are administration of vasodilators such as inhaled nitric oxide, prostaglandins, free radical scavengers, ischemic preconditioning, and use of therapeutic substances such as N-acetylcysteine and methylen blue.

We conclude that during OLT, blood loss, transfusion and fibrinolysis were higher in the group with severe PRS after reperfusion of the transplanted liver. Although post-operative complications like rejection, infection and the dialysis rate were not significantly different in the two groups, hospital stay was more prolonged in the group with severe PRS.

ACKNOWLEDGMENTS
This study was supported by the Department of Pathology and the Department of Biostatistics, Shiraz University of Medical Sciences. We thank Mr. Hamed Tabesh for his help with the statistical analysis of the data, Dr. Bita Geramizadeh for help with the pathological studies, and K. Shashok (AuthorAID in the Eastern Mediterranean) for improving the use of English in the manuscript.

REFERENCES
1. Miller RD. Anesthesia. New York, USA: Churchill Livingston Inc, 6th edition, 2005:2248-9.
2. Aggarwal S, Kang Y, Freeman JA, et al. Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. Transplant Proc 1987;19:54-5.
3. Kodakat SK, Ginsburg R, Gopal PB, et al. A case of post-reperfusion syndrome following surgery for liver trauma. Br J Anaesthesiol 2006;96:31.
4. Aggarwal S Kang Y, Freeman JA et al. Postreperfusion syndrome: hypotension after reperfusion of transplanted liver. Crit Care Med 1993;8:154-60.
5. Hilmi IA, Horton CN, Planisic RM, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. Liver Transplantation 2008;14:504-8.
6. Barbieri A, Zonta F, Saracino ML, et al. Evaluation of reperfusion syndrome after liver ischemia in the rat. J Surg Res 1996;62:153-8.
7. Martinez IG, Olmedilla L, Perez-Pena JM, et al. Response to clamping of the inferior vena cava as a factor for predicting postreperfusion syndrome during liver transplantation. Anesth Analg 1997;84:254-9.
8. Aggarwal S, Kang Y, Freeman JA, et al. Is there a postreperfusion syndrome? Transplant Proc 1989;21:3497-9.
9. Nanshima A, Pilly P, Crawford M, et al. Analysis of post revascularization syndrome after orthotopic liver transplantation: experience of an Australian liver transplantation center. J Hepatobiliary Pancreat Surg 2001;8:557-63.
10. Ayanoglu HO, Ulukaya S, Tukat Y, et al. Causes of postreperfusion syndrome in living or cadaveric donor liver transplantation. Transplant Proc 2003;35:1442-4.
11. Huguet BC, Gavelli A, Chieco PA, et al. Liver ischemia for hepatic resection: where is the limit? Surgery 1992;111:251-9.
12. Delva E, Camus Y, Nordlinger B, et al. Vascular oc-
inclisions for liver resections. Operative management and tolerance to hepatic ischemia: 142 cases. Ann Surg 1989;20:211-8.

13. Hasselgren PO. Prevention and treatment of ischemia of the liver. Surg Gynecol Obstet 1987;164:187-96.

14. Fredriks WM, James J, Bosch KS, et al. A model for provoking ischemic necrosis in rat liver parenchyma and its quantitative analysis. Exp Pathol 1982;22:245-52.

15. Rosser B, Gores GJ. Liver cell necrosis: cellular mechanism and clinical implications. Gastroenterology 1995;108:252-75.

16. Henrion J. Ischemic/reperfusion injury of the liver: pathophysiologic hypotheses and potential relevance to human hypoxic hepatitis. Acta Gastroenterology Belg 2000;63:336-47.

17. Kupiec-Weglinski JW, Busutill RW. Ischemic and reperfusion injury in liver transplantation. Transplant Proc 2005;37:1653-6.

18. Prote RJ, Bontempo FA, Knot EA, et al. Systemic effects of tissue plasminogen activator associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. Transplantation 1989;47:978-84.

19. Palomo Sanchez JC, Jimenez C, Moreno G, et al. Effects of intraoperative blood transfusion on post-operative complication and survival after orthotopic liver transplantation. Hepatogastroenterology 1998;45:1026-33.

20. Rouch DA, Thistlethwait JR, Lichtor L, et al. Effects of massive transfusion during transplantation on rejection and infection. Transplant Proc 1988;20:1135-7.

Human-headed winged bull in Louvre museum. It was usually placed as a guardian at certain gates or doorways of cities and palaces. The symbol is a combination of man, bull, and bird, and presumably offered protection against enemies (photo courtesy Dr. M. Salehipour).