Transpl Int (2001) 14: 80–86

ORIGINAL ARTICLE

Stefan Tange
Yvonne Höfer
Martin Welte
Matthias Anthuber
Karl W. Jauch
Edward K. Geissler
Wolfgang Ertel

Local secretion of TNF-α from the liver does not correlate with endotoxin, IL-6, or organ function in the early phase after orthotopic liver transplantation

Received: 25 October 1999
Revised: 7 July 2000
Accepted: 22 November 2000

S. Tange (✉) · M. Anthuber · K. W. Jauch
E. K. Geissler
Department of Surgery,
University Hospital Regensburg,
Franz-Josef-Strauss-Allee 11,
93055 Regensburg, Germany

Y. Höfer
Institute for Anaesthesiology,
Evangelic Hospital,
40217 Duesseldorf, Germany

M. Welte
Clinic for Anaesthesiology and
Operative Intensive Care Medicine,
Klinikum Benjamin Franklin,
Free University Berlin,
12203 Berlin, Germany

W. Ertel
Division of Trauma Surgery,
University Hospital Zurich,
8091 Zurich, Switzerland

Abstract Hepatic ischemia/reperfusion leads to an excessive release of proinflammatory cytokines, which promotes local and remote cell damage. The value of cytokine measurement in humans for predicting graft function after orthotopic liver transplantation (OLT) remains unclear. Therefore, in this study, tumor-necrosis-factor-α (TNF-α), interleukin-6 (IL-6), and endotoxin (ET) levels were determined in the blood taken from the hepatic veins of 31 patients who underwent OLT. Peak levels of TNF-α in hepatic venous blood were measured shortly after reperfusion and were significantly higher than concentrations in the systemic circulation. IL-6 concentrations, peaking 90 min after reperfusion, only correlated with postoperative pulmonary dysfunction. ET was detectable in 21 patients, but levels did not correlate with either IL-6 or TNF-α concentrations. Additionally, serum cytokine levels did not correlate with the duration of ischemia or with histological changes seen in liver biopsies. In general, our study suggests that local secretion of cytokines does not predict liver function in the early posttransplant phase.

Keywords Liver transplantation · Ischemia · Endotoxin · Cytokines

Abbreviations *ET* Endotoxin · *IL-6* Interleukin-6 · *OLT* Orthotopic liver transplantation · *TNF-α* Tumor-necrosis-factor α

Introduction

OLT has become an established procedure for end-stage liver disease. However, primary graft dysfunction and posttransplant pulmonary and renal failure still pose relevant clinical problems [19]. Attempts have been made to develop a strategy for determining graft function early after OLT. One approach has been to monitor cytokine release in the early postoperative phase. For instance, ET is one of the most potent stimulators of cytokine synthesis. As a result of gut ischemia, ET can be measured in the circulation before it is eliminated mainly by the reticuloendothelial system in the liver. Besides ET, ischemia/reperfusion is another stimulus for cells capable of cytokine synthesis. It has recently been demonstrated that resident liver macrophages (Kupffer cells) are activated by ischemia/reperfusion injury [4,29], with a subsequent release of proinflammatory mediators such as TNF-α [6] and IL-6 [3]. In particular, high concentrations of TNF-α are capable of inducing severe tissue damage. Furthermore, previous experimental studies have shown that an enhanced release of TNF-α by Kupffer cells following liver ischemia/reperfusion injury can not only lead to local tissue damage, but may also cause signifi-

cant tissue necrosis in remote organs [6]. Notably high TNF-α levels, compared to those of patients without graft rejection, have been measured in OLT patients experiencing a rejection episode [16]. IL-6, on the other hand, is known for its influence on protein synthesis in hepatocytes, especially for the induction of acute phase proteins. As for TNF-α, increased IL-6 concentrations were detected during rejection episodes in the serum and bile of kidney and liver transplants.

Although increased levels of circulating proinflammatory cytokines after transplantation are now a well accepted phenomenon, there is controversy about the predictive value of circulating cytokines for determining graft dysfunction in humans [13, 14, 15]. Consequently, the present study was carried out to determine if the local release of TNF-α and IL-6 into hepatic venous blood differed from systemic blood cytokine levels. Results were compared to endotoxin levels and various parameters of hepatic and pulmonary function.

Material and methods

Patients

Thirty consecutive patients undergoing 31 liver transplantations were enrolled in this study and followed up for 1 month (22 male, 8 female; mean age 49.1 ± 7.3 years, range 28–66 years) (Table 1). Posthepatitic cirrhosis was the most common indication, followed by hepatocellular carcinoma and alcoholic cirrhosis. Two patients died during the postoperative course. Five patients had to undergo emergency transplantation.

Surgical procedures

Liver transplantation was performed following the standard technique, as described previously [5]. A veno-venous-bypass was constructed in all patients. University of Wisconsin solution was used for graft preservation and benching. Prior to reperfusion, the liver was flushed with 500 ml of cold human albumin (5%). Initial reperfusion of the graft was established by declamping the portal vein, arterial recirculation followed approximately 20 min later. Immunosuppression was started intraoperatively with methylprednisolone (500 mg) and azathioprine (2 mg/kg). As postoperative immunosuppression, a quadruple regimen, of methylprednisolone (tapered to 10 mg/day within 6 weeks), azathioprine (1–2 mg/kg/day), anti-thymocyte-globulin (4 mg/kg/day, day 1–10) and cyclosporine (1–6 mg/kg/day) was administered.

For the sampling of blood from the hepatic vein, the standard central venous line was passed through the internal jugular vein to the vena cava inferior and finally into the hepatic vein. The correct position of the catheter was controlled using x-rays and by intraoperative digital palpation by the surgeons.

Collection of blood and biopsies

Blood was obtained from arterial lines placed into the radial artery and from the hepatic vein catheter. Blood samples were taken before laparotomy (BL), at the beginning of the anhepatic phase (AP), 10 min before reperfusion (0), and 5-, 15-, 30-, 60-, 90-, 120- and 240 min following reperfusion. Blood was immediately centrifuged to obtain serum, which was aliquoted and stored at –70 °C until assayed. The liver enzymes GPT, GOT and GLDH were measured daily during the immediate posttransplant phase and used for statistical evaluation of liver function. Intraoperative biopsies were performed on livers that showed visual evidence of poor reperfusion. All biopsies were stained by the hematoxylin & eosin method.

Table 1 Demographic data and indications for liver transplantation

Patients	
Mean age (years)	49.1 ± 7.3
Male/female	23/8
Indications for liver transplantation	
Posthepatitic cirrhosis	10
Hepatocellular carcinoma	6
Alcoholic cirrhosis	4
Primary biliary cirrhosis	3
Acute liver failure	3
Graft failure	2
Cryptogenic cirrhosis	1
Retransplantation	1
Carcinoid metastasis	1
Mortality (1-month)	2/30
Graft survival (1-month)	26/31

Cytokine assays

Serum levels of TNF-α were determined by measuring the cytotoxic effect on a murine fibrosarcoma cell line, WEHI 164 subclone 13 (kindly provided by Dr. S. Kunkel, Ann Arbor, MI), as previously described [12]. Briefly, 5×10^5 WEHI cells were incubated with serial dilutions of serum samples for 20 h in 96 – well microtiter plates (Greiner Labortechnik, Frickenhausen, Germany). During the last 4 h of incubation, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (MTT, 5 mg/ml; Sigma Chemical, Deisenhofen, Germany) was added to each well. Cellular activity was proportional to the formation of dark blue formazan, measured at 650 nm using a spectophotometer. The biological activity of TNF-α in serum samples could be completely abolished by the addition of a rabbit monoclonal anti-human TNF-α antibody (Genzyme, Boston, MA), demonstrating specificity of the WEHI 164 cytotoxicity assay. The detection sensitivity of the cytotoxicity assay was 0.1 U/ml [11].

An IL-6 dependent hybridoma cell line, 7TD1 (obtained from ATCC, Rockville, MD), was used to assay IL-6 levels [28]. Cells (1×10^4/well) were added to 96 – well microtiter plates and were incubated with serial dilutions of serum samples for 96 h. Proliferation of 7TD1 cells was measured using the MTT-assay, as described above. To further confirm that 7TD1 cells uniquely proliferated in response to IL-6, a monoclonal anti-human IL-6 antibody (Genzyme) was added to serum samples containing peak concentrations of IL-6. The antibody completely inhibited proliferation of 7TD1 cells, thus confirming the specificity of the assay.

Table 2 Spearman's correlation coefficient comparing mean values of ET, TNF-α and IL-6 (see Figs. 1, 2, 3), and the duration of ischemia and anhepatic phase, respectively

	Ischemia (Arterial/ hepatic vein)	Anhepatic phase (Arterial/ hepatic vein)
ET (Mean value)		
5–30 min	0.23/0.2	0.001/–0.17
60–120 min	0.12/0.27	–0.15/–0.18
5–120 min	0.18/0.23	–0.06/–0.09
TNF-α (Mean value)		
5–30 min	0.4/0.35	0.03/0.07
60–120 min	0.28/0.34	–0.07/–0.06
5–120 min	0.4/0.34	–0.05/0.002
IL-6 (Mean value)		
5–30 min	0.15/0.22	0.34/0.48
60–120 min	0.14/0.24	0.20/0.3
5–120 min	0.17/0.22	0.25/0.33

Endotoxin measurement

ET levels were determined with a modified turbidimetric limulus amoebocyte lysate test (Pyroquant GmbH, Walldorf, Germany) [2]. Samples were diluted 1:10 in pyrogen-free water and were heated at 100 °C for 10 min to remove nonspecific inhibitors. Kinetics of the reaction were determined spectrophotometrically (340 nm) every 30 s for 100 min, and measurements were based on ET standards (Novo Pyrexal, Salmonella abortus equi endotoxin, Associates of Cod, Woods Hole, Mass.). All measurements were performed in duplicate. The sensitivity of the assay was 1 pg/ml.

Statistical analysis

Data are presented as the mean ± standard deviation (SD). Spearman' s correlation coefficient was calculated to correlate cytokine levels with the duration of ischemia, anhepatic phase, or various parameters of individual organ function. The Wilcoxon matched-pair test was used to compare different serum samples, and the Mann-Whitney test was used for unpaired data. Significance is indicated at $P < 0.05$.

Results

Graft survival and ischemia

Overall one-month graft survival was 84% (26/31). Three re-OLTs had to be performed within the follow-up period, of which one patient re-entered the study. Three other patients who had received a first liver transplant before initiation of the study were included in the study for their second graft. Since two patients died during the study, 1-month patient survival was 93% (28/30). One patient died from cardiac arrest 2 h postoperatively, and the other due to multiple organ failure 3 days after OLT.

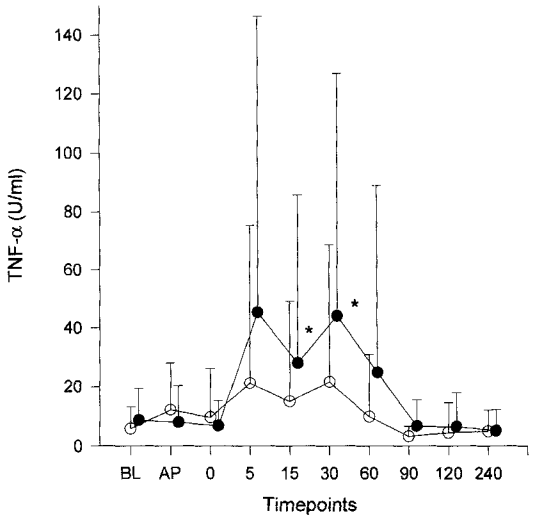

Fig. 1 Concentration of TNF-α in arterial (–○–) and hepatic vein (–●–) blood samples, obtained before laparotomy (*BL*), at the beginning of the anhepatic phase (*AP*), 10 min before reperfusion (0), and 5–240 min after reperfusion. Data are presented as the mean ± SD. Comparisons were made between arterial and hepatic vein samples, and a $*P < 0.05$ was considered significant

In spite of the use of improved preservation solutions, the duration of ischemia was kept as short as possible for better graft function. The mean total ischemia time was 535 ± 205 min (range 210–1050 min). Duration of ischemia with early graft loss did not differ from the duration of ischemia with long-term graft survival. Neither the TNF-α, nor IL-6 concentration correlated with the duration of ischemia (Table 2). In addition, no significant correlation could be detected between ET levels and either the duration of the anhepatic phase, or hepatocyte integrity, as measured by liver enzyme release and total ischemia time (Tables 2, 3).

In order to estimate the impact of organ preservation and to exclude preexisting liver damage, intraoperative biopsies were performed in grafts showing signs of injury. Biopsies from 13 transplants showed 5 grafts without pathological changes, whereas 8 were damaged by organ preservation; only 1 of the 13 grafts showed major signs of fatty change. However, there was no correlation between histological preservation damage and the duration of ischemia or cytokine concentrations (data not shown). Predictably, the levels of liver enzymes were significantly increased in the serum of patients with grafts showing histological damage, compared to those with no obvious damage (GOT day 1: 878 ± 956 vs. 94 ± 68 U/ml, GPT day 1: 591 ± 540 vs. 105 ± 83 U/ml, GLDH day 3: 308 ± 382 vs. 24 ± 27 U/ml, respectively).

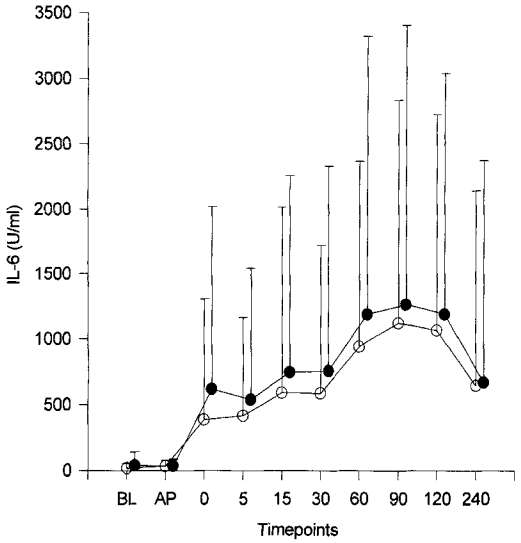

Fig. 2 Concentration of IL-6 in arterial (–○–) and hepatic vein (–●–) blood samples. Data are presented as the mean ± SD. Comparisons were made between arterial and hepatic vein samples. There was not a significant difference ($P < 0.05$) at any of the time-points tested

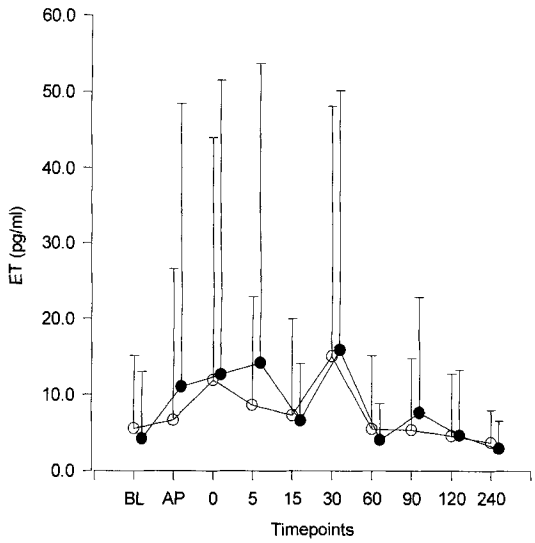

Fig. 3 Concentration of ET in arterial (–○–) and hepatic vein (–●–) blood samples. Data are presented as the mean ± SD. Comparisons were made between arterial and hepatic vein samples. There was not a significant difference ($P < 0.05$) at any of the time-points tested

Cytokine levels

To examine the local release of cytokines, the TNF-α and IL-6 levels of hepatic vein samples were compared to concentrations in the systemic circulation. Before laparotomy, TNF-α was detected at low concentrations in arterial blood and in blood from the hepatic vein (Fig. 1). Concentrations of TNF-α increased between 5 and 30 min after reperfusion of the liver, with a subsequent decrease to pre-OLT levels at 90 min. While similar concentrations of TNF-α in the systemic circulation and blood samples from the hepatic vein were measured before laparotomy, an approximately 2-fold higher level was observed in blood samples from the hepatic vein at 5, 15, and 30 min after reperfusion (Fig. 1). These data suggest that TNF-α is primarily secreted locally in the liver during OLT.

IL-6 was detected in small amounts before laparotomy and rose steadily to peak levels at 90 min after reperfusion, declining again after the operation (240 min). In contrast to TNF-α, there was no significant difference between either arterial- or hepatic vein blood IL-6 levels at any of the time points tested (Fig. 2).

Endotoxin levels

ET, a possible stimulator of cytokine synthesis, was detectable in the serum of 21 of the 31 transplantations performed (68%). ET serum concentrations increased during the anhepatic phase (0), and peak levels were observed between 5 and 30 min after reperfusion (Fig. 3). Arterial and hepatic vein blood samples showed similar concentrations of ET at all time points tested, except 5 min after reperfusion (Fig. 3). However, circulating ET levels (5–120 min) did not correlate with the concentrations of TNF-α ($r = 0.22$) or IL-6 ($r = 0.24$) at the same time points.

Cytokines, endotoxin and organ function

In order to estimate the influence of the local release of proinflammatory cytokines on hepatocyte integrity, cytokine levels were compared to liver enzyme measurements (GOT, GPT, GLDH). Using the mean values, no correlation was found between ET- , TNF-α-, or IL-6 concentrations and the levels of GOT, GPT, and GLDH (Table 3).

Since 15 patients had to remain on mechanical ventilation for more than 48 h post OLT, we compared the cytokine levels of these patients to those of patients without this complication. Results showed that IL-6 concentrations were significantly higher at all time points after reperfusion in both arterial and hepatic vein blood samples (Fig. 4). Particularly noteworthy was the rapid increase of IL-6 during the anhepatic phase. However, ET- and TNF-α concentrations, and the duration of ischemia did not differ significantly from those patients without prolonged respiratory complications. It is noteworthy that transfusion of red blood cells and fresh frozen plasma was significantly increased

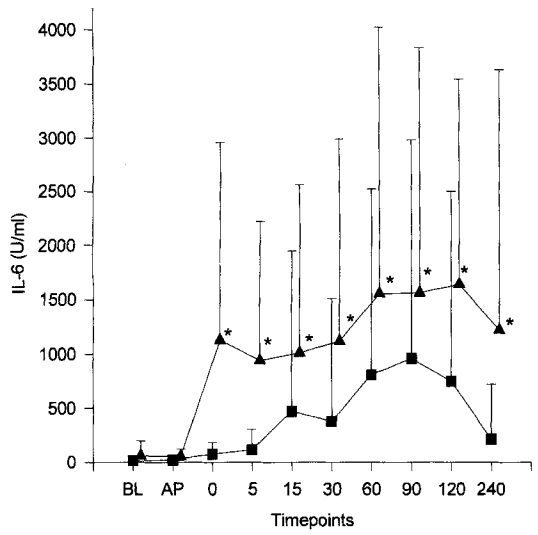

Fig. 4 IL-6 concentrations in hepatic vein samples from patients developing respiratory failure (-▲-; mechanical ventilation > 2 - days) postoperatively, compared to patients with an uneventful clinical course (-■-; mechanical ventilation ≤ 2 days). Data are presented as the mean ± SD, and a $*P < 0.05$ was considered significant

in patients developing respiratory failure after OLT, compared to patients without respiratory problems (23.1 ± 16.7 vs 9.6 ± 8.1 units; 49.2 ± 24.7 vs 22.7 ± 17.1 units, respectively).

Discussion

Hepatic ischemia and reperfusion due to liver transplantation results in detectable concentrations of ET and proinflammatory cytokines both in hepatic outflow as well as in the systemic circulation. The present study shows that in the early period of reperfusion, levels of TNF-α are significantly increased in blood samples from the hepatic vein, compared to the systemic circulation. This may indicate that the liver represents a major source of TNF-α after OLT, as has been demonstrated in animal models of liver ischemia/reperfusion injury. However, we could not show a correlation between the local release of TNF-α and stimulating factors such as the duration of ischemia or ET. Since previous studies indicate that proinflammatory cytokines in high concentrations may be partly responsible for tissue necrosis and the development of infection or trauma-related multiple organ dysfunction [1, 8], we suggest that a similar pathophysiological mechanism may be operative after OLT. In these previous studies, partial or total hepatic ischemia resulted in elevated serum concentrations of TNF-α.Furthermore, Wanner et al. [29] provide evidence that Kupffer cells are the principal source of overwhelming cytokine release after hepatic ischemia and reperfusion. Kupffer cells may trigger systemic inflammation both locally and in remote organs.

ET was detected in 68% of the patients. Because Kupffer cells have been shown to be a main source of ET clearance [20], the increase of ET during the anhepatic phase might be explained by the absence of these cells. Intraoperative manipulation of the intestine, or the partial gut ischemia resulting from taking down the porto-systemic bypass and the surgery associated with the portal-venous anastomosis, may also contribute to the increase of ET [7]. More specifically, we observed a concomitant increase in ET concentrations immediately after reperfusion, followed by a decrease of ET concentrations 15 min after reperfusion. It is possible that this rapid ET clearance is mediated by Kupffer cells of the reperfused graft. A second peak of ET, which appeared immediately after reestablishing hepatic arterial circulation, was probably due to a flush effect from insufficient perfusion of the liver acini by only the portal circulation [24]. How ET levels affect hepatocyte function remains controversial [21,25]. In this study we did not find a correlation between hepatocyte damage and ET, IL-6 or TNF-α. Although other reports show a correlation between increased TNF-α concentrations following ET administration [18, 22], our results could be explained by the fact that previous studies were either performed in animal models under standardized conditions or in healthy volunteers. In addition, there is evidence that intraoperatively administered immunosuppression can modify TNF-α and IL-6 concentrations [9, 17]. Therefore, performance of the present study in actual patients receiving a transplant introduces multiple physiological factors that could possibly have influenced TNF-α or

Table 3 Spearman's correlation coefficient comparing mean values of ET, TNF-α and IL-6 and the liver enzymes GPT, GOT, and GLDH on postoperative days 1, 3, and 5

5–120 min (arterial blood)	GPT Postoperative day			GOT Postoperative day			GLDH Postoperative day		
	1	3	5	1	3	5	1	3	5
ET	0.03	0.09	0.05	0.03	0.11	-0.08	-0.05	-0.15	-0.15
TNF-α	-0.31	-0.06	-0.06	-0.17	0.03	-0.23	0.05	-0.14	-0.14
IL-6	-0.04	-0.13	-0.16	0.19	-0.04	0.02	0.13	-0.05	0.03

IL-6 secretion. Our data suggest there is no significant correlation between ET levels and cytokine concentrations, even considering that peak cytokine concentrations can appear with delay after an ET stimulus.

IL-6 is a well known acute phase protein associated with sepsis and physical stress, including surgical procedures [26]. Although inconsistent changes in IL-6 levels have been detected with sepsis [10], increases of this cytokine appear to be predictive for infectious complications following OLT [13]. In the present study, IL-6 concentrations increased steadily during surgery, with a non-significant trend towards higher levels in hepatic venous samples, when compared to arterial samples. We regard this increase of IL-6 a result of general surgical trauma [26]. Comparisons between elective patients and those undergoing liver transplantation as an emergency procedure showed significant differences. Emergency patients presented with significantly higher IL-6 levels at the beginning, likely as a result of preexisting acute liver failure [23]. However, the higher IL-6 concentrations decreased to the same levels as those of patients without acute liver failure. In contrast to the observation by Steininger et al., according to which the liver appears to clear IL-6 from the systemic circulation [27], we actually detected higher serum concentrations in hepatic venous samples, than in arterial samples. These data suggest that cells within the liver are capable of synthesizing IL-6. However, in patients with impaired pulmonary function after OLT, the most significant increase in IL-6 concentrations was measured during the anhepatic phase. According to studies investigating respiratory failure, macrophages in the lung could be the main source for IL-6 under these circumstances.

As expected, liver enzymes were elevated after OLT, particulary in patients with grafts showing histological ischemia/reperfusion damage. Serum liver enzymes were significantly higher in these patients, compared to those of patients that received an organ not showing evidence of ischemia/reperfusion injury. We could not find a correlation between the duration of ischemia and hepatocyte damage, which might be due to relatively short preservation periods in general.

In summary, this study provides evidence for increased ET-, TNF-α-,and IL-6 release after ischemia/reperfusion in human OLT. TNF-α concentrations peaked at 5 and 30 min after reperfusion, and TNF-α levels were significantly higher in hepatic vein samples in the early reperfusion phase. IL-6 concentrations steadily increased throughout the operation in almost all patients, and increased IL-6 levels correlated with postopertive pulmonary disfunction. However, our data did not show a correlation between liver function and ET or cytokine concentrations, which is probably related to the multiple influences present with human OLT.

References

1. Ayala A, Perrin MM, Ertel W, Chaudry IH (1992) Differential effects of hemorrhage on Kupffer cells: Decreased antigen presentation despite increased inflammatory cytokine (IL-1, IL-6, and TNF) release. Cytokine 4: 66–75
2. Berger D, Marzinzig E, Marzinzig M, Beger HG (1988) Quantitative endotoxin determination in blood-chromogenic modification of the limulus amoebocyte lysate test. Eur Surg Res 20: 128–136
3. Busam KJ, Bauer TM, Bauer J, Gerok W, Decker K (1990) Interleukin-6 release by rat liver macrophages. J Hepatol 11: 367–373
4. Caldwell-Kenkel JC, Currin RT, Tanaka Y, Thurman RG, Lemasters JJ (1991) Kupffer cell activation and endothelial cell damage after storage of rat livers: effect of reperfusion. Hepatology 13: 83–95
5. Calne RY (1987) Recipient operation. In: Calne RY (ed) Liver Transplantation. 2nd edn. Grune & Stratton, London Orlando, pp 221–246
6. Colletti LM, Burtch GD, Remick DG, Kunkel SL, Strieter RM, Guice KS, Oldham KT, Campbell DA Jr (1990) The production of tumor necrosis factor alpha and the development of a pulmonary capillary injury following hepatic ischemia/reperfusion. Transplantation 49: 268–272
7. Deitch EA, Bridges W, Baker J, Ma JW, Ma L, Grisham MB, Granger DN, Specian RD, Berg R (1988) Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. Surgery 104: 191–198
8. Deitch EA (1992) Multiple organ failure: pathophysiology and potential future therapy. Ann Surg 216: 117–134
9. Dupont E, Schandene L, Denys C, Crusiaux A, Wybran J (1989) Assessment of production of tumor necrosis factor-alpha under the influence of immunosuppressive drugs. Transplant Proc 21: 70
10. Ertel W, Kremer JP, Kenney J, Steckholzer U, Jarrar D, Trentz O, Schildberg FW (1995) Downregulation of proinflammatory cytokine release in whole blood from septic patients. Blood 85: 1341–1347
11. Eskandari MK, Nguyen DT, Kunkel SL, Remick DG (1990) WEHI 164 subclone 13 assay for TNF: Sensitivity, specificity, and reliability. Immunol Invest 19: 69–79
12. Espevik T, Nissen-Meyer J (1986) A highly sensitive cell line, WEHI 164 clone 13, for measuring cytotxic factor/tumor necrosis factor from human monocytes. J Immunol Methods 95: 99–105
13. Függer R, Hamilton G, Steininger R, Mirza D, Schulz F, Mühlbacher F (1991) Intraoperative estimation of endotoxin, TNF-α, and IL-6 in orthotopic liver transplantation and their relation to rejection and postoperative infection. Transplantation 52: 302–306
14. George JF, Kirklin JK, Naftel DC, Bourge RC, White-Williams C, McGiffin DC, Savunen T, Everson MP (1997) Serial measurements of interleukin-6, interleukin-8, tumor necrosis factor-alpha, and soluble vascular cell adhesion molecule-1 in the peripheral blood plasma of human cardiac allograft recipients. J Heart Lung Transplant 16: 1046–1053

15. Grant SC, Lamb WR, Brooks NH, Brenchley PE (1996) Serum cytokines in human heart transplant recipients. Is there a relationship to rejection? Transplantation 62: 480–491
16. Imagawa DK, Millis JM, Olthoff KM, Derus LJ, Chia D, Sugich LR, Ozawa M, Dempsey RA, Iwaki Y, Levy PJ, Terasaki PI, Busuttil RW (1990) The role of tumor necrosis factor in allograft rejection. Transplantation 50: 219–225
17. Liao J, Keiser JA, Scales WE, Kunkel SL, Kluger MJ (1995) Role of corticosterone in TNF and IL-6 production in isolated perfused rat liver. Am J Physiol 268: R699–706
18. Luster MI, Germolec DR, Yoshida T, Kayama F, Thompson M (1994) Endotoxin-induced cytokine gene expression and excretion in the liver. Hepatology 19: 480–488
19. Matuschak GM, Rinaldo JE, Pinsky MR, Gavaler JS, Van Thiel DH (1987) Effect of end stage liver failure on the incidence and resolution of the adult respiratory distress syndrome. J Crit Care 2: 162–173
20. Maitra SK, Rachmilewitz D, Eberle D, Kaplowitz N (1981) The hepatocellular uptake and biliary excretion of endotoxin in the rat. Hepatology 1: 401–407
21. Mazuski JE, Platt JL, West MA, Simmons RL, Towle HC, Cerra FB (1988) Direct effects of endotoxin on hepatocytes: Synthesis of a specific secretory protein. Arch Surg 123: 340–344
22. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Ceramy A, Wolff SM, Wilmore DW (1988) Detection of circulating tumor necrosis factor after endotoxin administration. N Engl J Med 318: 1481–1486
23. Missale G, Ferrari C, Fiaccadori F (1995) Cytokine mediators in acute inflammation and chronic course of viral hepatitis. Ann Ital Med Int 10: 14–18
24. Post S, Palma P, Gonzalez AP, Rentsch M, Menger MD (1994) Timing of arterialization in liver transplantation. Ann Surg 220: 691–698
25. Saad B, Frei K, Scholl FA, Fontana A, Maier P (1995) Hepatocyte-derived interleukin-6 and tumor-necrosis factor alpha mediate the lipopolysaccharide-induced acute-phase response and nitric oxide release by cultured rat hepatocytes. Eur J Biochem 229: 349–355
26. Shenkin A, Fraser WD, Series J, Winstanley FP, McCartney AC, Burns HJ, van Damme J (1989) The serum interleukin 6 response to elective surgery. Lymphokine Res 8: 123–127
27. Steininger R, Roth E, Függer R, Winkler S, Längle F, Grünberger T, Götzinger P, Sautner T, Mühlbacher F (1994) Transhepatic metabolism of TNF-α, IL-6, and endotoxin in the early hepatic reperfusion period after human liver transplantation. Transplantation 58: 179–182
28. Van Snick J, Cayphas S, Vink A, Uyttenhove C, Coulie PG, Rubira MR, Simpson RJ (1989) Purification and NH2-terminal amino acid sequence of a T-cell-derived lymphokine with growth factor activity for B-cell hybridomas. Proc Natl Acad Sci USA 83: 9679–9683
29. Wanner GA, Ertel W, Müller P, Höfer Y, Leiderer R, Menger MD, Messmer K (1996) Liver ischemia and reperfusion induces a systemic inflammatory response through Kupffer cell activation. Shock 5: 34–40