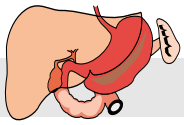

Anesthesia for Liver Transplantation

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Key words: liver transplant, anesthesia, blood loss

IMAJ 2002;4:55-62

Orthotopic liver transplantation is the most common liver transplant procedure and is performed by transplanting the donor liver to the same site after hepatectomy [1–10]. In heterotopic (auxiliary) liver transplantation, the donor liver is placed in the paravertebral gutter or pelvis without removal of the diseased liver [10]. The latter technique is frequently complicated by atrophy of the grafted liver (due to low portal and hepatic arterial blood flow), and is therefore only recommended for high risk surgical patients or those with reversible liver disease.

Pre-anesthetic evaluation

How does the pre-operative evaluation differ for an OLT patient and a routine patient?

Pre-operative evaluation is performed in two stages. In the early first stage all OLT candidates are examined by anesthesiologists; the later, second-stage evaluation is performed immediately before surgery.

How is the preparation phase organized?

Use of resources is the prime consideration during preparation for OLT. One should plan for an operating room time of 8 to 20 hours [1], with an average total time of 8.5 hours for anesthesia, 7 of which are devoted to surgery [Table 1].

The minimum anesthesia staff should be a 3:2 ratio of physicians to certified registered nurse anesthetists or technicians to deal with simultaneous administration of anesthesia and operation of the rapid-infusion system device and the thromboelastograph [2–6]. A courier, responsible solely for the transport of specimens and blood products, is indispensable.

What should be accomplished during the second-stage evaluation?

A brief second examination is performed immediately before surgery when a donor organ has been identified. Assessing any neurologic deterioration since the initial first-stage evaluation is necessary, and signs of progressive metabolic acidosis, infection or sepsis should be sought. Cardiovascular instability, pulmonary infection and severe coagulopathy should be corrected and treated.

The internist should ensure that the patient is in the best condition for surgery. Ideally, ascites should be controlled and nutrition improved, with prothrombin time showing a return toward normal. Coagulation status should be determined, and parenteral vitamin K should be given at least 3 days pre-operatively if possible, although it is not always possible to anticipate and schedule the operation (i.e., using cadaveric transplants). Vitamin K administration corrects coagulation defects within 24–36 hours, unless liver function is so poor that vitamin K-dependent proteins such as Factor V and prothrombin cannot be synthesized. Albumin, fresh-frozen plasma, and cryoprecipitate can be given immediately before surgery; platelets can be infused (if the count is < 50,000/mm^3) immediately after induction even before cannulation. Urine output and creatinine levels should be determined. If the recipient is cytomegalovirus immunoglobulin G negative, the status of the donor liver should be determined; if negative, the

Table 1. Mean operating room times during various periods of orthotopic liver transplantation at the Mayo Clinic

	Total time (min)		
Group	**Anesthesia**	**Surgical**	**Anhepatic**
First 100 procedures	510.1 ± 98.4	413.2 ± 87.5	130.4 ± 39.9
By diagnosis			
CAH (n = 24)	541.0 ± 76.4	433.0 ± 76.5	145.1 ± 76.5
PSC (n = 22)	558.9 ± 75.7	459.2 ± 7	125.0 ± 75.7*
PBC (n = 20)	444.0 ± 73.0**	7357.1 ± 73.0**	114.0 ± 73.0*
Retransplant (n = 17)	471.8 ± 90.3	378.3 ± 77.4	134.3 ± 48.1

* Significantly lower than for CAH ($P < 0.05$).

** Significantly lower than for CAH and PSC ($P < 0.05$).

CAH = chronic active hepatitis, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangiitis.

(From Rettke SR, Chantigian RC, Janossy TA, et al. Anesthesia approach to hepatic transplantation. *Mayo Clin Proc* 1989;64:224. By permission.)

OLT = orthotopic liver transplant

patient will need CMV-negative blood and prophylactic treatment.

Premedication

Since coagulation may be abnormal pre-operatively, intramuscular premedication is not advised. Hepatic encephalopathy is another contraindication [7,8]. If coagulation and level of consciousness are normal, standard medications are not contraindicated. The dose is usually adjusted downward because of reduced hepatic function, including drug elimination. Premedication is frequently reduced or even omitted. Preoperative counseling often suffices for the patient's preparation and allows family interaction with an alert individual before surgery. However, if a patient so desires, short-acting benzodiazepines are often appropriate.

What equipment is needed by anesthesia personnel?

Equipment used by anesthesia personnel can be divided into three categories:

- For *the "regular" major abdominal surgery "part of the case"*:

anesthesia gas machine, ventilator, positive end-expiratory pressure valves, humidifier, multiple-channel vital sign monitor, urinary catheter, automated record keeper (desirable, not routine), pulse oximeter, esophageal stethoscope, respiratory gas analyzer, nasogastric tube, warming blanket, medication infusion sets, supply cart, and telephone.

- For *the major vascular surgery "part of the case" with the potential for significant blood or contractility loss*:

invasive blood pressure monitoring capabilities (radial and femoral, because of frequent blood sampling from a non-heparinized line in a vasoconstricted, cold patient), cardiac output monitor, on-line mixed venous oximetry, cardiac defibrillator, blood pump and blood warmer, non-autologous infusion system, and autotransfusion system. The latter device may be advantageous even with an RIS [2], although most centers eliminate the autotransfusion system, if the RIS is present. For the last 5 years we have routinely used the surface probe of the transesophageal echocardiogram or portable echo device to identify and facilitate central (internal jugular vein) venipuncture and avoid inadvertent carotid puncture. We use it for pediatric patients and patients with poor clotting.

- For OLT "*part*":

two invasive arterial pressure monitors, the RIS, TEG, and venovenous bypass device. [See also Table 2 for adult setup for OLT]

How much bleeding is expected in OLT?

This is highly variable, ranging in different series from 1 to more than 100 units of red blood cells and fresh frozen plasma [1,4,11–16]. Estimated blood loss ranges from 10 to 1,000 ml/kg (average > 100 ml/kg) [17]. The clinical significance of coagulopathy is confirmed by the correlation between its preoperative severity and intraoperative blood product requirements. Patients with hepatocellular disease and poor preoperative coagulation profile require more blood products [4].

What is the relationship between intraoperative bleeding and the type of liver disease?

Statistically significant differences for RBC replacement according to the diagnostic group have been reported. Patients with chronic active hepatitis tend to require more blood and blood products than do patients with perisclerosing cholangitis [4], although the latter tend to require more blood than those with primary biliary cirrhosis. Patients in the last two categories are usually diagnosed earlier, treated earlier, and suffer less parenchymal damage with less severe subsequent clotting abnormalities.

When patients were classified into risk categories for likelihood of bleeding (according to age, weight, diagnosis, coagulation status, previous operation), there was a significant difference between high risk and low risk cases in adults [4]. The median requirement for RBCs and FFP in those classified as high risk cases was almost twice the amount needed in low risk cases, although the average use was similar. This observation probably reflects that a few low risk patients had substantial bleeding that necessitated a large number of blood units.

A more specific isolation of the relationship between blood and blood components consumed intraoperatively and the extent of liver disease was found with elevated PT (> 15.0 seconds) and presence of ascites. Pediatric patients have a tendency toward a lower estimated blood loss, but mean loss in milliliters per kilogram is similar [1].

What are the recommendations for blood and blood product availability?

- ***Adults*** – Preliminary reports of the 1981–83 experience from the largest OLT center in the United States cited median and maximum intraoperative RBC use in adult patients of 28.5 and 251 units respectively [3]. When the blood bank initiates an OLT program, it should plan for the extreme possibility of blood loss, even though later reports [2,4], with and without autotransfusion (autologous) systems, claim lower median and maximum consumption of blood and blood products from 1985 to 1989 [5,6].

Based on these data, we set aside blood products in two locations: the operating room (20 units of packed RBCs, 20 units FFP, 20 units cryoprecipitate) and the blood bank (200 units packed RBCs) [1].

- ***Children*** – For pediatric patients, we prepare half of the adult blood requirement in the operating room (10 units of each) and a quarter (50 units) in the blood bank.

CMV = cytomegalovirus
RIS = rapid-infusion system
TEG = thromboelastrograph

RBC = red blood cells
FFP = fresh frozen plasma
PT = prothrombin time

Table 2. Adult set-up for orthotopic liver transplantation

Medications

Thiopental: 3 x 20 ml (25 mg/ml)
Succinylcholine: 2 x 10 ml (20 mg/ml)
Pancuronium: 20 ml (1 mg/ml)
Fentanyl: 20 ml or more (50 µg/ml)
Lidocaine: 5 ml (20 mg/ml)
Ephedrine: 10 ml (5 mg/ml)
Atropine: 3 ml (0.4 mg/ml)
Dopamine: 6 mg x kg wt, in 1,000 ml NS (10 ml/hr = 1 µg/kg/min
(Use to improve renal perfusion. Note: The larger volume allows more accurate administration in adults.)
Phenylephrine: 10 mg/250 ml (mix if patient unstable)
Cephazolin*: 1 g (q 4 hr)
Clindamycin*: 900 mg
Gentamicin*: 2.5 mg/kg/dose q 8 hr
Methylprednisolone: 1 g x 2 (1 g when anhepatic, 2 mg/kg before leaving operating room)
Immuran: 2 mg/kg when anhepatic, 2 mg/kg before leaving operating room
Calcium chloride (injection): 10 ml x 20 vials
Sodium bicarbonate: 50 ml amps x 15
Epinephrine: 3 or more of 1/10,000 injection (10 ml)
Insulin (regular or Humulin U-100): 10 ml
50% Dextrose: 50 ml (used if required to lower potassium: 5 g glucose/unit insulin)

Equipment

Peep valves (5–20 cm)
Blood infusion equipment
Rapid infusion device (~40 kg or more)
Warming blanket and Bair Hugger for both lower and upper body (2 heating plants required)
Circuit humidifier/heater: Mandatory! (Note: Must be able to reach 45°C, not 41°C)
Oximetrix computer*
TEG: Stored in an operating room dedicated for OLT. Do not set up unless you are trained
Reflective wraps (for heat and extremities), if available
Blood collection tubes
2 Alton-Dean high pressure blood warmers

Monitors

ECG
Invasive pressures:
Arterial (radial, contralateral to VVB)
Femoral or second radial (When setting up for 2 radials: arm board, arrow guidewire kit)
CVP
Pulmonary artery (If needed)
Note: Do not use heparinized saline as flush, use NS
Be very careful that your lines are properly marked
Place BP cuff on right arm (opposite VVB side)
Esophageal stethoscope; nasogastric tube
Temperature (esophageal and intravascular)
Pulse oximeter
Capnograph/gas monitor
Twitch monitoring
PA catheter (with oximeter*)
TEG*
TEE with 2D probe, sterile gel, and 2 sets of 8.5 size gloves

* Optional

Catheter trays

Prepare for the following lines:

a. VVB Return Line (venous line for return to the patient from the centrifugal pump): Use a 8.5 F (6.5 cm long) or 10F (10 cm long) basilic catheter. If no antecubital line is possible, and the subclavian route is chosen, use the 10 cm length "femoral" catheter rather than the shorter basilic. Note: These catheters do not have diaphragms; you must connect a catheter to them. If a 9 F PA catheter introducer sidearm sheath is used, the port may leak at the pressures encountered by the VVB; if you use the PA catheter, be certain to use the diaphragm cap. This line must be extremely reliable, as the flow will be > 1 L/min and typical pressures are > 200 mmHg.
b. Right IJV line available for a PA catheter 9 Fr introducer. If a PA catheter is inserted, this line will not perform well as a volume infusion line. (Even with the 7 Fr PA catheter at 400 ml/min, the pressure will rise well above the RIS limit of 300 mmHg).
c. Additional volume line: Possibilities include a basilic on the opposite side as that for (a); a second PA catheter introducer in the RIJV or subclavian. In some patients, (b) and (c) may be replaced by a double lumen, 12 Fr catheter if there is no expected need for a PA catheter. The double lumen, 12 Fr size cannot be used for VVB. One of its lumens alone is inadequate for the RIS. By comparison, one 9 Fr PA catheter introducer can easily handle the 400 ml/min bolus flow of the RIS.
d. 2nd arterial line: Usually a 4 Fr, 15 cm, single lumen polyurethane femoral line, opposite side from the VVB. In very thin patients, the 8 cm, 3 Fr size may work. This requires a separate table/work area than that for the central lines in the neck.

PA = pulmonary artery, VVB = venovenous bypass, NS = normal saline, RIS = rapid infusion system, TEG = thromboelastograph, TEE = trans-esophageal echocardiogram, CVP = central venous pressure, BP = blood pressure, IJV = internal jugular vein

Anesthetic induction

What drugs should be used?

Rapid-sequence induction is performed because many of these patients have ascites and, perhaps, the equivalent of a full stomach. Delayed gastric emptying often exists in patients taking cyclosporine orally. Thiopental 4 mg/kg, ketamine 1–2 mg/kg, or etomidate 0.3–0.5 mg/kg, is used. Succinylcholine 1–2 mg/kg is added to facilitate tracheal intubation while cricoid pressure is maintained. The induction agents are protein bound, and the free drug fraction is increased in liver disease when serum albumin is low, leading to an enhanced effect. Thiopental and etomidate are metabolized in the liver but their activity is terminated by redistribution. Hence, their duration of action is normal unless the doses are large or repeated.

Anesthetic management

Narcotics

Anesthetic maintenance is largely similar to that in other major abdominal surgery. A narcotic can be successfully used in patients with hepatic disease despite the pharmacologic consequences of decreased clearance and prolonged half-life [Table 3]. Fentanyl, sufentanil and alfentanil are suitable opioid analgesic agents because they have short half-lives and inactive metabolites. Interestingly, fentanyl does not decrease hepatic oxygen and blood supply or prevent increases in demand when used in moderate doses (50 µg/kg bolus and 0.5 µg/kg/min infusions) [9]. Studies comparing fentanyl and morphine pharmacokinetics in adult patients with normal or abnormal liver function have not shown a

Table 3. Anesthetic drugs in liver disease

Class of drug	Drug	Effect of decreased serum albumin	Effect of decreased hepatic metabolism	Other effects
Induction agents	Thiopental	Increased free drug	Increased elimination half-life	
	Ketamine		Prolonged action, decreased clearance	Phase 1 metabolism affected
	Etomidate	Increased free drug	Increased elimination half-life	
Opioid analgesic agents	Meperidine Phenoperidine Fentanyl		Prolonged effect	Decreased first-pass metabolism
	Sufentanil	Increased free drug	Prolonged effect	Decreased first-pass metabolism
	Morphine			Narcotic effect terminated by redistribution and extrahepatic glucuronidation
Benzodiazepines	Diazepam Chlordiazepoxide Midazolam	Increased free drug	Prolonged action, decreased clearance	Phase 1 metabolism affected
	Oxazepam Lorazepam		Normal clearance and duration of action	Phase 2 metabolism spared
Beta-adrenergic blocking agents	Propranolol	Increased free drug	Increased oral bioavailability, decreased clearance	Decreased first-pass metabolism, reduced dose for treatment of portal hypertension
Local anesthetic agents	Lidocaine		Decreased clearance, increased elimination half-life	
Neuromuscular blocking agents	Succinylcholine			Decreased plasma cholinesterase, slightly prolonged apnea
Nondepolarizing muscle relaxants	Pancuronium	Bound to hemoglobin	Prolonged elimination half-life	Significantly metabolized. Altered pharmacokinetics in patients with hepatic or biliary disease
	d-Tubocurarine	No effect	Prolonged elimination half-life	Significantly metabolized
	Vecuronium	No effect	Prolonged effect in large doses	Significantly metabolized. Altered pharmacokinetics in patients with hepatic or biliary disease. Metabolized to 3-acetyl derivative
	Rocuronium	Possibly bigger dose needed due to increased volume of distribution	Prolonged effect, due to reduced clearance (less than vecuronium and pancuronium)	Minimal active metabolite formation
	Atracurium	No effect	Action unaffected by hepatic and renal disease	Significantly metabolized. Elimination by Hoffman degradation and ester hydrolysis

(Modified from McEvedy BA, Shelley MP, Park GR. Anesthesia and liver disease. *Br J Hosp Med* 1986;36:26.)

different effect on disposition and elimination in adults, or of alfentanil in children [9].

Inhalation agents

Halothane is avoided in favor of isoflurane for OLT. Halothane, enflurane and isoflurane all reduce liver blood flow, but halothane reduces hepatic arterial flow to a greater extent [9]. The use of halothane is not advised because of its potenial to cause hepatic damage. Nitrous oxide has been used for many years without increased anesthesia-related postoperative hepatic complications. However, it is often considered counterproductive because of its sympathomimetic effect and accumulation in the intestinal lumen, with the potential for subsequent distension in protracted cases. Another reason to avoid nitrous oxide is that potenial air emboli created during the vascular anastomosis may increase.

Surgical stages in OTL [10]

What is the pre-anhepatic phase?

The first stage in OLT is the pre-anhepatic phase, which lasts from skin incision to the point at which the native liver is freed to its vascular pedicle. The skin incision is wide, bilateral and subcostal, with cephalic extension to the xiphoid. The xiphoid process is removed without entering the thorax.

What is the anhepatic phase?

The second stage, the anhepatic phase, begins with clamping of the suprahepatic and infrahepatic inferior vena cava, portal vein and hepatic artery, after which the diseased liver is removed. This stage includes the hepatectomy and ends when vascular anastomosis of the IVC and portal vein is complete; the infrahepatic IVC anastomosis is prepared but not completed until late in this stage.

What Is the neohepatic phase?

In the third stage, the neohepatic or postanhepatic phase, the donor liver is incorporated into the recipient's circulatory system by releasing, in sequence, clamps from the portal vein, the infrahepatic IVC, and the suprahepatic IVC. The portal artery anastomosis is then performed, and after adequate hemostasis the bile duct is reconstructed. If a patient has a normal

extrahepatic bile duct system a duct-to-duct anastomosis is performed, whereas an abnormal system (biliary atresia, biliary cirrhosis, perisclerosing cholangitis) necessitates a Roux-en-Y choledochojejunostomy. Finally, an intraoperative cholangiogram is obtained to assess patency of the biliary system and biliary drainage.

What does the anesthetist need to know about venovenous bypass?

• ***Indications*** – During the anhepatic phase, cross-clamping of the IVC and portal vein for hepatectomy reduces venous return to the heart and cardiac output by about 50%, creating congestion of the IVC and portal system. VVB is suggested for venous decompression, improved hemodynamic stability, and decreased intraoperative blood loss [11,12]. In addition, VVB has been reported to improve renal function, eliminate gastrointestinal hemorrhage, decrease operative mortality from 10% to 1%, and provide additional time for completion of the vascular anastomoses.

• ***Technique*** – The extracorporeal bypass circuit was accomplished traditionally through cannulas surgically placed into the femoral and portal veins for blood drainage, and into the axillary vein for blood return. Blood is pumped from the portal and femoral veins by a centripetal pump without heparin, although the tubing may be heparin bonded. A small dose of heparin, 1,000-2,000 units, may be added to the bypass cannula. The VVB flow rate is up to 40% of cardiac output; hemodynamic changes usually do not occur if adequate flow is maintained.

• ***Routine use*** – Routine use of VVB during the anhepatic phase is somewhat controversial [12]. It is not recommended in younger patients or those in reasonably good physiologic condition who are able to respond to the sudden loss of venous return with vasoconstriction and tachycardia. Vigorous volume infusion often results in some improvement, yet a penalty of fluid overload is paid when the liver is revascularized and venous return is restored. Some transplant centers use VVB routinely, while in others various bypass techniques are employed only for specific diagnoses or when suprahepatic IVC occlusion is not tolerated [12]. There are few centers that do not use it at all. Some centers use standard bypass in only 17% of cases and a variation of the technique (piggyback) in 68% of cases [13]. Perhaps the more consistent approach for VVB use in OLT in the last decade was its routine use only in patients with proven cardiovascular disease. Otherwise, in pediatric patients, young adults and those with non-proven cardiac involvement, a trial of vena cava occlusion (supra and infra-hepatic) with fluid and cathecholamine administration may be indicated [1,14].

What physiologic changes should be expected during the pre-anhepatic phase?

Intraoperative changes in physiologic variables are listed in Table 4.

• ***Cardiovascular/Hemodynamic*** – At the beginning of surgery, high filling pressure persists due to fluid overload, ascites, pleural effusion, pulmonary hypertension and a hyperdynamic cardiovascular state. Only if volume loss secondary to surgical bleeding, and continuous formation of ascites is not replaced adequately, filling pressures will be low. Surgical manipulation of major vessels reduces venous return, and prolonged hypotension may require adjustments of surgical technique. At the end of the pre-anhepatic phase, caudad traction on the liver to isolate the suprahepatic IVC may cause transient dysrrhythmias and hypotension. Marginal cardiac performance necessitates a vasopressor (e.g., dopamine 2–5 μg/kg/min as a starting dose). End-stage liver disease may increase catecholamine resistance, necessitating a higher dose.

Alpha-agonists are of questionable value since they increase peripheral and coronary resistance. At the same time, they may decrease shunt fraction and improve tissue perfusion. Continuous monitoring of mixed venous oxygen saturation (SvO_2) helps to assess preload and cardiac output, assuming oxygen-carrying capacity, oxygen consumption and myocardial contractility remain constant. Because of arteriovenous shunting, SvO_2 and cardiac output are expected to be falsely high; thus SvO_2 serves more as a trend monitor. A more reliable sign of inadequate tissue perfusion is metabolic acidosis.

• ***Coagulation*** – During the pre-anhepatic phase, a dilutional coagulopathy is superimposed on the underlying disease-induced coagulopathy. FFP (given via the RIS) corrects low coagulation factors, and platelet transfusion (not through the RIS) increases platelet count (40,000–50,000 per 10 unit transfusion). Cryoprecipitate, which contains fibrinogen, Factor VIII and Factor XIII, is rarely necessary during this period. Attempts should be made to correct coagulation problems during this stage.

• ***Temperature*** – Body temperature gradually decreases from the effects of anesthetics, muscle relaxants, cold environment and insufficient energy production by the liver. Warming the patient by using room-temperature forced air heaters (lower and upper body), and warming all fluids, may be crucial to keep the patient's temperature normal.

• ***Hypoglycemia*** – Hypoglycemia due to loss of liver gluconeogenic capacity may be a concern but has not been observed frequently. Transfusion of blood can maintain blood glucose at a normal level because each unit of whole blood contains 0.5 g of glucose before processing. When blood replacement is minimum, small intravenous doses of glucose avoid hypoglycemia.

• ***Hypocalcemia*** – Transient citrate-induced hypocalcemia from the banked blood may follow rapid transfusion. A 500 ml unit of whole blood contains 1.7 g of hydrated trisodium citrate. The amount of citrate in a unit of packed RBCs is variable. The volume and rate of transfusion correlate with a decrease of ionized calcium, but total calcium levels do not correlate with serum ionized calcium.

What physiologic changes should be expected during the anhepatic phase?

• ***Cardiovascular/Hemodynamic*** – Cross-clamping of the IVC, which heralds the start of the anhepatic phase, causes

Table 4. Characteristic intraoperative changes in physiologic variables

Neohepatic stage				
	Pre-anhepatic stage	Anhepatic stage	Early	Late
Cardiac output	High	Low	High	High
Heart rate	High	High	Low	High
Mean arterial pressure	Normal	Low	Very low	Normal
Filling pressure	Normal	Low	High	Normal
Vascular resistance	Low	High	Very low	Low
PaO_2	Normal	Normal	Normal	Normal
PCO_2	Normal	Low	Normal	Normal
Base deficit	Normal	High	Very high	Normal
Serum Na+	Low	Normal	Normal	Normal
Serum K+	Low	Normal	Very high	Low
Serum Ca2+	Normal	Very low	Low	Normal
Serum citrate	Normal	High	High	Low

(From Kang YG, Freeman JA, Aggarwal S, et al. Hemodynamic instability during liver transplantation. *Transplant Proc* 1989;21:3489–492. © 1989. Reprinted by permission of Appleton & Lange, Inc.)

significant hypotension due to reduced venous return. The loss of portal blood flow has little effect on total venous return, especially in patients with significant collateral flow. Reduced right and left-sided filling pressures, systemic and pulmonary pressures, as well as cardiac and increased heart rate, systemic and pulmonary resistance are all related to reduced venous return [Table 4]. There are less acute changes in systemic vascular resistance and afterload associated with this type of venous inflow (anhepatic) occlusion compared with major arterial occlusion (i.e., aortic occlusion) where reduced cardiac output is partly related to extreme afterload and hypertension.

• ***Coagulation*** – At the onset of VVB, heparin effect may be detected by the TEG because a small dose of heparin may be added in the bypass cannula. This effect lasts for only 30–60 minutes. Dilutional coagulopathy may continue, although surgical bleeding is less severe owing to bypass decompression. Marked fibrinolysis related to progressively increased levels of plasminogen activators, which do not undergo hepatic clearance, can occur during the anhepatic phase. Administration of platelets and ε-aminocaproic acid during this stage should be reserved for severe cases of bleeding due to thrombocytopenia or fibrinolysis in order to avoid thromboembolism in the unheparinized VVB system [12,15–19].

• ***Acid base*** – Progressive metabolic acidosis and increased lactate levels during the anhepatic phase result from rapid transfusion of blood with acid metabolites, deficient hepatic clearance of acidic substances, and stagnation of blood flow below the diaphragm. Reduced perfusion leads to anaerobic metabolism. The acidosis becomes persistent in patients with unstable cardiovascular function, leading to compromise of tissue perfusion.

Metabolic acidosis is treated with sodium bicarbonate in order to maintain a base excess no lower than -5 mEq/L, particularly at the end of the anhepatic phase and start of the neohepatic phase. Although this treatment may promote hypernatremia, hyperosmolarity and postoperative alkalemia, these conditions are considered benign compared with the hemodynamic deterioration induced by severe metabolic acidosis. Keep in mind, however, that severe myocardial depression and long-standing lactic acidosis are thought by many investigators to be worsened by the administration of bicarbonate.

What physiologic changes should be expected in the neohepatic phase?

• ***Cardiovascular/Hemodynamic*** – Before reperfusion of the new liver, preservative solution, air and metabolites must be removed by flushing, or severe hyperkalemia may result. To insure that a large amount of the preservative solution (0.5-1 L in an adult) has been flushed through the liver, the surgeon may intentionally "lose" 0.5 to 1 L of blood through the anastomosis. If a "split-liver" is being transplanted, one should be aware of potentially large blood loss that can occur on the cut surface. Abrupt hemodynamic changes occur on reperfusion of a grafted liver. Subsequent unclamping of the portal vein and infrahepatic IVC decreases preload into the VVB. This decrease is followed by restoration of venous return on unclamping of the suprahepatic IVC. At this point (within a few minutes), the picture of postperfusion syndrome (similar to post-acute arterial occlusion) appears. It consists of progressive bradycardia, hypotension, high filling pressures, and decreased systemic vascular resistance. The potential for severe arrythmia, induced by hyperkalemia (see above), and even cardiac arrest should be anticipated and treated with glucose-insulin and bicarbonate, with a defibrillator ready to be used.

• ***Cardiac output*** – During the early reperfusion period, thermodilution measurements of cardiac output are unreliable (falsely low) owing to rapid influx of cold preservation solution. In contrast, dye dilution technique cardiac output studies show a real increase in comparison with the anhepatic phase, although output values remain lower than baseline levels. In 30% of the cases in which extreme postperfusion hypotension (< 70% of baseline) occurs, it is likely related to vasoactive substances released from the grafted liver. It does not correlate with the degree of hypokalemia, and symptoms persist even after core temperature returns to > 34°C. The syndrome is treated with epinephrine (5–10 μg boluses) to restore heart rate and contractility.

Calcium chloride and bicarbonate are administered to treat hyperkalemia and acidosis. Calcium used prophylactically maintains cardiac output but does not prevent bradycardia and hypotension. Aggressive treatment of hyperkalemia is usually unnecessary because it disappears within minutes.

The acute reperfusion hemodynamic insult lasts 5–30 minutes, however filling pressures stay high for longer (30–120 min) while systemic vascular resistance remains low.

• ***Coagulation*** – Reperfusion of the new liver often induces a severe coagulopathy for several reasons: a) dilution by the preservative solution, b) release of heparin or heparin-like

substances from donor liver cells, c) fibrinolysis due to release of plasminogen activator from the donor liver, and d) inhibition of coagulation by unknown substances other than those mentioned [15].

The fibrinolysis is probably primary, although it can be secondary to disseminated intravascular coagulation because it is associated with high levels of fibrinogen, Factors V and VIII, and plasminogen activator and not Factor consumption. Indeed, about 30% of patients before surgery have high levels of fibrin degradation products, which suggest the presence of DIC [16].

Due to the "explosive" nature of fibrinolysis in early stage 3, occurring within 5 minutes after reperfusion of the graft liver, sudden quantitative changes in coagulation factors and fibrinolytic proteins is an unlikely cause. Qualitative changes probably account for the acute development of primary fibrinolysis. They may result from changes in cellular membrane permeability (even though the graft is preserved hypothermically in a solution with simulated intracellular composition).

• ***Specialized equipment*** – Throughout this section, references are repeatedly made to the RIS and TEG. A more detailed discussion of their function and use follows.

How does the rapid-infusion system work?

The RIS is designed to deliver low pressure, prewarmed, filtered, premixed and air-free blood at a controlled and rapid rate. It offers a faster alternative to all conventional fluid and blood replacement techniques and is capable of fluid infusion in a controlled manner at a rate up to 1,500 ml/min.

Avoidance of high pressure (> 300 mmHg), low temperature (< 35°C), and infusion of aggregates or air during rapid fluid delivery is ensured through the use of infusate temperature monitoring, ultrasonic air detectors, and pressure sensors in the fluid line. The infusate is warmed by an in-line heat exchanger and filtered through high capacity macro and microaggregate filters.

How does the thromboelastograph work?

Because of the possibility of severe coagulopathy, aggressive monitoring and proper treatment are essential. A simple coagulation profile (PT, PTT), platelet count, FDP, euglobulin lysis time, and fibrinogen level can be used but have drawbacks. As an alternative, the TEG has proved extremely valuable for relatively fast interpretation and understanding of the dynamic and complex coagulopathy pattern inherent in this procedure, thus guiding effective clinical therapy. Clinically useful information is available *within* 30 minutes [12].

Guidelines for coagulation therapy according to TEG monitoring

• ***Clot formation*** – The most important consideration in TEG analysis is the fact that all aspects (clotting time, strength, stability and kinetics) and overall pattern of the TEG profile provide a more comprehensive clinical assessment of a patient's hemostasis than does any one variable of the TEG or coagulation test profile. A patient can have abnormal onset and growth kinetics but still form a normal, stable clot. Thus, although bleeding time can be prolonged, it may not represent a significant clinical problem. On the other hand, a short onset with rapid growth, good strength and rapid lysis may predict or represent a dangerous clinical condition of consumption coagulopathy. The clinical picture and evolution/resolution of the coagulation status also have to be considered before treating coagulopathy according to TEG monitoring. This goal is accomplished hourly during massive transfusion or early in the neohepatic phase.

• ***Fibrinolysis*** – Although fibrinolysis increases progressively during OLT in > 80% of patients, it is severe on reperfusion in only 34% [18]. A high incidence of hypercoagulable states and pulmonary emboli in OLT patients, both with and without EACA treatment, has led to the suggestion that because fibrinolysis during OLT is a self-limiting process, pharmacological intervention is not necessary and might be harmful [19].

What are the recent innovations in liver transplantation?

• ***Split cadaveric-donor graft*** – OLT in small children has been limited by the shortage of suitable cadaveric donor organs. The number of new transplant candidates under 5 years of age has increased by 5% annually since 1988, while the annual number of CD transplants performed in this age group has fallen [6,20]. The split is done between the adult recipient, (using the extended right lobe), and the pediatric recipient (using the left lobe) of the CD graft. Split CD graft was the obvious technical solution to this problem of pediatric graft availability. However, in high urgency patients where emergency OLT was needed, and the technique of emergency living donor liver transplant could not be applied or was not yet developed (i.e., prior to 1999) [21], split CD transplantation of two grafts was the only solution.

• ***Living donor or living related liver transplantation*** – Initial reports about LDLT in the early twentieth century established the technical feasibility of the procedure [22,23]. The donor hepatectomy can include left lobes, left lateral segments [24], or extended right lobe. LDLT has some advantages for the pediatric recipient and the transplant population as a whole. These include increased graft availability and survival, and decreased morbidity, mortality, rejections, and cost. Potential donor evaluation should include bedside ABO blood type compatibility with the recipient (the only need in a cadaveric donor). Also necessary is the exclusion of acute, chronic or viral illness, and liver/biliary system function and anatomy assessment, as well as psychological assessment. Although the procedure is relatively safe for the donor, over 10% of donors have presurgical complications [25]. Surgical experience and technical modifications have resulted in significant reduction of these complications. The mortality risk of hepatic resection in

DIC = disseminated intravascular coagulation
FDP = fibrin degradation products

CD = cadaveric donor
LDLT = living donor liver transplant

non-cirrhotic individuals is extremely low when the operation is performed in an experienced center [25]. Emergency transplantation from living donors can increase OLT applicability from 10 to 37% with high (85%) survival rates [13]. Thus, where cadaveric organ donation is scarce, emergency LDLT can be applied to high urgency patients.

• ***New immunosuppressive drugs*** – Cyclosporin is the most commonly used maintenance immunosuppressive drug. Steroids are almost invariably added [12]. Azathioprine may be used as a third agent to reduce the dose of cyclosporine and, in some cases, may replace cyclosporine altogether when the latter is contraindicated or can no longer be used because of adverse side effects.

Anti-lymphocyte globulin preparations, including the monoclonal antibody OKT-3 [22], have been given prophylactically and for specific indications to prevent rejection. OKT-3 reacts against all mature T lymphocytes.

Other new drugs have been developed and tested in multicenter trials in the last decade [6]. The most prominent is tacrolimus (FK506), which became an established immunosuppressant agent for primary and rescue therapy (when experiencing rejection or poor tolerability to cyclosporin) in patients with liver, kidney and pancreas transplants.

After transplantation

During the ICU stay, additional procedures may be needed to identify and treat sources of infection, bleeding, or graft failure. Such procedures are perfomed in up to 50% of the post-OLT patients, and in 50% of these patients more than one procedure is needed [1]. Because the procedures are relatively short and the patients are already intubated, major issues concerning anesthesia are few. However, bleeding or hemodynamic instability is always a concern.

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