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Total Hepatectomy and Liver Transplantation as Two-stage Procedure

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Objective
This article describes the experience with a bridging procedure for a prolonged anhepatic period during clinical liver transplantation in case of special emergency situations.

Summary Background Data
Hepatic necrosis due to fulminant hepatitis or acute graft failure, as well as severe liver trauma are well-known and accepted indications for urgent liver transplantation. Prerequisite is the allocation of a suitable donor organ. If no allograft is available in time, patients with "toxic liver syndrome" or exsanguinating hemorrhage have been shown to benefit from advanced total hepatectomy.

Methods
As a modification of the standard one-stage procedure, recipient hepatectomy and subsequent liver transplantation are performed in two separate operations. To bridge the prolonged anhepatic period and to allow decompression and return of venous blood, an end-to-side portocaval shunt is constructed temporarily.

Results
Thirteen of thirty-two patients underwent hepatectomy but not transplantation subsequently, and died within 34 hours after progressive deterioration. In 19 of 32 patients, transplantation was realized 6–41 hours after hepatectomy; 9 of 19 patients died, mostly from sepsis. Ten of nineteen liver recipients survived the procedure including three unrelated late deaths; presently, seven patients are alive with a follow-up of 3 to 46 months.

Conclusions
Two-stage total hepatectomy with temporary portocaval shunt, and subsequent liver transplantation can be a life-saving approach in patients most likely to die of the sequelae of advanced liver or graft necrosis or exsanguination that cannot be controlled by conventional treatment or immediate liver transplantation.

Liver transplantation (LTx) has become the treatment of choice for many patients with terminal liver disease. Apart from organ preservation, recipient selection and management, and immunosuppression standardization of the operative procedure is one of the essentials that made this possible.

The standard operation as practiced today has evolved from constant efforts in experimental and clinical work pioneered by T.E. Starzl, and followed by other traditional liver transplant centers, e.g., Cambridge, Hannover, and Groningen.[1,2] Over the years, numerous minor and major modifications and improvements have led to a surgical technique that can be applied in a routine manner, and with great safety. In principle, the recipient operation, which is timed only after a donor organ has been allocated can be divided into two parts: the dissection phase when the diseased liver is removed, and the phase of implantation of the new liver with reconstruction of vascular and biliary anastomoses. Usually, these two steps are done within the same session immediately after each other to keep the anhepatic phase as short as possible.

There are, however, exceptions from this rule that may force a surgeon to do the recipient hepatectomy before a donor organ is available, and postpone the replacement when an allograft is found to a second operation; this approach is described as the "two-stage" procedure. To bridge the prolonged anhepatic period after total hepatectomy, a portocaval shunt (HpcS) renders venous decompression possible.

From our own clinical observations with instantaneous improvement after removal of failing livers, we found that in exceptional situations it is advantageous to have a patient who is anhepatic than to leave a necrotic liver *in situ,* which has an extremely high mortality. This therapeutic concept, its clinical background, the operative technique, and our preliminary experience with four patients was described in detail, and presented at the International Organ Transplant Forum held in Pittsburgh 1987.[3] We are aware of other surgeons who have adopted this approach, and treated patients successfully. The two-stage procedure can also be applied in other emergencies, e.g., massive otherwise unsalvageable liver trauma.[4]

Since introduction of this concept, the time has come to update the experience that has accumulated. Therefore, we reviewed our own consecutive series of 32 patients treated by total hepatectomy as a two-stage procedure to be followed by liver transplantation. The results of this critical analysis are summarized.

PATIENTS, INDICATIONS, AND TECHNIQUE

In 1986, the first patient at our institution was treated by total hepatectomy and portocaval shunt (HpcS) according to the concept as described previously. Within the following years, a total of 34 such procedures have been performed in 32 patients; two patients each were hepatectomized twice, and subsequently retransplanted. The 17 males and 15 females had an age ranging from 18 months to 62 years, including five children (< 16 years).

There were two additional pediatric liver recipients with retransplantation for primary nonfunction, and chronic rejection, respectively. Both had failed primary grafts removed with preservation of the retrohepatic inferior vena cava. Because of small size and patient age (8 months, and 14 years, respectively) instead of an external veno-venous bypass, internal venous decompression was achieved by a temporary portocaval shunt. This procedure was chosen as bridging of the anhepatic period, which was prolonged to 196 and 285 minutes, respectively, due to reduction hepatectomy of the donor organs. Since HpcS and LTx were performed in the same session those two patients are not included in the following analysis.

The original liver diseases in all 32 patients were as follows: fulminant viral hepatitis (n = 5), postnecrotic or cryptogenic cirrhosis (n = 5), primary biliary cirrhosis (n = 2), extrahepatic biliary atresia (n = 2), Budd-Chiari syndrome (n = 3), angio- or hemangiomatosis (n = 2), liver trauma (n = 6), hepatocellular carcinoma with or without cirrhosis (n = 3), bile duct carcinoma without or with primary sclerosing cholangitis (n = 3), and colorectal liver metastasis (n = 1).

When looking at the individual indications for 34 hepatectomies that were not necessarily identical to the underlying liver diseases, two important aspects need to be emphasized and explained precisely. First, there are two major indication categories. With introduction of this procedure some years ago our primary objective was to treat patients with nonfunctioning grafts and hemodynamic and renal instability. These fatal complications are a consequence of acute hepatic necrosis.[5,6] The full-blown picture is equivalent to a 3- or 4-organ failure, which can well be circumscribed by the term "toxic liver syndrome." This would be characterized by complete liver necrosis associated with cardiovascular shock, renal, and perhaps respiratory failure. In 27 of 34 patients this toxic liver syndrome was present, despite every resuscitation effort available, including artificial ventilation, hemodialysis, and vasopressive support. Six patients had severe hemorrhage from the liver, which could not be managed by conventional surgery, and in one patient, a proximal bile duct tumor was found to be nonresectable without hepatectomy. In these latter patients, the principal indication for hepatectomy was confined to the liver, and not complicated by multiorgan failure.

The second aspect concerns the sequence of hepatec-

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Table 1. INDICATIONS FOR TWO-STAGE TOTAL HEPATECTOMY (HpcS) AND LIVER TRANSPLANTATION (LTx)

Indications	HpcS Before LTx	HpcS After LTx
"Toxic liver syndrome"	6	21
Liver trauma	2	
Fulminant hepatitis	1	
Postnecrotic cirrhosis	1	
Postop liver failure	2	
Primary nonfunction		11*
Acute rejection		5†
Delayed graft failure		3
Hepatic artery thrombosis		2
Hemorrhage	5	1
Liver trauma	4*	
Hemangiomatosis	1	
Chronic rejection		1
Nonresectable tumor	1	
Proximal bile duct carcinoma	1	
Total	12	22

Two patients had two subsequent hepatectomies:
* Liver trauma, and primary nonfunction.
† Two recurrent acute rejections.

tomy (HpcS) in relation to liver transplantation (LTx). A so-called "primary" hepatectomy was done in 12 patients who never had a liver transplant; principal indications were severe liver trauma or acute hepatic failure. In contrast, 22 "secondary" procedures were carried out in patients with graft failure after previous liver transplantation; graft loss was due to primary nonfunction (n = 11), irreversible acute rejection (n = 5), and various other reasons. The maximum interval between previous LTx and hepatectomy was 28 days; five livers were removed during the transplant operation immediately after revascularization. The distribution of indications and sequence of hepatectomy and transplantation is summarized in Table 1.

The surgical technique can be described briefly. In the first stage, the necrotic or ruptured hepatic parenchyma was removed after dissection of the hilar structures as well as the hepatic veins, and temporary cross-clamping of the large vessels. With the inferior vena cava retained, an end-to-side portocaval anastomosis, which allowed systemic and portal venous drainage and decompression, was constructed. During the anhepatic period, the patients were monitored for any hemodynamic and metabolic disturbances. To prevent the development of severe lactate acidosis, bicarbonate hemodialysis or continuous arteriovenous hemofiltration with sodium bicarbonate-buffered replacement fluids was used prophylactically.[7,8] Orthotopic liver transplantation using standard techniques began as soon as an allograft was available.

RESULTS

The two-stage procedure includes total hepatectomy and subsequent liver transplantation (HpcS + LTx). Unfortunately, in 13 of 32 patients, the second step — implantation of a new liver — could not be performed. Despite intensive medical support, none of those patients showed any signs of improvement or at least stabilization after hepatectomy; instead, all had a rapidly progressing clinical deterioration leading to death from multi-organ failure. Although donor organs would have been available, transplantation was not considered successful to rescue those patients. The maximum survival time observed without a liver was 34 hours and 35 minutes, with a mean of 649 ± 560 min (Fig. 1).

Nineteen of thirty-two patients had the full procedure; after "primary" (n = 8) or "secondary" (n = 11) hepatectomy, liver transplantation was performed after an anhepatic period between 395 and 2489 min (mean 987 ± 433 min; maximum 41 hr 29 min). In accordance with response to therapy, two subgroups were identified: nonsurvivors (n = 9), and survivors (n = 10), respectively. The nonsurvivors died of sepsis or acute respiratory distress syndrome 1 to 46 days after transplantation. Three patients with late death were included in the survival group. They had a benefit from total hepatectomy, but died from causes not related to the procedure: peritonitis (112 days), fulminant recurrent hepatitis B (3 months), and recurrent bile duct cancer (22 months). At present, seven patients are alive and well with a maximum follow-up of 46 months. Thus, 10 patients were considered as long-term survivors after two-stage hepatectomy and subsequent liver transplantation in this series (Table 2).

To look for an explanation with regard to outcome, we tried to compare the nonsurvivors and the survivors. There were no significant differences in age of the patient, type of indication, or duration of the anhepatic period. However, with development of a toxic liver syndrome from devitalized parenchyma, there was an increased risk of sepsis in the later course, whereas the chance of survival seemed more favorable in patients with a short previous history, e.g., after liver trauma or primary nonfunction. Among the survivors, there were two patients with two subsequent hepatectomies and liver transplants that are described in more detail later.

Patient 7

After a squash match, a 21-year-old woman had extensive and progressing subcapsular liver hematoma that could not be controlled by two repeated operations with deep mattress sutures, left lateral segmentectomy, and perihepatic packing. Because of exsanguinating hemorrhage, total hepatectomy was performed leaving the pa-

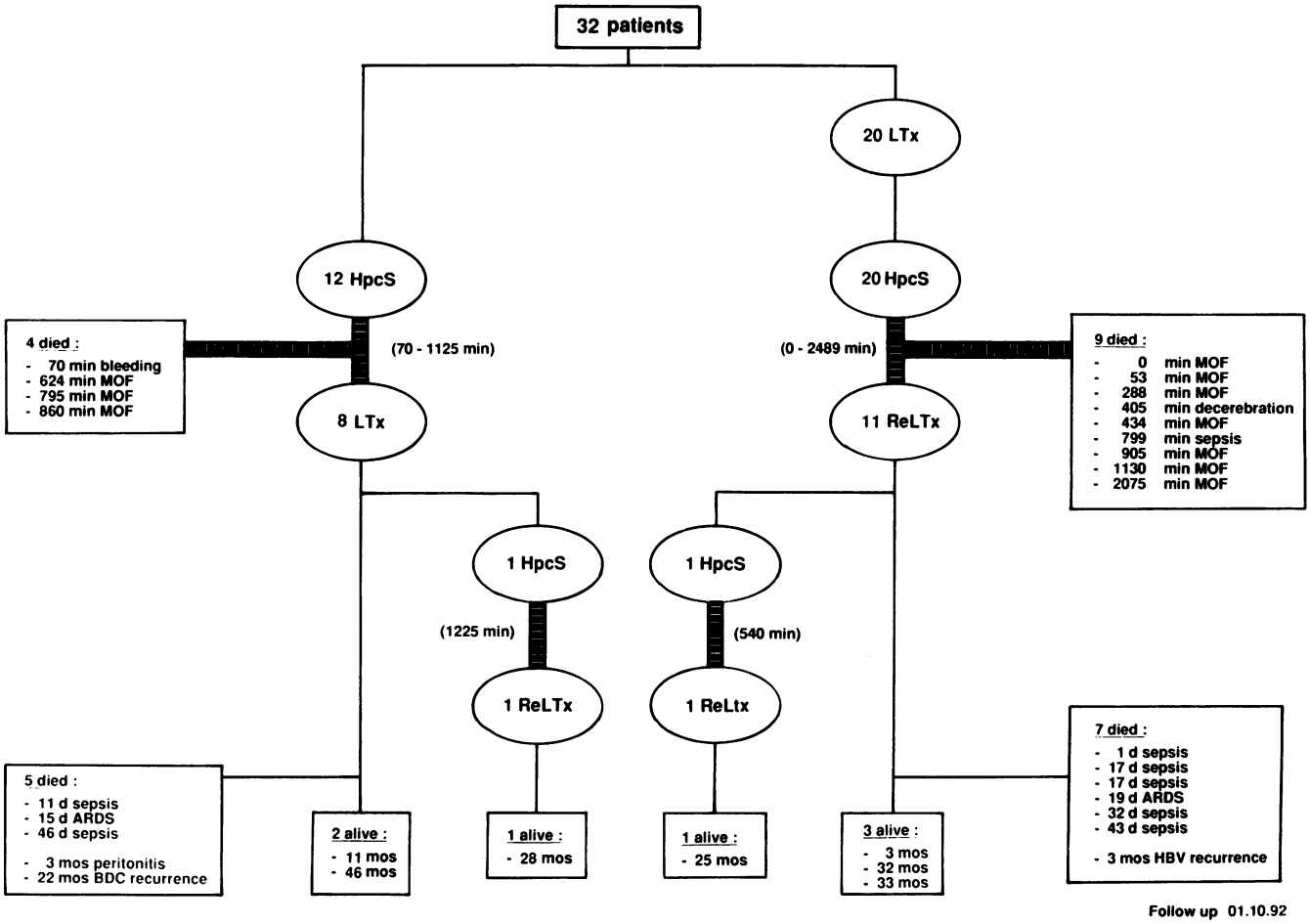

Figure 1. Results of two-stage total hepatectomy (HpcS) and liver transplantation (LTx) in 32 patients. MOF = multi-organ failure, ARDS = acute respiratory distress syndrome, BDC = bile duct carcinoma, HBV = hepatitis B. Anhepatic period in parenthesis.

tient anhepatic for 16 hours and 20 minutes with completely stable circulation and renal function. The first liver graft showed no primary function and was removed 1 day later because the patient had a "toxic liver syndrome," transaminases exceeding 4000 U/l, no clotting factor or bile production, hemodynamic instability necessitating high-dose vasopressive support, increasing respiratory insufficiency, and acute renal failure. The patient was anhepatic for another 20 hours and 25 minutes with continuous sodium bicarbonate hemofiltration before a second liver transplant could be performed successfully (Fig. 2).

Patient 8

A 12-year-old girl received a liver transplant for Budd-Chiari syndrome. Six days later, she developed a toxic multi-organ failure from acute hepatic rejection, which could not be reversed despite switching the patient to FK 506. She underwent hepatectomy and remained anhepatic for 17 hours and 43 minutes before receiving a second transplant. Again, massive acute rejection occurred and was the indication for a second hepatectomy; 9 hours later she had a third liver transplantation, and recovered completely.

DISCUSSION

Liver transplantation is still an "unfinished product."[9] The steadily widening application of this treatment modality inevitably leads to confrontation with exceptional situations that can impose major challenges. Undoubtedly, acute hepatic necrosis, e.g., due to fulminant hepatitis or graft failure, is a typical emergency leading to death

Table 2. SURVIVORS AFTER TWO-STAGE TOTAL HEPATECTOMY (HpcS) AND LIVER TRANSPLANTATION (LTx)

Patient No.	Age, Sex (yr)	Indication	Sequence of Operations	Anhepatic Period (hr, min)	Survival Time (mo)
1	57, m	Bile duct carcinoma	HpcS → LTx	14, 23	22 (died: tumor recurrence)
2	14, f	Liver trauma (bleeding)	HpcS → LTx	14, 45	46
3	62, m	Postop liver failure	HpcS → LTx	18, 45	3 (died: peritonitis)
4	42, m	Primary non-function	LTx → HpcS → LTx	17, 17	3 (died: hepatitis B recurrence)
5	48, f	Delayed graft failure	LTx → HpcS → LTx	21, 45	33
6	54, m	Primary non-function	LTx → HpcS → LTx	9, 32	32
7*	21, f	Liver trauma (bleeding)	HpcS → LTx	16, 20	28
		Primary non-function	→ HpcS → LTx	20, 25	
8*	12, f	Acute rejection	LTx → HpcS → LTx	17, 43	25
		Acute rejection	HpcS → LTx	9, 0	
9	37, m	Postnecrotic cirrhosis	HpcS → LTx	7, 33	11
10	32, m	Primary non-function	LTx → HpcS → LTx	20, 38	3

* Two patients had two subsequent hepatectomies.

if not recognized and treated at once. Adequate therapy in most cases would mean urgent liver transplantation, which can usually be achieved within a few days.

However, allocation of a suitable donor organ is not always possible in time. Even more, some patients develop a so-called "toxic liver syndrome" with multi-organ failure or are bleeding heavily from an unsalvageable liver wound not allowing enough time to wait for an allograft. To rescue those patients, immediate total hepatectomy may be the only chance. When this was done for the first time at our institution, we were in a desperate situation; to our knowledge this had never been done before in humans. We had to look carefully for the justification of such an undertaking.

In reviewing the literature, we found several important articles that should become the experimental background of our new clinical approach. The technique of total hepatectomy for the purpose of physiological studies in dogs was first described by Mann in 1921.[10] Various technical modifications followed including the idea to preserve the inferior vena cava, and construct a portocaval shunt.[11-14] Finally, liver transplantation without vena cava interruption was performed in dogs and later in humans.[15-17] This modification, recently termed "piggyback operation," which also became an essential prerequisite for the performance of partial liver transplantation in children, laid the technical basis for our present concept of two-stage hepatectomy.[18-20]

Even more important, however, was the objective of this procedure, why should there be an advantage to have a patient anhepatic? The mortality of acute hepatic necrosis is known to be close to 100% when complicated by advanced coma, renal failure, pulmonary insufficiency, and especially cardiovascular shock.[5,21,22] The pathophysiologic mechanism responsible for the development of arterial hypotension is not yet known. Contributing factors could be a decreased hepatic clearance for endogenous vasodilators or the release of toxic compounds by the necrotic liver.[6] At least, this would be a simple but convincing explanation for our clinical observation in patients with acute graft failure who had an immediate reversal of the unresponsive shock upon total hepatectomy.[3] Experimental data from a study supporting this view in hepatectomized pigs showed a significant increase of plasma norepinephrine levels within 30 minutes.[23] In a recent report on three patients with fulminant hepatitis, hepatic devascularization was followed by a reduction of lactoacidosis.[24] Thus, the potential advantage of total hepatectomy in some very critical situations is hemodynamic and metabolic stabilization, which cannot be achieved by other measures of resuscitation.

After our preliminary report and with more experience, we wanted to prove whether our previous assumption that hepatectomy can be a life-saving procedure was still valid. Thirteen of thirty-two patients died after hepatectomy without a chance to undergo transplantation; they did not respond but went into multi-organ failure with progressive hemodynamic and metabolic derangements. Their fatal outcome underlines the severity of the extreme clinical status. With full medical support, anhepatic survival was possible for 34 hours. Despite the fact that there was clinical improvement and stabilization at least temporarily, 9 of 19 hepatoectomized and transplanted patients died, mostly of sepsis. However, 10 patients survived this procedure including seven patients who were alive after 3 to 46 months. It should be emphasized that all those patients were in extremies, and were

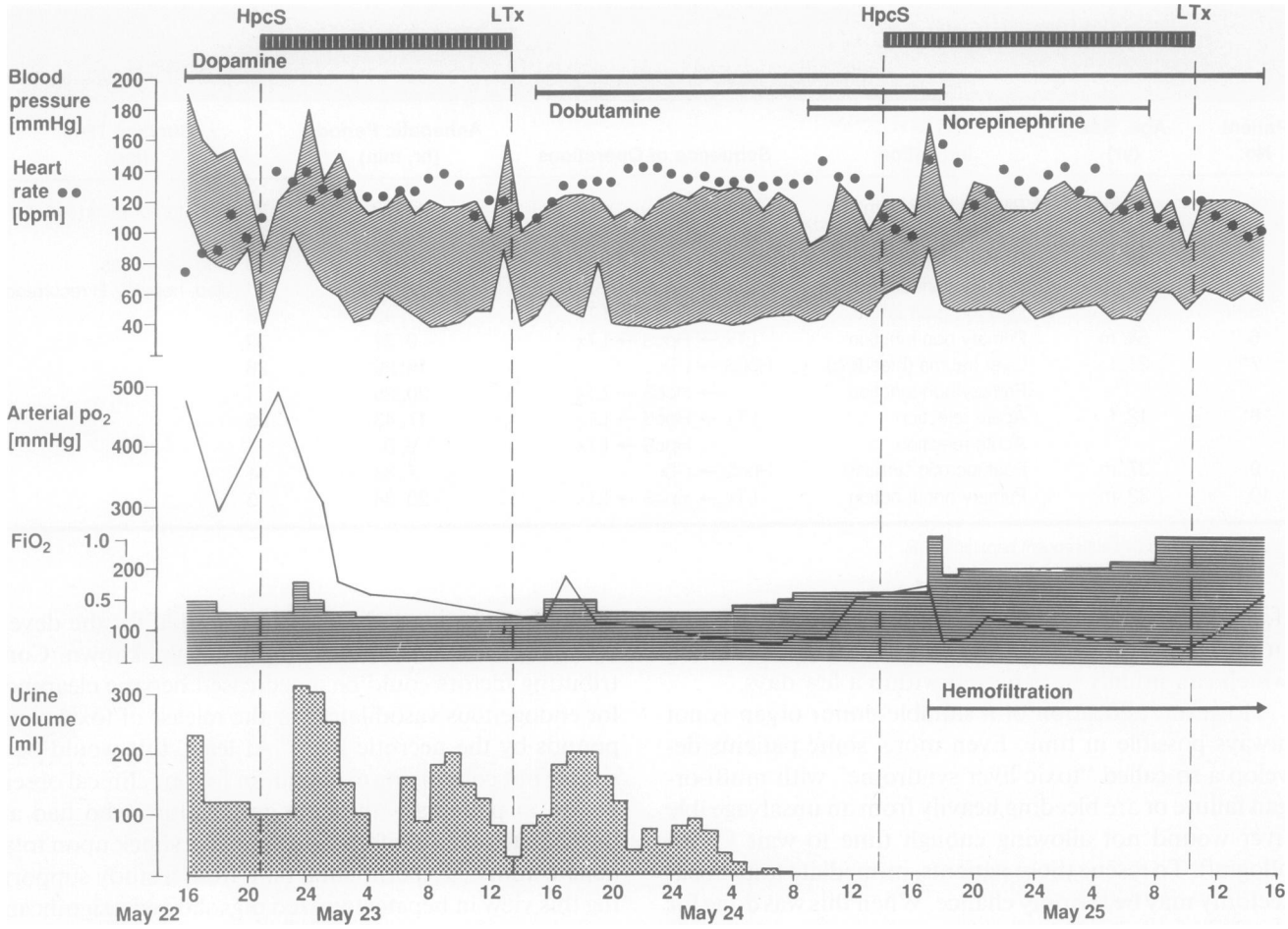

Figure 2. Clinical course of a 21-year-old woman with two subsequent hepatectomies performed for liver trauma and primary nonfunction. The diagram shows the circulatory, respiratory, and renal function.

far beyond any reasonable chance of survival. Thus, every single patient who could be rescued must be considered a success, and demonstrates the effectiveness of hepatectomy as an exceptional but potentially life-saving approach. These results further justify its application especially in a setting where donor organs are not readily available, otherwise urgent transplantation would be preferable.

On the other hand, those results open up a number of new questions. How can patients be identified who have a good chance to benefit from hepatectomy? The major indications for this approach have been outlined before, "toxic liver syndrome" or exsanguinating hemorrhage. Our still limited experience indicated that the etiology of liver failure and the period of time before hepatectomy could play important prognostic roles; most patients with unsalvageable trauma and an early decision for hepatectomy survived. Contrary, prolonged ischemia and extended hepatic necrosis carried an increased risk of infection leading to death from sepsis despite successful transplantation. Thus, leaving a large mass of devitalized liver tissue inside the patient should be avoided under all circumstances.

This leads us to the question, is excision of the liver really necessary or would devascularization be sufficient? From our own experience, we would argue against hepatic inflow occlusion in those patients. With ligation of the hepatic artery, the efferent blood vessels remain open allowing venous drainage of toxic metabolites from the necrotic liver.[25] This type of hepatic devascularization, called "functional hepatectomy," does not provide for a complete exclusion of the liver from the patient's circulation, and has no advantage at all over "anatomic hepatectomy," which technically has never been difficult in our hands.[24] It could even have a disadvantage in increasing the risk of hepatobiliary sepsis.

The last but crucial question is how long can an anhepatic phase be tolerated? There are few experimental data available in the literature that show a survival of hepatectomized pigs to be in the range of 20 to 40 hours.[23,26] Because in our own clinical series, it was not the objective to extend the anhepatic period as long as

possible, the maximum time span observed was 41 hours. At the moment it is probably impossible to define a cutoff point for a good prognosis because survival depends on the clinical status of the patient at the time of hepatectomy and the effectiveness of supportive therapy.

In conclusion, this update of total hepatectomy and subsequent liver transplantation performed in two stages demonstrates that the procedure can be life-saving in exceptional situations in which the likelihood to die from liver necrosis or bleeding is high. An essential prerequisite for success seems to be early decision and performance of hepatectomy before the patient has reached the stage of terminal, and irreversible multi-organ disease. If this procedure is done in time, there is a good chance to rescue patients with liver transplantation even after a prolonged anhepatic period.

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