Published in final edited form as:
Semin Liver Dis. 1985 November ; 5(4): 344–348. doi:10.1055/s-2008-1040631.

Advantages of Venous Bypass During Orthotopic Transplantation of the Liver

BYERS W. SHAW Jr., M.D., **DOUGLAS J. MARTIN, M.D.**, **JOSE M. MARQUEZ, M.D.**, **Y. G. KANG, M.D.**, **ALAN C. BUGBEE Jr., Ph.D.**, **SHUNZABURO IWATSUKI, M.D.**, **BARTLEY P. GRIFFITH, M.D.**, **ROBERT L. HARDESTY, M.D.**, **HENRY T. BAHNSON, M.D.**, and **THOMAS E. STARZL, M.D., Ph.D.**
Departments of Surgery and Anesthesiology, University of Pittsburgh Health Center, University of Pittsburgh, Pittsburgh, Pennsylvania

The anhepatic phase of an orthotopic liver transplantation procedure occurs when the surgeon has removed the native liver (along with the intrahepatic portion of the vena cava) and is involved in sewing in the donor organ. During this interval, the inferior vena cava is cross-clamped at the diaphragm and at a point just above the entry of the renal veins. The result is a complete interruption of venous return from the inferior vena cava, as is evident from a sudden decrease in both central venous and pulmonary arterial wedge pressures, resulting in a profound reduction of cardiac output.[1]

The portal vein is also clamped, of necessity, during this phase. A sudden and marked increase in hydrostatic pressure in both the portal and systemic venous beds thus occurs. This not only causes damage to the kidneys, bowel, and pancreas, but also can profoundly exacerbate hemorrhage from the tissues that were cut during the recipient hepatectomy.

Early Approaches to the Problem

Early attempts at transplantation of the liver in dogs required the use of some means of relieving pressure in the obstructed portal vein because dogs usually died 20 to 30 minutes after clamping the portal vein. To avoid this problem, Starzl routinely constructed an end-to-side anastomosis between the divided portal vein and the vena cava just below the liver, then bypassed flow from the lower vena cava to the superior vena cava (via the jugular vein) using passive shunts.[2]

Similar shunts were used during the first human trials of orthotopic transplantation of the liver. However, pulmonary embolism played a major role in the deaths of three of the first four patients in the Denver experience.[3] The passive shunts were thought to be the major cause.

In previous studies, Starzl's group had also shown that dogs that were made cirrhotic (by chronic bile duct ligation) did not require shunting.[1] Apparently, adequate portal decompression was provided by the formation of spontaneous shunts through collaterals resulting from chronic portal hypertension. This finding led Starzl to attempt the next few clinical transplants without the use of shunts. Starzl's group subsequently found that, in general, all humans, not just those with portal hypertension, tolerated the anhepatic phase much better than did dogs.

Reprint requests: Dr. Shaw, Dept. of Surgery, University of Nebraska Medical Center, 42nd and Dewey Avenue, Omaha, NE 68105.

From March 1, 1963, to March 1980, the group in Denver was involved in the transplantation of the liver in 170 patients using azathioprine and prednisone for immunosuppression. Other modalities, such as antilymphocyte serum or its globulin derivative and thoracic duct drainage, were also used as adjuvant immunosuppression during the latter part of this period. Although these drug regimens were able to provide more than 50% 1-year kidney graft survival, they proved unsatisfactory for liver transplantation.[4] Rejection remained the major source of morbidity and mortality. Technical improvements continued to be important during this period, but ultimately, their capacity to improve patient survival was severely handicapped because of rejection.

Beginning in March, 1980 cyclosporine was introduced in Denver as an immunosuppressant for liver recipients. The subsequent improvement in survival rates was dramatic. Although by no means eliminated, rejection had been ameliorated considerably. As a result, Starzl and his group, now in Pittsburgh, rapidly expanded their experience. By late Spring, 1982, 42 adults had received liver transplants under cyclosporine therapy.

Among this group of 42 adults, four (9.5%) were considered operative deaths. In addition, the death of a number of other patients ultimately appeared to be related to a difficult operative course. With 1-year survival rates in adults having risen from 26% to more than 60% after the introduction of cyclosporine, morbidity and mortality related to operative difficulties gained increasing attention.

A review of the causes of these operative failures revealed that many could be eliminated if the hemorrhage and cardiodynamic instabilities occurring during the anhepatic phase could be avoided. With this goal in mind, the group in Pittsburgh, with the help of the cardiac surgeons under the direction of Dr. H.T. Bahnson, undertook a trial of venous bypass in the summer of 1982. This technique employed a conventional cardiopulmonary bypass apparatus with a roller head pump and cardiotomy reservoir. It required that the patient be given systemic anticoagulation. Heparin was chosen because it was a satisfactory anticoagulant for cardiac surgery and it could be reversed readily with protamine.

Between June 15 and September 6, 1982, 12 patients received transplants using this method of venous bypass. Nine were adults. Three of these nine patients died in the operating room: two from uncontrolled hemorrhage, the third of cardiac arrest during a retransplant procedure. Four of the remaining six patients died in less than 3 months. Only two obtained long-term survival. Mean operative blood loss in these patients was 53.1 ± 33.0 (SD) units of packed red blood cells (PRBC), considerably more than the blood losses experienced in previous cases without the use of bypass. The problems, for the most part, appeared related to the need for anticoagulation and the resultant exacerbation of both preexisting coagulopathies and the fibrinolytic phase following revascularization of the hepatic allograft.

Despite these discouraging results, the potential advantages that the system might offer were quite clear. The three children and several adults who did not experience bleeding diastheses obtained marked stabilization of cardiodynamic parameters during the anhepatic phase. As if to underscore the need for some form of bypass further, after this method was abandoned in September, two more adults died on the operating table while undergoing transplantation without bypass, largely as the result of their inability to tolerate the severe hemodynamic insults of the anhepatic phase. With this experience behind them, the group in Pittsburgh returned to the laboratory to develop a bypass system that would not require anticoagulation of the recipient

Bypass Without Heparinization

In the fall of 1982, the team in Pittsburgh began performing liver transplants on dogs using a closed circuit bypass apparatus that did not require that the animals be heparinized. The initial suggestion that this might prove successful came from one of the cardiac surgeons at the University of Pittsburgh Health Center, B.P. Griffith. The technique employed the same centrifugal force pump that the cardiac team had been using to pump blood through an extracorporeal membrane oxygenator used to support infants for long periods of time. The pump offers the advantage of being less traumatic to red blood cells and, because it can be safely used in a closed system, a reservoir is not required.

The results of these experiments were presented previously.[5] The success of the technique led to the initial clinical trials of the system in February 1983.[6] The subsequent use of this method of bypass during liver transplantation in 57 adult patients was the subject of another report.[7] The substance of the latter article will be reviewed herein.

MATERIALS AND METHODS

A total of 129 adults were transplanted in Pittsburgh between March 9, 1980, and March 22, 1984. Of these, 63 were operated on without the use of bypass, nine with the heparinized system, and 57 with the system that does not require anticoagulation. Cardiopulmonary data were obtained on a subgroup of 28 patients who were studied prospectively in the operating room with multiple lumen, oximeter tipped, pulmonary artery catheters. Parameters were recorded at predefined intervals during the transplant procedure, and mean values were compared using the paired *t* test. These data were also compared in a less rigid fashion to data obtained previously in a number of patients transplanted without bypass.

Retrospective renal function data were available on 38 and 49 patients in the nonbypass and bypass groups, respectively. The means of the preoperative and of the maximum postoperative serum creatinine (during the first 3 days after transplantation) were compared using unpaired and paired *t* tests. The mean operative blood losses for 43 and 36 patients, respectively, were also compared using unpaired *t* tests and the median values were compared with rank sum analysis. Finally, life-table survival curves were generated for each group (exclusive of the heparinized patients) and compared using the standard error of the survival probabilities for each interval.

RESULTS

Cardiodynamic Data

The cardiodynamic profiles obtained are shown in Table 1. These show that both central venous and wedged pulmonary artery pressures were sustained at levels equal to those measured just before placing the patient on bypass and completing the hepatectomy. During the period of bypass, the cardiac index decreased, but the arterial-venous oxygen content difference remained unchanged, reflecting adequate tissue oxygenation. Thus, the decrease in cardiac index was apparently an appropriate response to a measured decrease in body temperature and removal of the liver. Using the Fick equation, a significant decrease in oxygen consumption was calculated.

These data are in contrast to those obtained in a previous study that reported a 50% to fivefold reduction in cardiac index during the anhepatic phase in those patients undergoing transplantation without the use of bypass. During bypass, flow rates through the system have ranged from 800 ml/minute to more than 5000 ml/minute, representing anywhere from 25 to 75% of the measured cardiac output at the time.

Renal Function

In those patients transplanted without bypass, the mean maximum serum creatinine within 3 days after transplantation was 3.0 mg/dl. This represented a mean change of + 1.29 (± 1.95) mg/dl. Six of these patients, who did not have overt renal failure preoperatively, required dialysis during the first week after the liver transplant. In contrast, the maximum creatinine averaged 1.5 mg/dl in the bypass group, and none of these patients required dialysis after the liver transplant.

Operative Blood Loss

Bypass also had a dramatic effect on the mean operative blood loss for liver transplantation in adults. The mean number of units of PRBCs transfused decreased from 33 ± 25 in the nonbypass group to 19 ± 8 ($p<0.01$) in the bypass group and the median loss (perhaps a more indicative figure because of the tremendous standard deviation in the mean calculations) decreased from 27 to 16 units ($p<0.05$).

Survival Data

At 30 days, the bypass group obtained a 91% survival versus 73 % for the nonbypassed group ($p<0.004$). However, at 90 days, this advantage was no longer statistically significant. To find the cause of this phenomenon, the overall group of patients was broken down into categories, depending upon preoperative risk factors (see accompanying article by Shaw et al in this issue of *Seminars*). Patients were assigned to one of three status groups. Status 1 patients were low risk, status 2 were medium risk, and status 3 were high-risk patients. A patient could be placed in the high-risk group for either physiologic or technical reasons. The latter were those patients who had had major surgery involving the liver or bile ducts, such as portocaval shunt or multiple attempts at biliary reconstruction, or those with documented portal vein thrombosis.

Bypass improved 30-day survival in all three status groups. This advantage continued beyond 90 days for both status 1 and status 2 patients. However, the high-risk group who had undergone bypass and who had an early 30% survival advantage over nonbypassed patients (61.5 % versus 31%), suddenly experienced a marked increase in mortality between 30 and 90 days postoperatively, so that by the end of 6 months, survival was equivalent to the nonbypassed group. Of further note, the only long-term survivors in the status 3 bypass group were the two patients placed in that group by virtue of technical rather than physiologic reasons. In contrast, three of the four technically high-risk patients in the nonbypass group died in the operating room and the fourth within 48 hours of surgery.

FURTHER THOUGHTS ON VENOUS BYPASS

In the 15 months since the original report of the intraoperative, hemodynamic, and postoperative advantages that venous bypass offers patients undergoing orthotopic transplantation of the liver, the group in Pittsburgh has had experience using the technique in well over 100 additional adult patients. Clearly, liver transplants can be accomplished in adults without this methodology. However, the technique has proved to be so successful and so easily done on a routine basis, that it becomes almost inconceivable that anyone should want to do so. For purposes of added safety and greater simplification, fully heparin-bonded, single-piece tubing circuits are now available commercially. Full heparin coating of the entire tubing circuit virtually eliminates the chance of clots forming in the tubing should flow through the bypass need to fee interrupted for any reason during the bypass phase.

Morbidity from the procedure has been limited to the occurrence of groin or axillary seromas in approximately 25% of patients. The incidence of these can be minimized by

more careful dissection of the axillary or saphenous veins to avoid injury to small lymphatics and by careful closure of the wounds in layers.

On the other hand, one patient had a massive and immediately fatal pulmonary embolism soon after starting bypass. This patient had polycystic disease of the liver and the primary indication for transplantation was massive hepatomegaly causing symptoms of inferior vena cava obstruction. In retrospect, this problem should be added to acute Budd-Chiari syndrome as the two diseases for which venous bypass is contraindicated. The risk of entraining preexisting clot from the venous beds and then embolizing them centrally far outweighs the advantages of the technique.

A more subtle but no less important advantage of bypass is the list of operative options that it offers to the surgeon who employs it. All of these options are based on the single fact that the bypass allows a longer anhepatic phase. During this period on bypass, bleeding is not constantly accelerating because of the rapid buildup of hydrostatic pressure in obstructed venous beds. Patients with less resilient cardiac function no longer begin the alarmingly sudden deterioration in hemodynamic status that so often typified anhepatic phases without bypass lasting more than about 30 to 45 minutes. This extra time and, more importantly, the knowledge that one will have this extra time if needed allows the surgeon to tailor the transplant procedure to the individual patient. Thus, if he finds that the recipient hepatectomy is particularly difficult and that meticulous dissection and careful hemostasis are not going to be possible, he has the option of halting the dissection, gaining complete control of any bleeding points created up to that point, and then waiting for the arrival of the donor liver in the recipient operating room. Once the donor organ is ready for implantation, the surgeon can place the recipient on bypass, and then rapidly excise the liver. More than 1 hour can be spent with the liver removed and with full visualization of the entire field, obtaining reasonable hemostasis. Thus, the bypass prevents the prolonged period of steady blood loss that might have resulted had the surgeon not had this option and persevered along the original tack.

This is not to imply that the bypass allows for reckless abandon or that it is a substitute for careful surgical technique. In fact, many surgeons may still prefer to carry out a carefully hemostatic dissection in any case that will allow it, which will be the overwhelming majority of cases. However, it does provide a certain degree of comfort to know not only that the patient is going to be quite stable during that time when the inferior vena cava and the portal vein have been clamped and transected, but also that one can exercise one of several options for accomplishing the native hepatectomy.

Although no mention has been made of the use of bypass for children, it has been used occasionally for children undergoing transplantation in Pittsburgh. It is not used more often mainly for two reasons. First, children almost never need it. In most instances, they tolerate the anhepatic state much better than do adults. Secondly, the initial work in the laboratory raised genuine concerns over the potential dangers of low rates of blood flow in plastic tubes without the use of anticoagulants.

The developmental laboratory work on heparinless bypass, reported by Denmark et al,[5] revealed that when flow in the unheparinized system decreased below about 800 ml/minute, platelet counts and fibrinogen levels decreased and fibrin split products began to accumulate. This suggested that coagulation was being activated as the blood passed more slowly through the tubing, and although no emboli were apparent, this was taken as a warning sign that a lower limit of flow should be set. Accordingly, when the system was first used clinically, a lower limit of 1000 ml/minute was used as the level of flow below which bypass would be terminated. The degree of caution attending the application of

something new like this for patients was understandably high. As a further safety measure, the initial tubing circuit used clinically was partially constructed of heparin-bonded plastic tubing. The Pittsburgh group recently reported that subsequent work in the laboratory and a limited experience clinically suggest that the safe lower limit of flow rate might be much lower.[8] One must exercise considerable caution, however, since 2 of 40 dogs in this study died suddenly from pulmonary emboli while on low-flow bypass. These latest studies were done without the use of any heparin-bonded tubing. Other recent work in the laboratory indicate that a completely heparin-bonded tubing circuit allows one to interrupt flow in the tubing completely for upward of 15 to 20 minutes without clot formation.

Thus, safe bypass is possible in children, even at markedly reduced flow. However, the likely ratio of benefits to risks for most children will be low enough to require a much more selective use of venous bypass. Those children with poor cardiac reserve or who appear unable to tolerate a test clamping of the portal vein and vena cava are probably candidates for venous bypass.

SUMMARY

Venous bypass restores normal hemodynamic physiology during the critical anhepatic phase of orthotopic transplantation of the liver. Its routine use in adults undergoing transplantation in Pittsburgh has resulted in lower operative blood losses, a lower frequency of postoperative renal failure, and a greater probability of survival for all but the highest risk patients. Because it allows for a longer anhepatic phase, the surgeon has the option of tailoring the native hepatectomy to the needs of the individual case, even to the point, in difficult cases, of obtaining most of the hemostasis after removal of the native liver, but before sewing in the donor organ. Selective use of bypass in children may offer similar advantages.

Acknowledgments

Supported by Research Grants from the Veterans Administration and Project Grant No. AM-29961 from the National Institutes of Health, Bethesda, Maryland.

References

1. Pappas G, Palmer WM, Martineau GL, et al. Hemodynamic alterations caused during orthotopic liver transplantation in humans. Surgery 1971;70:872–875. [PubMed: 4941999]
2. Starzl TE, Kaupp HA, Brock DR, et al. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 1960;111:733–743. [PubMed: 18979655]
3. Starzl TE, Marchioro TL, Von Kaulla KN, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963;117:659–676. [PubMed: 14100514]
4. Starzl TE, Iwatsuki S, van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982;2:614–636. [PubMed: 6749635]
5. Denmark SW, Shaw BW Jr, Griffith BP, et al. Veno-venous bypass without systemic anticoagulation in canine and human liver transplantation. Surg Forum 1983;34:380–382.
6. Griffith BP, Shaw BW Jr, Hardesty RL, et al. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 1985;160:270–272. [PubMed: 3883552]
7. Shaw BW Jr, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524–534. [PubMed: 6385876]
8. Kam I, Lynch S, Todo S, et al. Low flow veno-venous bypasses in small animals and pediatric patients undergoing liver replacement. Surg Gynecol Obstet. 1985 In press.

TABLE 1

Cardiopulmonary Profiles in 28 Patients Undergoing Venous Bypass Without Anticoagulation

	Before Bypass		Bypass		
Variable*	**Mean**	**SD**	**Mean**	**SD**	**P†**
T (°C)	34.9	.98	33.8	1.16	0.0002
HR (bpm)	85.6	14.3	84.1	14.2	
MAP(mmHg)	75	17.1	83	17.6	
PAO (torr)	12.0	4.2	10.5	3.3	
CVP(mmHg)	9.9	4.4	9.2	4.9	
pCO_2 (torr)	33.3	5.2	29.9	4.8	0.0125
PO_2 (torr)	380	92.4	398	91.6	
SaO_2	0.9854	0.0915	0.9896	0.0160	
PvO_2 (torr)	65.5	16.3	70.8	21.5	
SvO_2 (torr)	0.904	0.0598	0.927	0.0496	
Hb(g/dl)	9.62	1.16	10.2	1.42	
pHa	7.42	0.07	7.40	0.08	
CI (liters/min-m^2)	4.37	1.44	3.44	1.09	0.0079
SI	51.7	15.9	41.4	13.6	0.0121
RVSWI	5.11	3.21	3.52	3.17	
LVSWI	43.4	14.3	39.7	11.4	
SVRI	443.7	233	660	366	0.0109
PVRI	34.3	23.9	44.1	39.1	
$avDO_2$	2.04	.81	1.87	.59	
VO_2/m^2	83.0	24.7	61.7	20.5	0.0009
O_2 transport	1087	391	917	342	

*T: temperature; HR: heart rate; MAP: mean arterial pressure; PAO: pulmonary arterial wedge pressure; CVP: central venous pressure; pCO_2: partial pressure of carbon dioxide; pO_2: partial pressure of oxygen; SaO_2: arterial oxygen saturation; PvO_2: mixed venous oxygen pressure; SvO_2: oxygen saturation pulmonary artery; Hb: hemoglobin; pHa: arterial pH; CI: carciad index; SI: saturation index; RVSWI: right ventricular stroke work index; LVSWI: left ventricular stroke work index; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; $avDO_2$: arteriovenous oxygen content difference; VO_2/m^2: oxygen consumption.

†Paired *t* test.