# Portacaval Shunt for Type II Hyperlipidemia[1]

447

Thomas E. Starzl, Lawrence Koep, and Richard Weil, III

Amelioration of Type 2 hyperlipidemia by completely diverting portacaval shunt was first reported in 1973 (Starzl et al). Since then, 5 additional patients have been similarly treated by us and others have been treated elsewhere. The compiled first cases have been published (Starzl, Putnam and Koep 1978) and, doubtless more will be added by Stein in his review later today. My remarks today will be confined to a brief description of 6 patients treated at the University of Colorado from one month to 6 1/2 years ago.

## Case Material

All 6 patients had Type 2 hyperlipidemia. Familial studies always were obtained to determine the probability of the homozygous or heterozygous state. The conclusions were compatible with tissue culture analysis of cholesterol synthesis. Five children had homozygous disease. A 52 year old man was heterozygous.

The 6 patients had been followed in established lipid centers during long periods of study and treatment. The referring physicians were H.P. Chase of Denver (Case 1), D.W. Bilheimer, J.L. Goldstein, and M.S. Brown of Dallas (Case 2), N.B. Javitt of New York and J. Rey of Paris (Case 3), E.H. Ahrens of New York (Cases 4 and 6), and E.J. Schaefer of Bethesda (Case 5). By collaborating with authorities in the field, three objectives were met. First, the patients were assured accurate diagnosis as well as trials with the most advanced methods of non-surgical treatment including (Cases 3 and 5) plasma exchange. Second, sophisticated studies of cholesterol and/or bile acid metabolism at the referring institution were obtained before and after the brief (one to two weeks) admission to Colorado General Hospital for surgical care. Finally, the aftercare and conclusions about the clinical results were the purview of objective observers who were not notable proponents of a surgical approach. Data and photographs were provided by the referring physicians, of whom some have published separate investigations.

The preoperative cardiovascular status of the patients was variable. In addition to aortic stenosis, (gradient 56 mmHg) Patient 1 had had a myocardial infarction 1 1/2 months before portacaval shunt, leading to a large left ventircular aneurysm. Patient 6 had had a myocardial infarction treated 5 years earlier with a triple coronary artery bypass; the diseased residual vessels were not susceptible to further reconstruction. Patients 2 and 5 had continuous angina pectoris and multiple coronary artery lesions, and in

[1]This work was supported by research grants from the Veterans Administration; by grant numbers AM-17260 and AM-07772 from the National Institutes of Health, and by grant numbers RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institute of Health.

addition Patient 2 had a large intraluminal plaque occupying two thirds of the ascending aortic lumen. Patient 3 had large asymptomatic intraaortic plaques in the chest and abdomen. Patient 4 had aortic stenosis with a gradient of 35 mmHg during a cardiac output of 5 1/min. Tendinocutaneous xanthomas were present in each case, and were exceptionally prominent in Patients 1, 2 and 5. The average serum cholesterol concentrations before portacaval shunt are shown in Table 1. These values usually were obtained during a low cholesterol diet and in spite of medicinal therapy. All 6 patients had normal liver function tests.

## Results

There was no operative mortality nor any surgical complications. Five of the 6 patients are still alive. The first patient died suddenly 18 1/2 months after operation, probably from a cardiac arrhythmia.

### Effect of serum cholesterol

A fall in serum cholesterol concentrations was already identifiable within a few postoperative weeks, and by August and September 1979, were at the levels shown in Table 1. In some patients, slow declines continued for a year or longer after operation. Late secondary rises of serum cholesterol concentrations were not seen. Low density lipoprotein (LDL) falls paralleled those of cholesterol.

### Effect on xanthomas

In Cases 1-5, there was a remarkable involution of the tendinocutaneous xanthomas which was evident within a month or two by a softening of these lesions and by the development of redundant overlying skin folds. Complete disappearance in the oldest cases required one to 3 years. Patient 6 who had minimal xanthomas has been followed for too short a time to see a definite change.

### Cardiovascular disease

During the first 16 months postoperatively, the aortic valve gradient in Patient 1 fell from 56 to 10 mmHg, but she had a large ventricular aneurysm and residual stenoses of the right, left main, and circumflex coronary arteries. An error was made at that time by deciding against coronary revascularization since the patient's death 2 1/2 months later was apparently due to a cardiac arrhythmia.

Patient 2 had myocardial ischemia and persistent angina. Ultimately, she underwent aortic and mitral valve replacement and double coronary artery bypass. She is now 5 years postoperative and asymptomatic under treatment with a low cholesterol diet, cholestyramine, and Atromid-S. Patients 3-6 have not had follow up angiographic studies.

### The effect on the liver

Standard liver function tests have not been perturbed except for minor and generally persistent increases in alkaline phosphatase and serum transamin-

ases. Patient 3 has had slightly elevated blood ammonia concentrations. None of the patients have had encephalopathy nor have they experienced pyschological disturbances.

Patient 1 had a liver biopsy at the time of and 6 months after portacaval shunt. The liver was examined again after her death at 18 1/2 months. The findings in the second 2 specimens included hepatocyte atrophy, depletion of rough endoplasmic reticulum, deglycogenation, and fatty infiltration. These same hepatic changes have been documented after complete portal diversion in all species so far studied including rats, dogs, swine, subhuman primates and humans (Putnam, Porter and Starzl, 1976).

## Physique

The growth and development of the children have been uninterrupted or in some instances somewhat more rapid than preoperatively. Growth spurts were not seen of the magnitude of those following portacaval shunt for glycogen storage disease.

## Discussion

Most of the reported patients with Type 2 hyperlipidemia treated with portal diversion have had reductions in serum cholesterol although the degree has been variable (Starzl, Putnam and Koep 1977). Thrombosis of the portacaval shunt with restoration by collaterals of hepatopetal splanchnic flow has been a well documented cause of failure.

The antilipidemic effect of portacaval shunt has not been satisfactorily examined. It does not depend upon the prior existence of high serum lipids. A fall in serum cholesterol and often in triglycerides and phospholipids can be produced with this procedure in normal rats, dogs, pigs and monkeys as reviewed by Starzl, Putnam and Koep (1978). The penalty is damage to the liver which is striking by histopathological criteria but which is more subtle as measured by liver function. The eventual consequence in pigs, dogs, and monkeys is hepatic encephalopathy and death within a few months. In rats and humans, portacaval shunt is compatible with long survival inspite of the fact that the morphologic changes produced in the liver are no less severe. The antilipidemic effect is probably due in part to reduced hepatic cholesterol synthesis by the altered liver (Starzl, Putnam and Koep 1978), but other mechanisms may play a significant role.

Appreciation of the potential hepatic and cerebral complications of portacaval shunt dictated our earlier policy of treating only patients with homozygous disease who were refractory to medical therapy and who seemed to have a grim short term prognosis. The fact that our first 5 patients were children may have contributed to their resistance to encephalopathy. The fate of our heterozygous adult patient will be a matter of great interest in assessing broader applicability of portal diversion for the treatment of hyperlipidemia.

The hope that vascular disease might be controlled or even regress has been supported by observations such as those in Case 1. However, a complete reversal of vascular lesions which possess a fibrotic component is often not a realistic hope even though there is dramatic resolution of the visible peripheral xanthomas and objective evidence that the same can occur within the heart valves and blood vessels. An aggressive surgical approach such as that taken in Case 2 might have saved our first patient. The combination

of coronary revascularization plus portacaval shunt used in Cases 2 and 6 deserves further trials.

Table 1. Patients with type II hyperlipidemia treated with portal diversion at the University of Colorado Health Sciences Center.

| No. | Age/Sex | Date Shunt | Cholesterol (mg%) Before | After* | Clinical State |
|---|---|---|---|---|---|
| 1 | 12 F | 3/1/73 | 770 | 290 (38%) | Died after 18 1/2 months |
| 2 | 7 F | 10/4/74 | 1000 | 400 (40%) | Excellent |
| 3 | 8 M | 8/5/75 | 1000 | 510 (51%) | Excellent |
| 4 | 5 M | 12/14/78 | 800 | 515 (64%) | Excellent |
| 5 | 14 M | 6/19/79 | 880 | 600 (68%) | Excellent |
| 6 | 52 M | 8/7/79 | 575 | 390 (68%) | Too soon to evaluate |

*Last values for living patients in late August and early September, 1979. Percentages are those of preoperative values.

References

Putnam CW, Porter KA, Starzl TE (1976) Hepatic encephalopathy and light and electron micrographic changes of the baboon liver after portal diversion. Ann Surg 184: 155-161

Starzl TE, Chase HP, Putnam CW, Porter KA (1973) Portacaval shunt for the treatment of hyperlipoproteinemia. Lancet 2: 940-944

Starzl TE, Putnam CW, Koep LJ (1978) Portacaval shunt and hyperlipidemia. Arch Surg 113: 71-74