

Commentary

Portal Diversion

Treatment for Glycogen Storage Disease and Hyperlipemia

PORTAL vein diversion has been used for many years to stop or prevent hemorrhage from esophageal varices or, less commonly, to treat intractable ascites. Since both the bleeding and ascites formation are due, at least in part, to blockage of the splanchnic venous return at or near the liver, the objective has been purely hemodynamic: relieve the obstruction, and the resulting portal venous hypertension will also be relieved.

Within the last few years, a new dimension has been added to the old operation of portacaval shunt by employing this procedure to favorably alter the course of patients with two inborn errors of metabolism, glycogen storage disease, and type II hyperlipoproteinemia. We will discuss the potential postoperative risks borne by patients submitted to portal diversion for these new indications and the probable mechanisms that explain the benefits of portacaval shunt—these have been clarified by some recent advances in hepatic physiology.

Glycogen Storage Disease

The first portal diversion¹ for hepatic glycogen storage disease was performed more than 11 years ago in a girl who is still alive. By short-circuiting splanchnic venous blood around the liver, it was hoped to make glucose more readily available to peripheral tissues, and thus to relieve hypoglycemia and incidentally to deglycogenate the liver and palliate other metabolic derangements such as acidosis. In order to avoid the potential complication of hepatic encephalopathy, which commonly follows portacaval shunt in dogs, the operation of portacaval transposition² was selected, whereby the bypassed portal flow is replaced with venous blood from the suprarenal inferior vena cava.

Transposition was also performed by Riddell et al³ of Bristol, England, in a boy who is still alive 9½ years later. In that patient, the caval-to-portal venous anastomosis clotted⁴ so that the liver was not provided with replacement flow as was intended. After a second patient of ours died from complications of the transposition,⁵ the simpler and technically safer operation of end-to-side portacaval shunt was used in all seven subsequent cases at our cen-

ter¹ and in all cases described elsewhere. Our seven survivors with end-to-side portacaval shunt have been followed up for periods of from one to three years.

The specific enzyme deficiencies in the Colorado cases⁶ were of glucose-6-phosphatase (type I disease) in five patients, amylo-1-6-glucosidase (type III B) in three patients, and phosphorylase (type VI) in one patient. Preoperatively, all the children had retardation of growth, and all but the one with type VI disease had episodic hypoglycemia and acidosis.

After portal diversion, the survivors had accelerated growth, and in all but one the height increase was in a spurt. The preexisting hypoglycemia was not relieved in some children but was variably improved in others. Liver size was either diminished or remained unchanged. In the latter event, the relative degree of hepatomegaly was steadily reduced as body growth occurred. When present, other metabolic abnormalities including secondary hyperlipemia, hyperuricemia, and platelet dysfunction were usually ameliorated. All other authors who have recorded their experience with portal diversion for glycogen storage disease have also emphasized a high degree of palliation in their patients.^{1,6-8}

Hyperlipemia

In glycogen storage disease the liver is usually patently abnormal mainly because of the accumulation of glycogen, but also because of fibrosis, which occurs in a surprisingly high percentage of cases.¹ By contrast, the liver in homozygous type II hyperlipoproteinemia, the other metabolic disease for which portacaval shunt has been performed, is morphologically normal. The explanation for the elevated serum cholesterol and low-density lipoprotein levels in this autosomal, dominant-inherited disorder is by no means understood. Goldstein and Brown⁹ have suggested that there may be an absence of or defect in the cell surface receptor sites that normally bind and transport low-density lipoprotein cholesterol into the cell. Because cholesterol does not enter the cell, they suggest that there is an absence of the normal feedback suppression of cholesterol synthesis.

Whatever its cause, the homozygous form of type II hyperlipoproteinemia has a shockingly poor prognosis if there is no good response to medical therapy. Lipid-rich deposits are laid down in widely separated, superficial and deep

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Coronary arteriogram 16 months after portacaval shunt. Diffuse narrowing of coronary arteries seen in preoperative study had resolved except for three discrete areas of occlusive disease; note one (arrow).

parts of the body, including blood vessels, in which premature atherosclerosis is the consequence. Cardiac valves are similarly affected, and aortic stenosis is particularly common. The patients usually die of cardiovascular complications before 20 years of age.

In an effort to reduce the serum cholesterol and lipoprotein levels, and with the informed consent of the child and her mother, we performed an end-to-side portacaval shunt on March 1, 1973, in an 11-year-old girl with homozygous type II hyperlipoproteinemia that was refractory to medical treatment.¹⁰ The patient had suffered a myocardial infarction about two months previously. After surgery, the serum cholesterol values fell from about 800 mg/100 ml to levels that were consistently below 400 mg/100 ml. Unsightly xanthomas began to resorb from visible subcutaneous and tendinous locations. At the same time, attacks of the preexisting angina pectoris became less frequent and finally stopped.^{10,11}

The child had cardiac catheterization three months before, which was 16 months after the end-to-side portacaval shunt was performed.¹¹ On the second occasion, there was good evidence that reversal of aortic stenosis had occurred, with a diminution of the aortic valve gradient from 56 to 10 mm Hg. The coronary arteries were also thought to be less diseased than before, although three stenoses were still present (Figure). On Sept 23, 1974, the girl died suddenly while coming home from school.

At autopsy, 18½ months after portacaval shunt, the most important findings were present in the cardiovascular system.¹² The heart weighed 510 gm (normal, 200 gm). There was a large left ventricular aneurysm, which was the result of the old myocardial infarction. The three coronary artery stenoses identified by angiography three months earlier were still present, but there were no thromboses or areas of fresh infarction. The aortic valve easily admitted the tip of a finger. Many arteries, as well as the aorta, had residual xanthomatous deposits. The right and left lungs weighed 415 and 340 gm, respectively; histologic findings consistent with the chronic right-sided heart fail-

ure, from which she had suffered since the original myocardial infarction, were present. The conclusion was that death was caused by an acute cardiac arrhythmia related to the residual coronary artery disease or to the earlier myocardial infarction.

The portacaval shunt was widely patent. The liver, which weighed 618 gm, was grossly normal, and microscopically it was unchanged from the biopsy specimen that was obtained six months postoperatively.¹⁰ On light and electron microscopy, the most prominent findings were shrinkage of the hepatocyte size, depletion of rough endoplasmic reticulum, and the accumulation of intracytoplasmic lipid deposits. Hepatic function had not been changed by portacaval shunt, as judged by standard liver function tests.

We have performed a portacaval shunt on a second patient with the same diagnosis. This 7-year-old girl had preoperative serum cholesterol values that, while she was on a very low cholesterol diet, averaged 997 ± 47 (SD) mg/100 ml. Six months after the shunt, the cholesterol level measured in the same laboratory was 600 mg/100 ml (a 40% reduction), despite a relaxation of the diet. As in the first case, this child had aortic stenosis and angina pectoris; it is too early to say if these findings will be ameliorated.

Central Registry

A plea has been made by Ahrens¹³ that all patients with homozygous type II hyperlipemia who are treated by portacaval shunt be carefully studied and faithfully reported to a central registry. In this way, the lipid-lowering qualities of portal diversion will be promptly confirmed or denied, and in addition, clinical investigations that will shed light on the reasons for the antilipemic effect of the operation should be possible. So far, we have heard of seven more similar cases treated with portacaval shunt within the last few months, but without enough details to warrant comment.

At the present time, we believe that portacaval shunt for hyperlipemia should be restricted to the highly lethal homozygous type II variety and then only if medical management fails. The certain establishment of the diagnosis and the appropriate investigation of each case require that such patients be seen in institutions that have a sophisticated interest in lipid metabolism. It is hoped that the proper study of these cases will lead to information that can be applied to other forms of hyperlipemia and the resulting premature atherosclerosis.

Mechanisms for Metabolic Change

Publications from our laboratory for the past ten years that have been summarized recently^{14,15} have shown that venous blood returning from the splanchnic organs has special liver-supporting qualities that are not provided by equal volumes of other kinds of venous or arterial blood and that can affect hepatic hypertrophy, hyperplasia, and basic function. These qualities have been ascribed mainly to the endogenous hormones, especially insulin, that are released by the splanchnic viscera and thus arrive at the liver in high physiologic concentrations. The importance

of such hormone effects on the liver probably assumes increased pertinence in hepatic homeostasis because the richness in nutrients of the same portal blood presumably contributes to important hormone-substrate interrelationships.

With end-to-side portacaval shunt, both nutritional and hormonal substances are diverted extrahepatically and may have contributed to the desired postoperative effects, both in glycogen storage disease and in hyperlipemia. Recent animal studies have demonstrated that hepatic cholesterol synthesis is greatly and permanently depressed after portal diversion, thus probably explaining most of the lipid-lowering influence of this procedure.¹⁶

Other observations^{11,17} have suggested that an increased peripheral insulinemia after portacaval shunt may explain the accelerated growth of children with glycogen storage disease. Ahrens¹³ has speculated on further possibilities and has suggested studies by which these hypotheses could be validated or repudiated.

Potential Hazards

Collectively, the special hormonal and nutritional ingredients described in portal venous blood have been termed *hepatotropic* substances. Their diversion from the liver, as with a portacaval shunt, produces derangements in either morphologic features or function of the liver; in animals this may become severe and life-threatening. The most serious complication, and one that remains a potential specter, is hepatic encephalopathy. In dogs, seizures, coma, and death occur regularly within a few weeks after portacaval shunt, at the same time as the rough endoplasmic reticulum of the hepatocytes is decreased in amount, undergoes noticeable dilatation, and is depleted of ribosomes.¹⁶ Other changes in the liver cells include deglycogenation and the widespread accumulation of lipid vacuoles in the cytoplasm.

Fortunately, the human appears resistant to the toxic effects of portal diversion. This species difference has made it possible to consider portal diversion for its metabolic effects in patients. Detectable clinical morbidity involving the liver-brain axis has not been seen in our patients who have been followed up for as long as 11 years.

Nevertheless, the clinical applications accept a "trade-off" of distinctly suboptimal conditions of liver perfusion in return for metabolic improvements that are derived from these suboptimal conditions. Realization of this fact will encourage a conservative and discriminating attitude

about the recommendation of portacaval shunt for metabolic purposes.

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