

## LIVER FUNCTION IN ADVANCED HEART DISEASE

BY

M. S. LOSOWSKY, H. IKRAM, H. M. SNOW,\*  
F. E. HARGREAVE, AND P. G. F. NIXON

*From the Departments of Medicine and of Thoracic Surgery, The General Infirmary at Leeds*

Received October 28, 1964

Anatomical and functional damage to the liver have been demonstrated in patients with heart failure (Sherlock, 1951; White *et al.*, 1951, 1955), but the relation between histological and biochemical changes is not close. We have repeatedly observed evidence of liver failure occurring unexpectedly after an uneventful operation for advanced heart disease, and this suggested that the study of liver function by sensitive and varied methods in patients with differing degrees of congestion of the liver might throw some light on the mechanism of the liver disorder and might indicate a method of selecting the patients at risk from this complication of surgical treatment.

This communication describes such a study. In addition to carrying out the routine tests of liver function, the technique of the diagnostic cardiac catheterization was modified to permit the estimation of hepatic blood flow with indocyanine green and the assessment of hepatic storage and transport function by means of the bromsulphthalein (BSP) infusion test. In certain patients these tests were repeated after the venous congestion had been relieved by medical or surgical treatment.

### SUBJECTS AND METHODS

*The Patients.* Fourteen patients with severe heart disease were selected for study because they were considered to have chronic venous congestion of the liver. The patients ranged from those with increased jugular venous and right atrial pressures only, to those with gross increase in these pressures with hepatomegaly, ascites, and œdema. The clinical degree of congestion of the liver was arbitrarily graded from 0 to + + + + according to the physical signs. The clinical details of the patients are listed in the Table.

In no patient was there any clinical or radiological evidence of pulmonary embolism, and in the 4 who came to necropsy, pulmonary embolism was not found. No patient had a history of any other ætiological factor known to produce liver disease, and none was cyanosed.

*The Investigation.* Before cardiac catheterization, routine tests of liver function (serum bilirubin, serum albumin and globulin, serum glutamic oxaloacetic and glutamic pyruvic transaminases, serum alkaline phosphatase, zinc and thymol turbidities, and prothrombin time) were performed by standard techniques, and a standard BSP retention test was carried out as described below.

The measurement of hepatic blood flow and the BSP infusion test were performed at the same time as diagnostic cardiac catheterization. Patients were supine, fasting, and premedicated with nembutal, omnopon, and scopolamine at the time of the tests.

Cardiac catheterization was accomplished with a No. 8 Cournand catheter via the right femoral vein; pressures were recorded with a Statham P23G strain gauge using the sternal angle as baseline. The right atrial pressure was taken as the maximal value during the cardiac cycle, at the end of a normal expiration.

Hepatic blood flow was measured as described by Leevy *et al.* (1962) using a constant infusion of indocyanine green injected into an arm vein, samples of arterial and hepatic venous blood being taken at frequent

\* In receipt of a Nuffield Foundation award.

intervals when blood levels were constant. The Cambridge dye-dilution ear-piece was used to ensure a constant arterial level of the dye. Before starting the infusion an initial measured priming dose of indocyanine green was rapidly injected intravenously, and arterial samples taken frequently during the next ten minutes for calculation of plasma volume by extrapolation of the curve to zero time.

Following the determination of hepatic blood flow, the BSP infusion test was carried out as described by Wheeler, Meltzer, and Bradley (1960b).

Liver biopsy, using the Vim-Silverman needle, was performed without complications in 3 patients, and the liver was examined histologically very soon after death in 4 additional patients who died subsequently.

Arterial oxygen saturation was measured by means of a Kipp hæmoreflector.

*Note on the BSP Tests.* The standard test consisted of measurement of BSP concentration in arterial blood exactly 45 minutes after a single intravenous injection of 5 mg./kg. body weight. The normal result is taken as a retention of less than 5 per cent at 45 minutes.

This simple test has been widely used as a sensitive and relatively specific test of liver function. However, prolonged infusion of BSP into the circulation might be expected to provide a greater challenge to the removal capacity of the liver, and might therefore be a very sensitive method of estimating this type of function. Furthermore, the method can be adapted to give information about the disturbances of physiological mechanisms responsible for removal of BSP from the circulation.

The handling of BSP by the liver has two components, first a storage phase (S) within the liver, which is directly proportional to the plasma level, and secondly secretion of the dye into the bile (Cantarow *et al.*, 1948; Wheeler *et al.*, 1960a, b; Schoenfield, Foulk, and Butt, 1964a). There is evidence (Wheeler *et al.*, 1960a, b; Schoenfield, McGill, and Foulk, 1964b) that secretion of BSP into the bile is limited by a maximal rate which has been termed the transport maximum (Tm). Wheeler *et al.* (1960b) have shown that a study of blood levels during infusions of BSP at different rates can be used in man to obtain measurements of hepatic storage capacity and transport maximum for BSP.

Since the procedure is rather complex, we felt it desirable to ensure that in our hands the method gave results comparable with those of other authors. Measurements were, therefore, made on 3 healthy volunteers, and all gave results, both for S and Tm, which were well within the normal ranges obtained by all other authors.

The lower limit of normal for Tm is probably not less than about 5.5 mg./min. (Wheeler *et al.*, 1960b; Combes *et al.*, 1963; Williams *et al.*, 1964; Schoenfield *et al.*, 1964a). The lower limit of normal for S is not yet clearly defined. In the original series of Wheeler *et al.* (1960b) the lowest value quoted for S in a normal subject was 23 mg./mg./100 ml., but the scatter of values is rather wide, while in the series of normal females reported by Combes *et al.* (1963) the lowest value obtained was 26.3 mg./mg./100 ml. In the normal subjects of Schoenfield *et al.* (1964a) the lowest value for S was 39.3 mg./mg./100 ml. and 2 standard deviations from the mean gives a lower limit of normal of about 32 mg./mg./100 ml., while Williams *et al.* (1964) refer to results in which a similar lower limit would be about 41 mg./mg./100 ml. In all it appears that the lower limit of normal for S is unlikely to be below about 20 mg./mg./100 ml.

## RESULTS

Patients and their diagnoses and treatments together with the results of the special BSP studies are listed in the Table. Arterial oxygen saturation was above 89 per cent in all 13 patients in whom it was measured. Right atrial pressures ranged from 5 to 35 mm. Hg above the sternal angle. The correlation between right atrial pressure and the standard BSP test is noted below.

Serum bilirubin was less than 1 mg./100 ml. in 6 out of 13 patients and less than 2 mg./100 ml. in 12 out of 13 patients. There was no significant correlation between serum bilirubin and S or Tm.

Abnormalities in other routine liver function tests appeared in only 6 patients in all. The only abnormalities found were in serum albumin (4 patients), prothrombin time (3 patients), and alkaline phosphatase (3 patients). Of these 6 patients, 3 had the lowest recorded values for S and Tm.

Hepatic blood flow was measured in 5 subjects, including the 2 with the lowest values for S, and the lowest value obtained was 420 ml./sq. m./min., and thus all measurements were above the lower limit of normal obtained by Leevy *et al.* (1962) for this method.

The standard BSP test was abnormal in every one of the 10 patients in whom it was performed, and the degree of abnormality was closely related to the height of the right atrial pressure ( $p < 0.001$ ) (Fig. 1). The BSP infusion test was performed in all 14 patients. If the figure of 20 mg./mg./100 ml.

TABLE  
CLINICAL AND BROMSULPHTHALEIN TEST DATA

Patient No., sex, and age (yr.)	Diagnosis*	Approximate duration of liver congestion	Approximate clinical severity of liver congestion	S (mg./mg./100 ml.)	Tm (mg./min.)	Standard BSP clearance (% at 45 min.)	Comment
1 F 25	MI, PH	2 wk.	+++	55	5.6	29	6 mth. after pericardectomy
2 (a) M 20	CP	6 mth.	++++	2	3.8	60	
(b)				5	4.6	19	
3 F 45	MS, MI	9 yr.	+	17	3.8	16	
4 M 54	MS, AI	2 yr.	++++	10	3.3		
5 F 24	ASD, APVD	—	0	52	7.5	8	
6 F 53	MS	1 yr.	++	61	1.0		
7 M 57	CB, myoc. isch.	2 mth.	+++	65	4.9		
8 (a) M 46	MS, MI, TI	3 yr.	++	42	1.3	42	After 2 wk. of digitalis and diuretics, poor response
(b)				47	0.8	30	
9 F 40	MI	9 mth.	+	25	4.3	6	
10 (a) F 57	MS	7 yr.	+++	2	1.2	72	6 mth. after valvotomy
(b)				36	5.1	25	
11 (a) M 19	MI, PH	3 yr.	+	34	3.6	12	1 mth. after Starr prosthesis inserted
(b)				37	5.7	5	
12 (a) M 45	MS, PH	10 yr.	+++	9	4.0	46	After 3 wk. of digitalis and diuretics
(b)				50	4.7	15	
13 F 32	MS	6 yr.	++	23	3.5		
14 F 30	MS, TI	3 yr.	+++	28	1.8	32	

\* MI=mitral incompetence; PH=pulmonary hypertension; CP=constrictive pericarditis; MS=mitral stenosis; AI=aortic incompetence; ASD=atrial septal defect; APVD=anomalous pulmonary venous drainage; CB=chronic bronchitis; myoc. isch.=myocardial ischaemia; TI=tricuspid incompetence.

is taken as the lower limit of normal for S, then only about one-third of our patients had abnormal values (Table and Fig. 2). Using 5.5 mg./min. as the lower limit of normal for Tm, this was abnormal in all except 2 of our patients (Table and Fig. 2), and of these 2, one had only a raised right atrial pressure and had never had clinical signs of congestive heart failure, and the other had had right heart failure for only two weeks and in this latter patient the Tm was only just above the lower limit of normal at 5.6 mg./min. There was a statistically significant relationship ( $p < 0.05$ ) between the result of the standard BSP test and both S and Tm.

Studies were repeated following relief of venous congestion in 5 patients. In 3 this was achieved by operation and in 2 by medical treatment. In 4 patients with serum bilirubin levels above 1 mg./100 ml. the value had returned to normal after treatment in each case. The standard BSP test showed clear improvement in all 5 patients, but in no patient was it back to normal after treatment. Treatment was followed by a conspicuous rise in S in 2 patients and a similar rise in Tm in 2 patients, with changes probably within the limits of error of the methods in the remainder (Fig. 3). The one patient with a poor response to treatment showed very little change in S or Tm.

Histology in the 7 patients (3 by biopsy and 4 at necropsy) showed no evidence of cardiac cirrhosis, and these included the most severe examples of functional disorder.

#### DISCUSSION

The results of this study confirm that severe impairment of liver function may occur in heart failure.

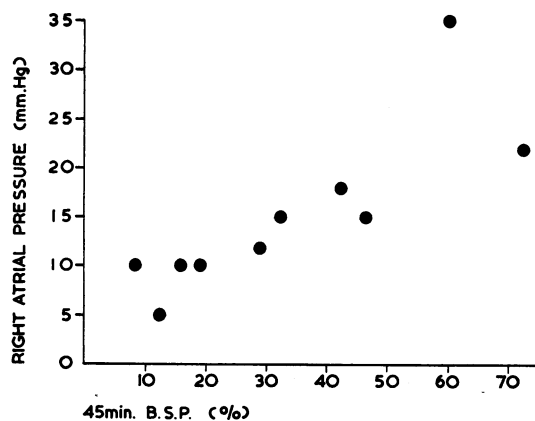


FIG. 1.—Results of the standard BSP clearance test plotted against right atrial pressure. A close correlation is shown.

In confirmation of the findings of other workers (Kugel and Lichtman, 1933; Chávez, Sepúlveda, and Ortega, 1943; Felder, Mund, and Parker, 1950; Sherlock, 1951; Evans *et al.*, 1952; White *et al.*, 1955; Levine and Klatskin, 1964) the serum bilirubin in our patients was frequently above the upper limit of normal of 1 mg./100 ml. Pulmonary embolism did not contribute to the rise in serum bilirubin in any of these patients, as far as could be ascertained by clinical, radiological, and necropsy studies, though clinical jaundice was never more than minimal. Thus, though some rise in serum bilirubin is not infrequent in uncomplicated heart failure, these findings do not contradict those of earlier workers (Kugel and Lichtman, 1933) who suggested that marked jaundice is usually associated with pulmonary embolism. The absence of a conspicuous rise in serum bilirubin occurred despite values for right atrial pressure as high as 36 and 22 mm. Hg indicating that severe obstruction to bile flow is not necessarily produced by pressures of this magnitude as has been suggested might occur (Sherlock, 1945).

Apart from these slight rises in serum bilirubin, abnormalities in any of the commonly used liver function tests were infrequent in these patients. Transaminases and turbidity tests were normal in all, and abnormalities in one or other of prothrombin time, alkaline phosphatase or plasma albumin concentration occurred in only 6 patients, usually only when hepatic storage capacity was severely depressed. Thus, it appears that the conventional liver function tests reflect only severe functional impairment in the liver damage of heart failure.

2Q

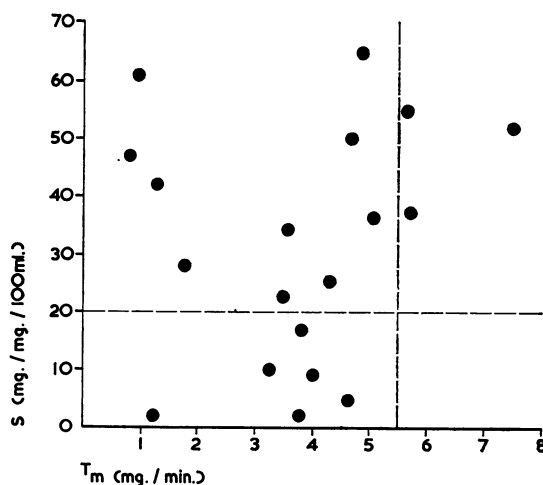


FIG. 2.—Hepatic storage capacity (S) and transport maximum (Tm) for BSP in patients with congestion of the liver. The broken lines indicate the approximate lower limits of normal for S and Tm (see text). Values for Tm are almost always abnormal before treatment while values for S are frequently normal.

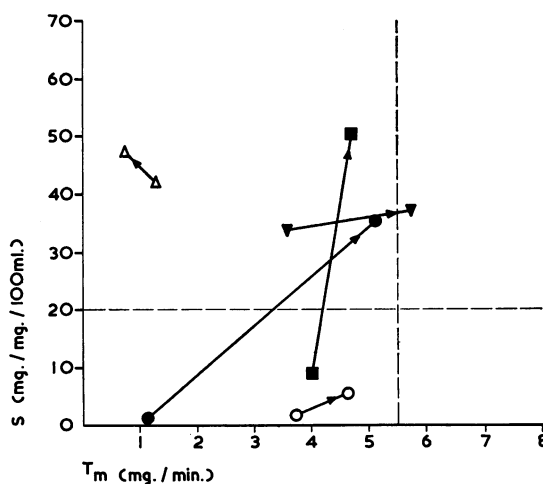


FIG. 3.—Changes in hepatic storage capacity (S) and transport maximum (Tm) for BSP after medical or surgical treatment. In 2 patients there was a steep rise in S and in 2 patients there was a similar rise in Tm; changes in the remaining patients are probably within the limits of error of the method.

In contrast, the standard BSP clearance test was always abnormal in these patients, and would thus appear to be a very sensitive index in this type of liver damage. The removal of BSP from the circulation is probably not interfered with by bilirubin unless the concentration of bilirubin is greater than about 2 mg./100 ml. (Zieve, Hanson, and Hill, 1951), and thus the small increases in serum bilirubin could not explain the abnormal BSP tests in these patients.

Assuming a lower limit of normal for transport maximum of 5.5 mg./min., values were abnormal in all except 2 of our patients, and of these 2 one had only a raised right atrial pressure and had never had clinical signs of congestive heart failure, and the other had been in heart failure for only two weeks, and in this latter patient the Tm was only just above the lower limit of normal. It therefore appears likely that the Tm is affected early in the course of congestion of the liver.

Assuming a lower limit of normal for S of 20 mg./mg./100 ml., only about one-third of these patients had abnormal results, while even if the lower limit of normal is put as high as 40 mg./mg./100 ml. only about two-thirds of the results were abnormal, suggesting that perhaps storage capacity is affected later than excretory capacity in the congested liver. In confirmation of this it was found that in no patient was the storage phase (S) grossly abnormal unless the congestion was severe, or of some years' duration, or both. Even though the load of BSP presented to the liver is very much greater in estimating S and Tm than in the standard test, it might be expected that the results would be related, and both S and Tm did show a significant correlation with the standard test.

The results of this study suggest that the mechanism responsible for the abnormalities of liver function in advanced heart disease may be the venous congestion alone. Evidence in favour of this is the highly significant correlation between the right atrial pressure and the standard BSP test, in confirmation of the findings of other workers (Evans *et al.*, 1952), and the improvement in this test after treatment. The normal values for S and Tm in control subjects and in some of the patients makes it unlikely that the premedication contributed significantly to the low results. The notable rises in S and Tm that can occur after relief of the congestion by medical or surgical treatment also suggest that impairment of function might be directly due to the congestion. In the patients treated medically, improvement in the removal of BSP from the circulation might also be explained by the stimulation of microsomal enzyme activity by some of the drugs used (Fouts, 1963; Burns, Conney, and Koster, 1963), enabling the infused BSP to be metabolized more rapidly. However, in 3 of our patients, improvement followed operation, and in 2 of these no drugs were being administered for some weeks before the second series of measurements. This too would favour the view that congestion itself directly impairs liver function and that relief of congestion can result directly in improvement.

A reduction in blood flow to the liver may occur in some patients with heart failure (Myers and Hickam, 1948), but this did not appear to contribute to the mechanism of liver damage in our patients since measurements showed normal liver blood flow even in those with the most severe abnormalities in the BSP tests. Though significant arterial unsaturation was not present in these patients, in the absence of information about the oxygen content of the portal blood reaching the liver it is unwise to rule out the possibility that anoxia contributed to the impairment of liver function, though this seems unlikely.

Cardiac cirrhosis was not found in any of the 7 patients in whom histology was available, and thus the abnormalities cannot be attributed to liver damage consequent upon fibrosis, and presumably the derangements in liver function in all these patients were potentially reversible.

In attempting to determine the patients at risk from liver failure after major cardiac surgery we wished to compare a number of tests of liver function to decide which were both sensitive enough and simple enough to be used as a routine, and it appears that the conventional BSP retention test satisfies both these requirements.

We have shown that severe functional impairment of the liver occurs without cardiac cirrhosis, and in view of the poor correlation between the more minor histological changes and biochemical abnormalities it seems that liver biopsy is unlikely to be of much help in the assessment of patients for major heart surgery.

The BSP infusion test provides information about the mechanism of the functional abnormality, but is extremely time-consuming for routine use. Its value in indicating the risks of operation in these patients can only be defined by a large series of measurements, but it is suggestive that our patient with the lowest value both for S and Tm developed post-operative jaundice.

This study indicates the need for reopening the question of liver damage in heart failure in the context of the selection of patients for major cardiac operations. The results suggest that the standard BSP retention test and right atrial pressure may be valuable and convenient parameters for repeated observations in a large-scale prospective study.

#### SUMMARY AND CONCLUSIONS

Liver function tests including measurement of hepatic blood flow, and storage and transport functions of the liver for bromsulphthalein have been performed in 14 patients with advanced heart disease and hepatic venous congestion.

The more usual tests were often normal despite considerable impairment of function as indicated by the BSP tests.

The standard BSP retention test was abnormal in all patients and closely paralleled the right atrial pressure. The transport maximum for BSP was abnormal in almost all patients, while storage capacity for BSP was abnormal only if congestion was of some years' duration or if there were gross physical signs or both.

Histology and measurements of hepatic blood flow demonstrated that these abnormalities in liver function were not due to cardiac cirrhosis or to impairment of blood flow to the liver.

Improvement in liver function after medical or surgical treatment, together with the close relationship between the standard BSP test and right atrial pressure, confirmed that congestion itself was the basic cause of the liver dysfunction.

In view of the occurrence of liver failure following major cardiac surgery, it is suggested that assessment of liver function may be of help in defining the patients at risk, and that the standard BSP test may be a convenient test for repeated routine use.

We would like to thank the physicians and surgeons who referred patients and the Nuffield Foundation for financial support.

#### REFERENCES

- Burns, J. J., Conney, A. H., and Koster, R. (1963). Stimulatory effect of chronic drug administration on drug-metabolizing enzymes in liver microsomes. *Ann. N.Y. Acad. Sci.*, **104**, 881.
- Cantarow, A., Wirts, C. W., Jr., Snape, W. J., and Miller, L. L. (1948). Excretion of bilirubin and bromsulphthalein in bile. *Amer. J. Physiol.*, **154**, 211.
- Chávez, I., Sepúlveda, B., and Ortega, A. (1943). The functional value of the liver in heart disease. An experimental study. *J. Amer. med. Ass.*, **121**, 1277.
- Combes, B., Shibata, H., Adams, R., Mitchell, B. D., and Trammell, V. (1963). Alterations in sulfobromophthalein sodium-removal mechanisms from blood during normal pregnancy. *J. clin. Invest.*, **42**, 1431.
- Evans, J. M., Zimmerman, H. J., Wilmer, J. G., Thomas, L. J., and Ethridge, C. B. (1952). Altered liver function of chronic congestive heart failure. *Amer. J. Med.*, **13**, 704.
- Felder, L., Mund, A., and Parker, J. G. (1950). Liver function tests in chronic congestive heart failure. *Circulation*, **2**, 286.
- Fouts, J. R. (1963). Factors influencing the metabolism of drugs in liver microsomes. *Ann. N.Y. Acad. Sci.*, **104**, 875.
- Kugel, M. A., and Lichtman, S. S. (1933). Factors causing clinical jaundice in heart disease. *Arch. intern. Med.*, **52**, 16.
- Leevy, C. M., Mendenhall, C. L., Lesko, W., and Howard, M. M. (1962). Estimation of hepatic blood flow with indocyanine green. *J. clin. Invest.*, **41**, 1169.
- Levine, R. A., and Klatskin, G. (1964). Unconjugated hyperbilirubinemia in the absence of overt hemolysis. Importance of acquired disease as an etiologic factor in 366 adolescent and adult subjects. *Amer. J. Med.*, **36**, 541.
- Myers, J. D., and Hickam, J. B. (1948). An estimation of the hepatic blood flow and splanchnic oxygen consumption in heart failure. *J. clin. Invest.*, **27**, 620.
- Schoenfeld, L. J., Foulk, W. T., and Butt, H. R. (1964a). Studies of sulfobromophthalein sodium (BSP) metabolism in man. I. In normal subjects and patients with hepatic disease. *J. clin. Invest.*, **43**, 1409.
- , McGill, D. B., and Foulk, W. T. (1964b). Studies of sulfobromophthalein sodium (BSP) metabolism in man. III. Demonstration of a transport maximum (Tm) for biliary excretion of BSP. *J. clin. Invest.*, **43**, 1424.
- Sherlock, S. (1951). The liver in heart failure. Relation of anatomical, functional, and circulatory changes. *Brit. Heart J.*, **13**, 273.

- Sherlock, S. P. V. (1945). Jaundice in heart failure. *Quart. J. Med.*, **14**, 222.
- Wheeler, H. O., Epstein, R. M., Robinson, R. R., and Snell, E. S. (1960a). Hepatic storage and excretion of sulfobromophthalein sodium in the dog. *J. clin. Invest.*, **39**, 236.
- , Meltzer, J. I., and Bradley, S. E. (1960b). Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanesthetized dog, in normal man, and in patients with hepatic disease. *J. clin. Invest.*, **39**, 1131.
- White, T. J., Leevy, C. M., Brusca, A. M., and Gnassi, A. M. (1955). The liver in congestive heart failure. *Amer. Heart J.*, **49**, 250.
- , Wallace, R. B., Gnassi, A. M., Kemp, N. F., Price, H. P., and Leevy, C. M. (1951). Hepatic abnormalities in congestive heart failure. Needle biopsy studies. *Circulation*, **3**, 501.
- Williams, R., Cartter, M. A., Sherlock, S., Scheuer, P. J., and Hill, K. R. (1964). Idiopathic recurrent cholestasis: A study of the functional and pathological lesions in four cases. *Quart. J. Med.*, **33**, 387.
- Zieve, L., Hanson, M., and Hill, E. (1951). Studies of liver function tests. II. Derivation of a correction allowing use of the bromsulphalein test in jaundiced patients. *J. Lab. clin. Med.*, **37**, 40.