

Jaundice following open-heart surgery

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Singh, H. M., and Baker, J. T. (1974). *Thorax*, 29, 68-74. Jaundice following open-heart surgery. A study was made into the factors influencing the onset of jaundice in 102 patients undergoing valve replacement during cardiopulmonary bypass. Postoperative jaundice appeared to be correlated with double valve replacement, the co-existence of an uncorrected valvular lesion, length of perfusion and myocardial ischaemia times, and also the age of the patient. Factors appearing not to be correlated with the onset of jaundice included pre-operative pulmonary artery pressure, cardiac index, parameters of preoperative renal and hepatic function, and the amount of blood used during bypass. The biochemical features of the jaundice seemed to follow a pattern not previously recognized in this context, with sometimes considerably raised bilirubin levels in association with virtually normal levels of transaminases and alkaline phosphatase.

Jaundice in the early postoperative period is a well recognized complication of cardiopulmonary bypass, although its causes are not always obvious. Lockey *et al.* (1967) considered a high central venous pressure and the use of homologous blood as important causes, haemolysis, heart failure, and infection being contributory to it. Mundth, Keller, and Austen (1967), who described three jaundiced patients in low output state postoperatively, suggested that long-standing postoperative pulmonary hypertension and biventricular failure were of aetiological importance. However, Sanderson, Ellison, Benson, and Starr (1967) considered that shock and anoxia were causative factors, but that haemolysis and preoperative cardiac-pulmonary and hepatic status bore no relation to the aetiology of postoperative jaundice.

Because of these various views, a study of 102 patients undergoing prosthetic cardiac valve replacement was undertaken from January 1971 in an attempt to evaluate possible causative factors in its genesis. An incentive to the study was the relatively high incidence of postoperative jaundice; 21% of the patients had serum bilirubin levels above 6 mg % with 13 deaths (13%).

MATERIALS AND METHODS

The 102 cases comprised 53 males and 49 females, their ages ranging from 9 to 69 years; 42 were aged

between 41 and 50 years and 35 between 51 and 60 years. Table I shows the various procedures performed.

TABLE I

Replacements Carried Out	No. of Patients
Mitral valve replacement	50
Aortic valve replacement	32
Mitral valve replacement + aortic valve replacement	13
Mitral valvotomy + aortic valve replacement	3
Mitral valve replacement + aortic valvotomy	2
Mitral valve replacement + tricuspid valve replacement	1
Mitral valve replacement + aortic valve replacement + tricuspid valve replacement	1
Total	102

PREOPERATIVE CLINICAL STATUS Fifty-seven patients were in grade IV and the remainder in grade III of the New York Heart Association classification. There was a previous history of jaundice in nine patients and the liver was palpably enlarged in 23 patients (23%).

The main pulmonary artery pressure (systolic) was below 40 mmHg in 40 patients, between 41 and 80 mmHg in 39 patients, and above 80 mmHg in 12 patients. The cardiac index (Fick principle) measured at preoperative investigations in 78 patients was below 2 l/min/m² surface area in 16 patients, between 2 and 3 l/min/m² in 40 patients, and over 3 l/min/m² in 32 patients.

Blood urea was below 40 mg % in 70 patients, between 40 and 60 mg % in 25 patients, and over 60 mg % in three patients. Creatinine clearance values, measured in 87 patients, were below 40 ml/min in 11 patients, between 40 and 80 ml/min in 55 patients, and above 80 ml/min in 21 patients.

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Table II shows preoperative serum bilirubin levels in our patients. Alkaline phosphatase was raised in 11 patients. Serum aspartate aminotransferase (SGOT) levels were above 40 units in eight patients and serum alanine aminotransferase (SGPT) levels were similarly raised in three patients.

TABLE II

Serum Bilirubin (mg/100 ml)	No. of Patients
Below 1	47
1·1 to 2	39
2·1 to 4	16
Total	102

ANAESTHESIA AND PERfusion Halothane was not used as an anaesthetic agent, and cardiopulmonary bypass with moderate hypothermia (28° – 30° C), using either a Kay-Cross disc oxygenator or a Rygg Kyvsgaard disposable bubble oxygenator, was employed in all patients. Priming fluid contained a minimum amount of blood and Ringer lactate solution. On bypass, serum potassium (K), haematocrit (PCV), and arterial and mixed venous P_{O_2} , P_{CO_2} , and standard bicarbonate (Astrup) were monitored. Addition of blood to the perfusate was indicated if the PCV fell below 30. Flow rates were between 2·4 and 3·0 l/min/m² surface area at all times. The average perfusion time for single valve replacement was 72 minutes and for double valve replacement 138 minutes. Table III shows the duration of myocardial ischaemia from intermittent aortic cross clamping. The average amount of blood used during the operation was 3·8 units ($\pm 1\cdot3$). All donors and recipients were screened for Australia antigen and were proved negative.

TABLE III

Ischaemic Period (min)	No. of Patients
Less than 20	54
20-40	24
Over 40	24
Total	102

POSTOPERATIVE PERIOD Blood gases, arterial and mixed venous, electrolytes, blood urea, PCV, and platelet counts were monitored frequently in the early postoperative period. Central venous pressures (CVP), mean blood pressure (BP), and hourly urine output were measured during this period. Liver function tests, direct and indirect serum bilirubin levels, Coombs' test, serum haptoglobin, fibrinogen titres, and fibrinogen degradation products were determined in those patients with jaundice persisting for more than 48 hours. Hepatic washout curves using indocyanine green dye were obtained in four patients. Bacteriological examination of the sputum, tracheal secretions, wound drainage, urine, and blood was available every day. Drugs such as chlorpromazine or novobiocin were not used.

Three groups of patients were identified by the levels of serum bilirubin in the postoperative period:

Group A: Serum bilirubin below 2 mg%

Group B: Serum bilirubin 2–6 mg%

Group C: Serum bilirubin over 6 mg%

Clinical and perfusion profiles were compared in the three groups, and to derive mean clinical values (MCV) scores of 0 were awarded to those with normal or average values for each parameter, 1 to those with a moderate increase in values, and 2 to those with grossly exaggerated values, after the method of Atkins (1958). The scores achieved in each group were divided by the number of patients in each group, and the answer (MCV) multiplied by 100 in order to achieve a manageable whole number for graphical purposes. A difference of 20 in the value of $MCV \times 100$ (P value $<0\cdot002$) was considered significant. A similar comparison was also made between 13 patients from group C who had a serum bilirubin level of over 6 mg% and succumbed from hepatorenal failure (group C1) and 10 patients in group C who had a similar rise but survived the operation (group C2).

RESULTS

In the first 48 hours after cardiopulmonary bypass (Fig. 1), 21 patients were in group A, and these were the patients who made an uneventful recovery; 61 patients were in group B, and all but two gradually recovered; the remaining 20 patients were in group C, and half the number of this group eventually died from complications of hepatorenal failure and infection. At the end of one week group A comprised 40 patients, group B 44 patients, and group C 18 patients.

Figure 2 shows positive correlations between double valve replacement, the presence of an associated uncorrected valvular lesion, length of perfusion and myocardial ischaemic times, and development of postoperative jaundice. But there was no correlation between the preoperative pulmonary artery pressure, cardiac index, serum bilirubin, blood urea, and creatinine clearance values, or the amount of blood used during cardiopulmonary bypass, and the development of jaundice. However, a significant number of patients (three) in group C gave a previous history of jaundice. As shown in Fig. 3, the survival of group C patients depended on age as well as on factors influencing the development of jaundice. Thus older patients in this group undergoing double valve replacement or having an associated uncorrected valvular lesion with single valve replacement, longer perfusion or myocardial ischaemic time invariably died; younger patients undergoing single valve replacement with a shorter perfusion time and a short myocardial ischaemic period developed jaundice but survived the operation.

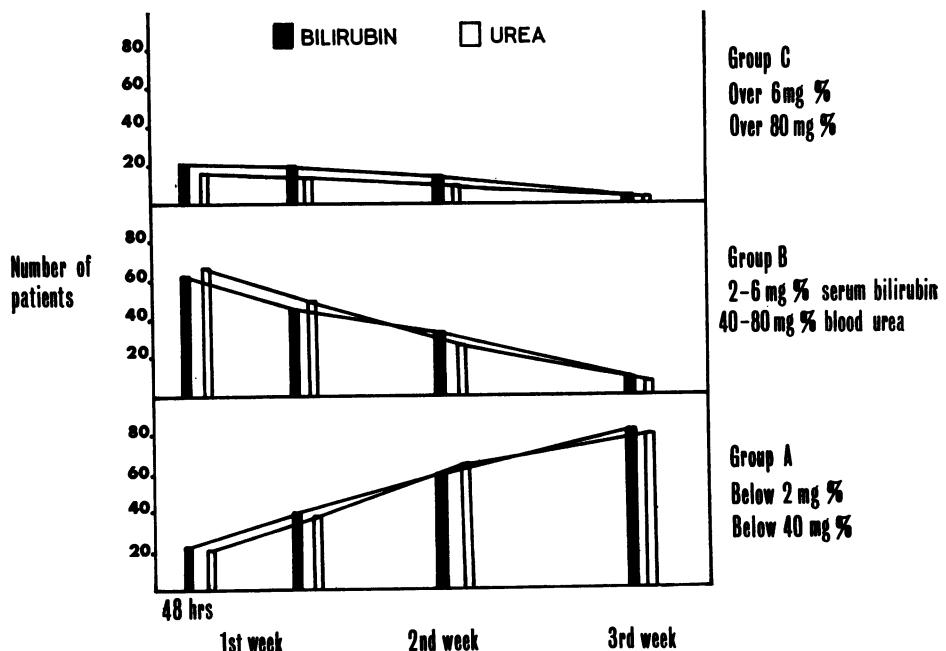


FIG. 1. Distribution of patients in the three groups after prosthetic valve replacement.

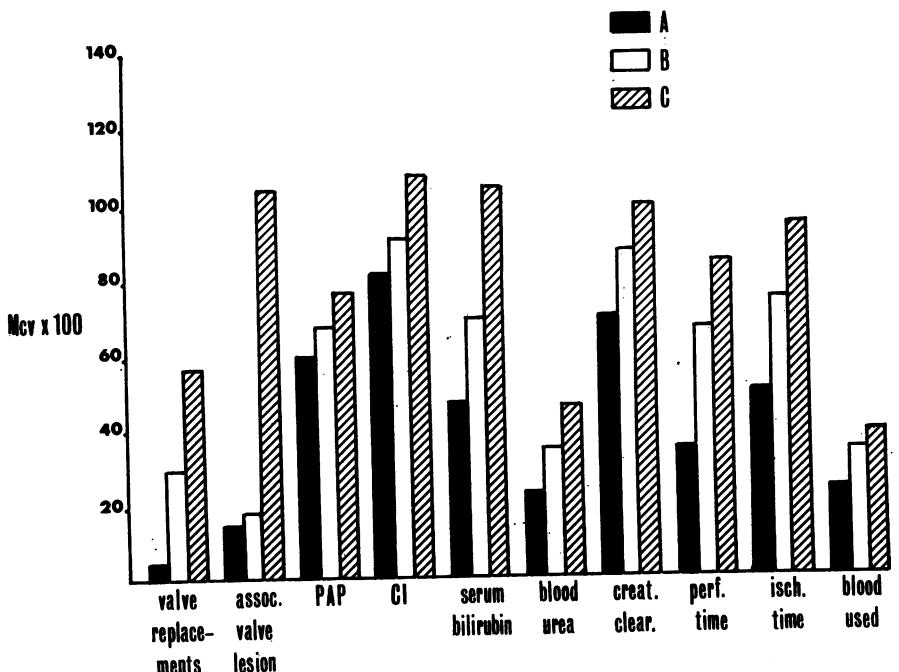


FIG. 2. Comparison of $MCV \times 100$ values of the risk factors in the three groups of patients.

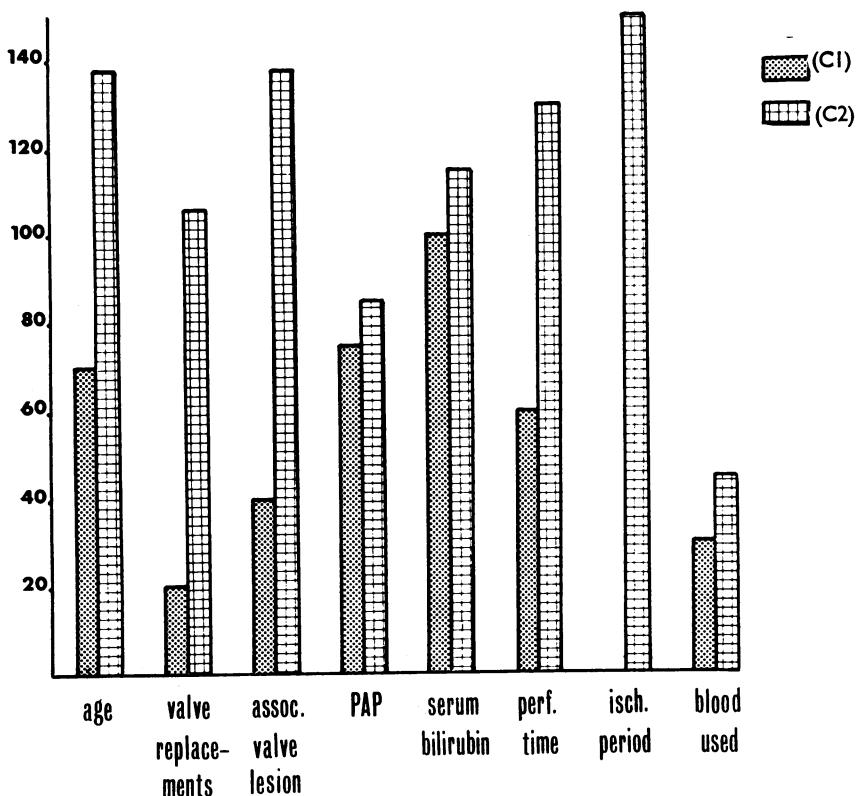


FIG. 3. Comparison of $MCV \times 100$ values of the risk factors in the subgroups C1 and C2.

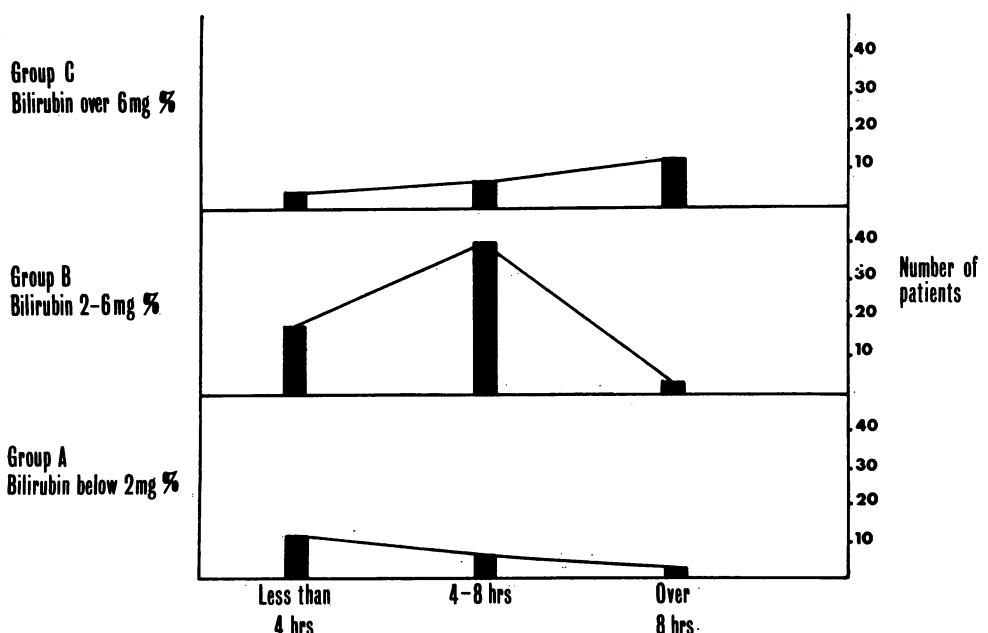


FIG. 4. Correlation of postoperative bilirubin level with duration of reduced venous oxygen saturations after valve replacement in the three groups of patients.

Figure 4 shows a direct correlation between the duration of a low mixed venous oxygen saturation immediately postoperatively and subsequent development of jaundice. This suggests that a prolonged low cardiac output state postoperatively plays a role in the development of jaundice. The level of BP, urine output, and arterial oxygen saturation did not show any significant correlation in this regard. The frequency of ventricular ectopics in the postoperative period was nearly twice in those who developed jaundice compared to those who did not. Although attempts to monitor the postoperative central venous pressure were made, several factors made the assessment of its significance difficult. There was considerable variation in each patient's CVP during the postoperative period. Together with this there was a considerable rate of blockage of intravenous catheters used in the measurement. Because of these difficulties it was impossible to achieve a meaningful assessment of the significance of postoperative central venous pressure in the aetiology of post-perfusion jaundice.

TYPES OF JAUNDICE Studies, mainly in group C patients, showed that in 18 of 21 patients the conjugated bilirubin formed 90% or more of the total bilirubin, and in the remaining three, who were known to regurgitate through the prosthesis, the level was 50–75% of total bilirubin. SGPT values were normal in all patients. A rise in alkaline phosphatase occurred in five patients at a time when the serum bilirubin level was dropping. Moderate to severe impairment of dye washout curves was seen in all the three patients studied. Low fibrinogen titres as well as the presence of fibrinogen degradation products were seen in seven patients. Alkalosis, hypoglycaemia, and a bleeding state were encountered terminally.

INFECTION The presence of infection was associated with a deteriorating clinical picture. Necropsy in eight of the 13 patients who died of hepatorenal failure revealed the infective states shown in Table IV.

TABLE IV

Infective State	No. of Patients
Gram-negative organism causing pneumonia and bronchopneumonia	6
E. coli peritonitis following peritoneal dialysis	1
Gram-negative septicaemia	1

DISCUSSION

Our findings are in agreement with those of Sanderson *et al.* (1967) that the preoperative car-

diac, pulmonary or hepatic status of the patients bore little relation to the development of jaundice in the postoperative period and, further, that the degree of haemolysis and incidence of infection played no part in its occurrence. Because of the difficulties in monitoring and the interpretation of postoperative CVP, it was impossible to clarify the significance of this parameter in the incidence of post-perfusion jaundice. However, in contrast with the conclusions of Lockey *et al.* (1967), it was felt likely that a high CVP merely indicated failure of the myocardial pump. The ensuing reduction of cardiac output would then be the more likely significant factor in the aetiology of jaundice. It can rightly be pointed out that this study did not in fact separate these factors definitively from one another, and one can only presume that the reduced cardiac output was the critical factor. Our findings suggest that the need for double valve replacement, the presence of a residual or associated valvular lesion, and longer perfusion and myocardial ischaemic time were more likely to result in jaundice in the post-operative period, particularly when there was a period of prolonged reduction of mixed venous oxygen saturation after valve replacement. Jaundice proved fatal in the elderly patients who had serum bilirubin levels of over 6 mg % during the first 48 hours. Our findings also suggest that the prolonged period of reduced cardiac output, as indicated by the low mixed venous oxygen saturation, was due to events occurring during cardiopulmonary bypass; the preoperative clinical and haemodynamic state did not appear to be causatively related. This finding, although at variance with the views of Mundth *et al.* (1967), who believed that jaundice could be attributed to pre-operative biventricular failure and raised pulmonary artery pressure, might suggest that the factors existing during cardiopulmonary bypass examined by us affected the outcome adversely in these patients, and that tolerance for these factors in the severely ill patient is very small indeed. The preoperative PAP and presence of biventricular failure did not appear to influence the occurrence of jaundice in the 102 cases studied.

The type of jaundice in this group of patients was characterized by the presence of conjugated hyperbilirubinaemia and moderately severe delay in the excretion of indocyanine green dye without any of the other hepatic function tests being abnormal. There was no rise in SGPT values to suggest hepatic necrosis nor was there any rise in alkaline phosphatase level to indicate obstruction at canalicular level. This last type of jaundice is encountered in the rare Dubin Johnson syndrome

where there is a defect in the excretion of the conjugated bilirubin and dyes such as bromsulphalein and indocyanine green from the hepatic cell into the bile canaliculi. The secretion of bilirubin in this situation seems to be the limiting step in the overall excretion of bilirubin. Conjugated bilirubin is less firmly bound to albumin than is free bilirubin and some enters the urine as seen in our patients.

It is interesting to contrast the cholestatic jaundice described in another group of patients post-operatively with that seen in those cases (Schmid *et al.*, 1965). Eleven cases were described occurring in the course of eight months at a German surgical centre. They all had considerably raised bilirubin levels with normal enzyme levels, and only moderately raised or even normal alkaline phosphatase. None of the operations involved perfusion, but included a series of major procedures such as gastrectomy and lobectomy. The condition was considered benign, but in fact six of the patients died of intercurrent disease such as pulmonary embolus. This would suggest that patients did not die with the commonly recognized features of hepatorenal failure but of some other cause. The high incidence of this unusual syndrome in the German centre and in Sully Hospital might suggest an endemic factor such as an infective agent. This unknown factor might then prime the liver to respond in this manner in the presence of a low cardiac output. However, in the other series involving both perfusion (Lockey *et al.*, 1967) and also hypothermia (Kingsley, 1966) a few similar cases can be seen when detailed liver function tests are studied. In the German group of patients hypotension and hypoxaemia were implicated in the aetiology (Lamont and Isselbacher, 1973).

We suggest that the period of low cardiac output following nonpulsatile flow during cardiopulmonary bypass might in some way lead to the post-conjugation block of bilirubin. A decrease in hepatic perfusion due to a combination of low cardiac output and splanchnic vasoconstriction with a reduction in portal blood flow has been postulated by Mundth *et al.* (1967) and others (Longerbeam, Lillehei, Scott, and Rosenberg, 1962; Shoemaker, Szanto, and Andersen, 1965) in the pathophysiology of postoperative jaundice. Whether a similar process is involved in the post-conjugation block at the hepatic cell level is unknown. That the process is reversible up to a certain stage is indicated by the recovery of three patients with a serum bilirubin of over 25 mg %.

We are continuing a further study of post-bypass jaundice using a comparison of decay

curves with indocyanine green and radio-isotopically labelled colloid. In this way we hope to separate disturbances of hepatic blood flow from a decrease in the extraction efficiency of indocyanine green. Studies of hepatic dysfunction in childhood (Stiehl, Thaler, and Admirand, 1972) suggest that phenobarbitone not only induces microsomal enzymes, thus increasing the glucuronidization of bilirubin, but also increases the transport of the complexed bilirubin from the hepatic cell. This would suggest a place for phenobarbitone prophylaxis in cases known to be at particular risk from this syndrome of hepatic dysfunction.

CONCLUSIONS

The longer the duration of reduced cardiac output in the postoperative period, as judged by low mixed venous oxygen saturation, the greater was the likelihood of jaundice appearing in the post-operative period. The causes of a low cardiac output state would seem to be attributable to the period of cardiopulmonary bypass procedure and bore little relation to the preoperative cardiac, pulmonary or hepatic status of the patient. It is unknown how the post-conjugation block at the hepatic cell level results from the low output state, and whether the antecedent period of non-pulsatile flow in any way contributes to it. The bilirubin levels were considerably raised in the more severe cases with normal transaminases and only moderately raised or normal alkaline phosphatases. Phenobarbitone therapy may be a useful prophylaxis for patients known to be at risk from this particular syndrome of hepatic dysfunction.

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