Postoperative Hyperbilirubinemia and Gilbert’s Syndrome in Patients Undergoing Cardiac Surgery

Abstract
We report a series of seven patients with Gilbert’s syndrome undergoing cardiac surgery. Early and transient increase of total, direct, and indirect bilirubin without other complications was observed. Although this is a benign process, we believe that this disease should be routinely included in the differential diagnosis of postoperative jaundice after cardiopulmonary bypass.

Keywords: Cardiac surgery, Gilbert’s syndrome, postoperative hyperbilirubinemia

Introduction
Postoperative hyperbilirubinemia is observed in 25%–35% of patients undergoing cardiac surgery. It usually has a benign and self-limited course although it is associated with higher hospital mortality.[1-3] Predisposing factors include preoperative hyperbilirubinemia,[1,2] elevated central venous pressure,[1,2] mechanical valve replacement,[1,2] prolonged cardiopulmonary bypass,[1,2] blood transfusion, and low cardiac output.[1,3] The etiopathogenesis is multifactorial and includes hemolysis associated with cardiopulmonary bypass and valve replacement, congestion, inflammation, and hepatic ischemia. Postoperative jaundice has been associated with increased total bilirubin at the expense of direct and indirect bilirubin.[1-3]

Gilbert’s syndrome is an autosomal recessive hereditary disorder characterized by a defect in hepatic bilirubin glucuronidation due to a mutation of the UGT1A1 gene encoding uridine diphosphate-5’-glucuronosyltransferase. Most subjects with Gilbert’s syndrome are homozygous for the variant (TA)7, and they often present with intermittent, nonhemolytic hyperbilirubinemia at the expense of indirect bilirubin.[4] It is estimated that approximately 9% of the population is homozygous although not all patients develop hyperbilirubinemia. The serum concentration of bilirubin may increase in some circumstances such as sleep deprivation, dehydration, surgical stress, physical exercise, fasting, and common diseases. Gilbert’s syndrome is a benign process without liver injury. It does not lead to reduced life expectancy and has even been suggested that the antioxidant effect of indirect bilirubin may exert a cardioprotective effect.[4]

Although it is a frequent disorder, the information on the evolution of serum bilirubin in cardiac surgical patients with Gilbert’s syndrome is controversial and limited to isolated cases.[5,6]

Case Report
We report a series of patients with Gilbert’s syndrome undergoing cardiopulmonary bypass. The clinical outcome and the evolution of the analytical parameters are described. This work has been carried out in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee. Written informed consent was obtained from all patients.

Six men and one woman (age 68.5 ± 9.8 years) underwent surgery for isolated aortic valve replacement,[3] repair of mitral and tricuspid valves,[3] and coronary artery bypass graft surgery.[1] Genetic diagnosis of Gilbert’s syndrome was performed by extraction of peripheral blood DNA, amplification by polymerase chain reaction and sequencing, resulting in seven cases homozygous for the variant (TA)7.

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The postoperative course was uneventful. Table 1 summarizes the serum concentration of liver function markers.

All patients had a preoperative total and indirect bilirubin concentration above normal. We observed an early and transient increase of total, direct, and indirect bilirubin in the postoperative period. The maximum concentration occurred at 6 h of the procedure, but in any case, it reached the double of the preoperative value. Subsequently, a gradual decrease took place [Figure 1]. Seventy-two hours after the intervention, the total, direct, and indirect bilirubin value was lower than the preoperative value. The three patients who had a repair of mitral and tricuspid valves showed a preoperative concentration of total, direct, and indirect bilirubin as well as a peak postoperative peak above the rest. This finding was interpreted as a consequence of hepatic congestion.

**Discussion**

Compared with other published studies, in our series, the increase of bilirubin was earlier and of shorter duration. Minami et al. observed an acute perioperative decrease in total and indirect bilirubin followed by a postoperative increase with a peak at the 4th postoperative day without exceeding the baseline value.[5] Subsequently, a gradual decrease was observed, and from the 16th postoperative day, the total and indirect bilirubin concentration was lower than the preoperative one. Nishi et al. demonstrated a postoperative increase of total, direct, and indirect bilirubin from the end of the intervention with a peak at the 5th postoperative day that doubled the preoperative value.[6] Subsequently, there was a progressive decrease in total and indirect bilirubin concentration reaching 50% of the preoperative value at 3 months after surgery.

In our series, we found that 1 week after the procedure, the total, direct, and indirect bilirubin concentration was lower than the preoperative one. This finding has been justified in patients undergoing mitral surgery by a reduction in hemodynamic overload when correcting the valve

![Figure 1: Mean serum concentration of bilirubin in preoperative and after 6, 24, 48, 72 h, 7 days and 1 month since the surgical intervention](image)

![Table 1: Plasma concentration of markers of liver function in preoperative and after 6, 24, 48, 72 h, 7 days, and 1 month since the surgical intervention](image)
incompetence. However, all of our patients, including the aortic and coronary patients, showed this same behavior so it is possible that other factors could be involved.

Regarding the other analytical parameters studied, we observed a transient increase in serum transaminases attributed to the inflammatory response associated with extracorporeal circulation. We also demonstrated a decrease in albumin and total protein content interpreted as a consequence of hemodilution and the adsorption of proteins on the oxygenator.

We can conclude that patients with Gilbert’s syndrome undergoing cardiac surgery present an early and transient increase of total, direct, and indirect bilirubin without other complications. Although this is a benign process, we believe that this disease should be routinely included in the differential diagnosis of postoperative jaundice.

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**Conflicts of interest**

There are no conflicts of interest.

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