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Bile duct ligation in rats: A reliable model of hepatorenal syndrome?

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Abstract

The two most widely used experimental models of advanced liver disease are the administration of carbon tetrachloride, and common bile duct ligation (BDL), however, neither has been systematically evaluated as a model of hepatorenal syndrome (HRS). The BDL model in rats, studied at diverse time points, induced a progressive renal dysfunction without structural changes in the kidney. The authors concluded that BDL is a good model for further studies of HRS and its treatment. However, the renal impairment observed at the acute phase of the BDL model is based on a different pathophysiology than that of HRS. Specifically, in acute obstructive jaundice, cholemia predominates over parenchymal liver disease (reversible at this stage without portal hypertension or cirrhosis) and independently induces negative inotropic and chronotropic effects on the heart, impaired sympathetic vasoconstriction response and profound natriuresis and diuresis that might lead to volume depletion. In addition, systemic endotoxemia contributes to the prerenal etiology of renal impairment and promotes direct nephrotoxicity and acute tubular necrosis. On the other hand, the renal failure observed in the chronic BDL model (with development of biliary cirrhosis, portal hypertension and ascites) shares pathophysiological similarities with HRS, but the accordance of the chronic BDL model to the diagnostic criteria of HRS (e.g. absence of spontaneous bacterial peritonitis, no renal function improvement after plasma volume expansion) should have been confirmed. In conclusion, we think that the BDL model is not suitable for the study of the natural history of HRS, but the chronic BDL model might be valid for the study of established HRS and its potential therapies.

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Key words: Obstructive jaundice; Rats; Bile duct ligation; Hepatorenal syndrome; Renal failure

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TO THE EDITOR

We read with great interest the article recently published in *World J Gastroenterol* by Dr. Pereira *et al*[1], which evaluated the reliability of the bile duct ligation (BDL) model in rats for the study of hepatorenal syndrome (HRS). The authors found that this experimental model induces progressive renal dysfunction without structural changes in the kidney, and they suggested that BDL in rats emerges as a good model for further studies of HRS pathophysiology and treatment. Upon reading this very interesting study, a number of questions a rose as to whether the renal dysfunction observed after BDL really represents HRS.

HRS is defined as a specific type of functional renal failure complicating advanced liver disease (e.g. decompensated cirrhosis, alcoholic hepatitis, or acute liver failure)[2,3]. The pathogenesis of this syndrome is the result of an extreme underfilling of the arterial circulation secondary to an arterial vasodilation located in the splachnic circulation. This underfilling triggers a compensatory response with activation of vasoconstrictor systems leading to intense renal vasoconstriction, especially to the renal cortex, and finally the glomerular filtration rate is decreased in the absence of underlying kidney pathology whilst tubular function is preserved[4]. Consequently, this specific type of functional renal failure observed in advanced liver disease must be differentiated by a number of non-functional causes of renal failure in this setting, e.g., other causes of prerenal azotemia or acute tubular

necrosis[3,4]. The distinction between HRS and other causes of renal failure that may occur in cirrhosis is problematic mainly due to the lack of a specific diagnostic test. A number of commonly used urinary indices (e.g. urinary sodium or osmolarity) cannot reliably distinguish HRS and acute tubular necrosis in the setting of cirrhosis, making this differentiation especially difficult[3,4]. For these reasons, the diagnosis of HRS is currently based on the exclusion of other disorders that could lead to renal failure in cirrhosis including shock (septic or hypovolemic), ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs[4]. An additional major criterion that should be fulfilled is that no sustained improvement in renal function occurs after expansion of plasma volume. In their study, the authors have not examined the accordance of the BDL model with these criteria, instead they characterize the BDL-induced renal dysfunction as "HRS" based solely on the absence of histopathological changes in the kidneys and on evaluation of diverse urinary indices. The histological analyses performed in the kidney are not described in detail but it is generally stated that BDL rats exhibited normal renal histology under the light microscope. This finding contradicts most previously published reports, which describe significant histological alterations, predominantly located in tubular epithelial cells, at various intervals of obstructive jaundice[5-10]. Furthermore, as already stated, urinary indices represent only minor and dispensable criteria for the diagnosis of HRS[4]. Taking into consideration these issues, a number of uncertainties are raised regarding the reliability of the BDL model for the study of HRS, which become more evident when considering the pathophysiology of renal failure complicating obstructive jaundice.

In rats, double ligation of the common bile duct with its dissection between the ligatures produces a well established experimental model of: (1) acute obstructive jaundice, studying different time points up to 2 wk after BDL; (2) progression of biliary fibrosis to cirrhosis, studying diverse time intervals up to 4 or 6 wk after BDL; and (3) secondary biliary cirrhosis, at 4 or 6 wk after BDL[11,12]. BDL produces a combined model of cholemia and parenchymal liver disease. The magnitude of contribution of any one factor in remote organ injury and systemic complications depends on the duration of the biliary obstruction. In acute obstructive jaundice, the liver presents typical changes of obstructive cholangiopathy, in the absence of cirrhosis or portal hypertension, which are at least partly reversible if biliary drainage is performed at this stage[13,14]. This initial phase of surgical jaundice is characterized by the effects of severe cholestasis and cholemia due to total obstruction of bile flow, with intestinal barrier failure and decreased reticuloendothelial system function. This predisposes the test subject to portal and systemic endotoxemia and susceptibility to postoperative septic complications and renal dysfunction[15,16]. Severe cholemia, predominantly and independently of liver parenchymal disease, affects the integrity of the cardiovascular system by inducing;s (1) negative inotropic and chronotropic effects on the heart[17,18]; (2) impaired sympathetic vasoconstriction response[19,20]; and (3) profound natriuresis and diuresis that may lead to volume depletion[21,22]. These factors produce systemic hypotension and renal dysfunction, especially when an interventional approach for the release of biliary obstruction is performed[22]. The etiology of renal impairment in this setting is profoundly prerenal and occurs in the absence of advanced and irreversible liver disease. In addition, it has been shown repeatedly that acute obstructive jaundice is universally complicated by extended bacterial translocation with portal and systemic endotoxemia[23-25]. These phenomena activate a systemic inflammatory response characterized by the release of numerous cytokines and proinflammatory mediators, which may lead to the development of the septic syndrome and multiple organ damage[26]. Endotoxin-induced renal injury is not only functional, through induction of a hypotensive response, but endotoxin also exerts direct nephrotoxic effects. The result is renal injury clearly characterized by histological alterations of acute tubular necrosis[27,28]. Given the central role of endotoxemia in obstructive-jaundice-induced systemic complications[16,25], we would expect that renal failure in obstructive jaundice would be accompanied by tubular injury. Despite the authors' findings of normal renal histology in BDL rats, there are numerous previous studies showing that the acute BDL model induces renal histopathological changes, predominantly in the tubular epithelium (acute tubular necrosis)[5-10]. For all these reasons, we think that the pathogenesis and the type of renal dysfunction that is observed during the acute phase of BDL are different from what we mean by the term HRS.

With regard to the chronic phase of BDL (after 4 wk of biliary obstruction), apart from cholemia, the factor severe parenchymal liver disease comes into play, significantly contributing to renal dysfunction[22]. This phase is characterized by development of biliary cirrhosis with portal hypertension, and ascites and more closely resembles clinical conditions complicated by HRS[11]. However, cholemia still exists to a considerable extent and acts on renal hemodynamics. Endotoxemia, with its consecutive systemic inflammatory response and bacterial translocation to remote organs, also exists, interacting with advanced liver disease per se in the development of renal dysfunction. Is the final result on kidney the development of HRS? In order to give a reliable answer to this question we should examine the accordance of the BDL model with the well-established diagnostic criteria of HRS, as we would do in a clinical setting. Rats with BDL for more than 4 wk are cirrhotic with ascites and have increased rates of bacterial translocation; therefore, spontaneous bacterial peritonitis should be excluded as an underlying cause of renal failure. We should also demonstrate the lack of response of renal function to volume repletion by isotonic saline. If these prerequisites are fulfilled, we would be more certain to characterize the renal failure observed in the chronic phase of BDL as HRS.

In conclusion, we think that the BDL model is not

suitable for the study of the natural history of HRS, because at the acute phase of extrahepatic cholestasis, the pathophysiology of the observed renal impairment seems to be different from that of HRS. However, renal failure observed in the chronic BDL model shares pathophysiological similarities with HRS. The accordance of the chronic BDL model to the diagnostic criteria of HRS, if confirmed, may provide us with a valuable experimental model for the study of established HRS and its potential therapies. Another important issue that remains to be elucidated is the comparison of the BDL model with the carbon tetrachloride model of cirrhosis, in order to examine the potential superiority of one model over the other for the study of HRS.

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