Systemic Hypotension and Renal Failure in Obstructive Jaundice—Mechanistic and Therapeutic Aspects

Jacob Green and Orl S. Better

ABSTRACT
The association between obstructive jaundice and postoperative acute renal failure has been originally described more than eight decades ago and is now a well-established clinical phenomenon. Acute renal failure occurs in 8 to 10% of patients requiring surgery for relief of obstructive jaundice and contributes to eventual mortality in 70 to 80% of those who develop it. A major factor that may underlie the susceptibility to renal failure in patients with obstructive jaundice is cardiovascular instability manifested as systemic hypotension and defective vascular reactivity. This article outlines the scope of the clinical association between jaundice and renal failure and reviews the clinical and experimental studies that have contributed to our understanding of the underlying pathophysiologic mechanisms for this phenomenon. A growing body of evidence emanating from these studies indicates that bile constituents (e.g., bile acids, bilirubin, cholesterol) do not exert a direct nephrotoxic effect. Rather, the retention of bile during cholestatic jaundice has deleterious effects on cardiovascular function and on blood volume. This, in turn, sensitizes the kidney to prerenal failure and acute tubular necrosis in postsurgical patients with obstructive jaundice. The institution of prophylactic measures based on the appreciation of these underlying pathogenic mechanisms may result in an improvement in the overall prognosis of jaundiced patients undergoing surgery.

For many years, surgeons were impressed by the frequent complication of hypotension and kidney failure after surgery on patients with obstructive jaundice. Increased recognition and awareness of this clinical problem have led to extensive clinical and laboratory investigation, resulting in a better appreciation of the relationship between the liver and the kidney. In 1911, Clairmont and von Haberer (5) first described the occurrence of renal failure developing after surgery for obstructive jaundice in five patients, all of whom died from acute renal failure. In 1930, Helwig and Schutz (6) coined the term "hepatorenal syndrome" to describe a set of patients who developed renal failure after biliary tract surgery. (Currently, the term "hepatorenal syndrome" is used to define a different clinical condition, summarized in Ref. 7.) Following these original observations, numerous clinical series have been reported in the literature, all of which point to a strong association between postsurgical renal failure and obstructive jaundice. A review of the different series (1-4, 8-12) indicates that the overall mortality rate for patients undergoing surgery for obstructive jaundice is 16 to 18%. Acute renal failure occurs in approximately 8 to 10% of patients requiring surgery for relief of obstructive jaundice and contributes to eventual mortality in 70 to 80% of those who develop it. Quite remarkably, despite advances in perioperative care, these figures have changed very little over the past 25 yr (13).

The incidence of postoperative acute renal failure in patients with obstructive jaundice seems to be directly related to the degree of jaundice. Thus, the incidence of renal failure in nonjaundiced patients is considerably lower than the incidence of this complication in jaundiced patients undergoing a similar type of operation. In a large series of 2,358 biliary tract operations performed on nonjaundiced patients, Glenn and McSherry (14) reported only three deaths from renal failure. All of these deaths were in patients with preexisting renal disease. In another series, the incidence of postoperative renal failure was 6.8% in 103 jaundiced patients, contrasted with an incidence of renal failure of only 0.1% in 2,353 emergency partial gastrectomies for perforated peptic ulcer. This low incidence of postoperative renal failure in nonjaundiced patients occurred despite the fact that many of these patients were in shock before resuscitation and despite the greater extent of this operation as compared with biliary surgery on the jaundiced patients.
The close link between high bilirubin levels and postsurgical renal failure has been substantiated by other investigators as well (8-12,15). In a prospectively studied group of patients, Dawson (16) measured creatinine clearance in 15 jaundiced patients both preoperatively and postoperatively and compared these results with the clearances from 12 nonjaundiced patients undergoing similar operations. A drop in creatinine clearance was noted in all of the jaundiced patients and in 10 of the 12 control patients; however, the fall in creatinine clearance was significantly greater in the jaundiced patients and was directly correlated with the serum bilirubin levels. Evans et al. (17), in a study of nine patients with obstructive jaundice, reported a decrease in the postoperative creatinine clearance from a mean of 85 to 55 mL/min. Although not compared with a nonjaundiced control group, there did appear to be a direct correlation between the preoperative bilirubin level and the postoperative decrease in creatinine clearance.

In view of the increased morbidity and mortality associated with obstructive jaundice, extensive amount of work has been done during the last 30 yr trying to address the following questions:

1. What is the effect of obstructive jaundice on kidney function?
2. What is the mechanism of the renal failure associated with obstructive jaundice? Is there a direct nephrotoxic effect of jaundice, or is renal failure attributable to altered cardiovascular function (pre-renal failure)?
3. Does jaundice (chole mia) have an effect of its own on kidney function that is independent of the renal failure associated with parenchymal liver disease?
4. Given the adverse effects of jaundice (chole mia) on kidney function, which of the bile components (bile acids, bilirubin, cholesterol) is the culprit?

Most, if not all, investigations into the effects of jaundice on the renal and cardiovascular systems have been undertaken in experimental animals. The most widely used animal model for obstructive jaundice is bile duct ligation (BDL). Animal models that have been used in this regard include the dog, rat, baboon, and cat. BDL animals develop early hyperbilirubinemia combined with hepatocellular damage. After several weeks, however, the magnitude of hyperbilirubinemia diminishes and liver disease progresses. In order to study the isolated effect of jaundice on kidney function and the circulation, an alternate model of jaundice has been developed in which bile is directly diverted into the blood by a surgical anastomosis of the bile duct to the venous systems (choledochocaval anastomosis, CDCA). In this model, which is described only in the dog and rat, a severe jaundice with serum bilirubin levels rising as high as 60 mg/dL develops within a few days. Liver function tests are only minimally altered, and the jaundice persists for as long as the anastomosis remains patent. Thus, the CDCA model is useful for studying the effects of jaundice in the absence of hepatocellular damage. The effect of isolated cholemia on kidney function and systemic hemodynamics has been also studied by direct infusion of bile constituents (bile, bilirubin, or bile acids) into the systemic or renal circulation.

In spite of the extensive amount of data gathered from experimental models with jaundice, extrapolation to the clinical condition of obstructive jaundice should be done with caution for the following reasons:

1. The BDL model is not a "pure" model of cholemia and is always associated with some degree of hepatocellular damage. Varying degrees of jaundice and liver disease may exist, dependent on the time that has elapsed from the surgery itself (e.g., days versus weeks). Because different experiments were performed at different postoperative times, it is hard to conclude whether changes in kidney function and systemic hemodynamics are due to jaundice or due to parenchymal liver disease. Moreover, there are both quantitative and qualitative differences, within and between species, with regard to peak levels of jaundice and of hepatocellular damage. It is also important to note that even the hyperbilirubinemia in the CDCA model is not totally a "pure" model. Thus, dogs with CDCA have a certain degree of liver damage as manifested by a rise in circulating liver cell enzymes and histopathologic changes in the liver (18).

2. The duration and severity of jaundice and hepatocellular damage in BDL models are markedly influenced by the type of surgical procedure used to ligate the common bile duct. Thus, double ligation of the common bile duct with its division between the ligatures results in a severe form of obstructive jaundice, which leads to relatively early death. In contrast, chronic BDL without sectioning of the common bile duct leads to a much milder and protracted disease course. This difference is ascribed to a more complete interruption of bile flow, which can be achieved by sectioning of the common bile duct.

3. Many of the experiments were performed under anesthesia, which in itself can influence renal and cardiovascular function (19).

4. BDL can induce significant biochemical, metabolic (e.g., weight loss), and hematologic changes (e.g., anemia) that can play independent contributing factors in the development of postoperative renal failure. Many of the studies did not have an appropriate control of these parameters between sham-operated and BDL animals.

The species variability in response to chronic BDL (CBDL) is clearly illustrated when one compares the postsurgical course between dogs and rats, the two most commonly models of jaundice. In the dog that has undergone BDL without resection, peak jaundice and hepatocellular damage occur by the seventh postoperative day. Thereafter, the plasma indices of hepatocellular damage and jaundice remain more or less stable. By the end of the third week, the hyperbilirubinemia begins to return to normal, but other indices,
such as the activity of alkaline phosphatase, remain higher than the preligation values. In this model, the rise in bilirubin is modest and usually never exceeds 5 mg/dL (20,21). Although peak jaundice and hepatocellular damage occur by the end of the first week in the dog that has undergone BDL with division or resection, the jaundice and hepatocellular damage are far more severe and their duration is considerably longer. In these dogs, the serum bilirubin rises as high as 15 mg/dL, and even by the eighth postoperative week, it is still elevated (22,23).

In the BDL rat, the changes in the postoperative hematology and biochemistry indices differ qualitatively and quantitatively from the dog and are dependent on whether the bile duct has been left intact, divided, or resected. In the BDL rat without division or resection, the peaks of jaundice and hepatocellular damage occur between the second and fifth postoperative days and return to normal by the end of the second week (24). In this model, the serum bilirubin often rises to 15 mg/dL. The hepatocellular damage and jaundice in the rat that has undergone BDL and division, similar to that seen in the dog, are more severe and result in the death of the animal by the end of the fifth postoperative week (24).

Aside from differences in biochemical changes after BDL, rats and dogs manifest variable responses with respect to salt and water homeostasis. BDL dogs at 6 wk postoperatively retain salt avidly (25). This often leads to anasarca and ascites. In marked contrast, most studies on rats with CBDL do not show retention of salt and water (26–30). In another rat model, where liver cirrhosis is induced by intermittent exposure to carbon tetrachloride, progressive salt retention takes place, followed by the appearance of ascites (31). Both CBDL dogs and rats with CCl₄-induced cirrhosis develop hypotension accompanied by an increased or unchanged cardiac output-hyperkinetic circulation (32,33). The Na retention state (which occurs in the face of normal GFR), as well as the systemic hemodynamic profile in these two models, mimics the events taking place in liver cirrhosis in human subjects (e.g., Laennec’s cirrhosis). However, salt and water retention is rare in patients with obstructive jaundice. In fact, patients with biliary cirrhosis have enhanced ability to excrete salt and do not develop edema until late in the course of their disease (34). Moreover, although the CBDL rat model may bear resemblance to clinical obstructive jaundice with respect to Na and water handling, it does not manifest the same hemodynamic profile as patients with biliary cirrhosis. Thus, as opposed to the hypotension observed in jaundiced patients (2,3), BDL conscious rats have normal systemic vascular resistance and are, to the most part, normotensive (27). When taken together, these data underscore the need for extreme caution when trying to extrapolate from experimental models of jaundice to the clinical condition of obstructive jaundice.

**ALtered Systemic hemodynamics in obstructive jaundice**

**Hypotension and Impaired Vascular Reactivity**

In 1932, Meakin (35) noted that, in a patient who had suffered from essential hypertension, blood pressure became normal when the patient developed “catarrhal jaundice” due to complete biliary obstruction. Blood pressure returned to elevated values long after the jaundice had dissipated. In reviewing retrospectively 100 consecutive cases of obstructive jaundice, Meakin found that systolic, diastolic, and pulse pressure tended to be lower than those observed in the normal population. Because most of these patients also had bradycardia, it was presumed that the hypotension is related to the bradycardia.

Independent observations in 1956 by Zollinger and Williams (2) established that jaundiced patients undergoing biliary surgery were more susceptible to a hypertensive crisis and renal failure after hemorrhage during surgery. In a subsequent study, the same investigators found that this increased susceptibility could be ameliorated by volume expansion before surgery (3). A predisposition of jaundiced patients to hypotension and renal failure has been suggested by others as well (36–38).

Both in vivo and in vitro studies in experimental models have established the vasodilatory properties of jaundice with or without concomitant liver disease. Studies performed by Williams et al. (3) in dogs with CBDL revealed that hemorrhage in jaundiced animals led to a 44% mortality rate compared with no mortality in the sham-operated, control group. The amount of blood required to lower the mean arterial pressure to 66 mm Hg in BDL animals was half the amount required in the control group. Cattel and Birnstingl (36) found no volume deficits in 25 jaundiced patients studied nor in BDL dogs. However, they did find that BDL dogs were more prone to hypotension with severe hemorrhage than were sham-operated animals. This alteration in the hemodynamic response to volume depletion is accompanied by baseline hemodynamic changes as well. CBDL dogs manifest systemic hypertension and diminished peripheral vascular resistance (32). Interestingly, hypertension induced in dogs by unilateral obstruction of the renal artery (a model mimicking renal artery stenosis) could be reversed after BDL of the same dog (39). The reduction in systemic blood pressure and vascular resistance in CBDL dogs is associated with blunted response to vasoactive agents (40–42). As shown in Table 1, other BDL animal models may have normal basal systemic blood pressure. In BDL rats, there may be a transient hypotension during the first 1 to 2 days after the procedure. However, blood pressure in BDL rats for periods longer than 1 wk is not different from their sham-operated counterparts (26,30). Likewise, studies of BDL in baboons revealed no statistically significant difference in blood pressure compared with control animals (43).
TABLE 1. Effect of Obstructive jaundice on hemodynamic indices and on Na⁺ handling

<table>
<thead>
<tr>
<th>Animal</th>
<th>Systemic Blood Pressure</th>
<th>GFR</th>
<th>RBF</th>
<th>Salt and Water Retention</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>↓</td>
<td>Normal</td>
<td>↓</td>
<td>++++</td>
<td>25,32,39,40,83,84</td>
</tr>
<tr>
<td>Rat</td>
<td>transient hypotension followed by normal blood pressure and peripheral vascular resistance</td>
<td>Normal</td>
<td>↓</td>
<td>a</td>
<td>26−30</td>
</tr>
<tr>
<td>Baboon</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
<td></td>
<td>43,44,85−88</td>
</tr>
</tbody>
</table>

*Most studies on rats with CBDL do not show retention of salt and water. However, salt and water retention was found in Sprague-Dawley CBDL rats by some investigators (28, 30). The cause of this discrepancy may be attributable to variations in strain of rats and to differences in dietary salt intake.

Notwithstanding the normal systemic hemodynamics under basal state, various experimental procedures may unmask the subtle deleterious consequences of CBDL or obstructive jaundice on the circulation. Thus, when BDL rats are bled to 10% of their total blood volume, the animals go into irreversible hypotension, whereas such bleeding is well tolerated by control rats. The susceptibility of the CBDL rats to hemorrhagic shock appears to be due to pooling of blood in the splanchnic circulation. This pool is unavailable for defense of the circulation during hemorrhage in CBDL rats. In baboons, in spite of normal systemic blood pressure at rest, there is blunted responsiveness of the skeletal muscle vasculature to norepinephrine (43). Interestingly enough, the vascular response to vasoactive agents varies among different vascular beds. Thus, in the BDL baboon model, the blunted vasopressor response of the peripheral vasculature is associated with enhanced pressor responsiveness of the renal and cerebral vessels (44).

The isolated effect of cholestasis on systemic hemodynamics has been studied in dogs with CDCA. By using this model, Alon et al. (45) were able to demonstrate the development of hypotension and reduced total peripheral resistance in conscious animals. The tendency to hypotension is associated with a blunted pressor response to vasoactive agents and to volume expansion. In vitro studies have provided additional evidence to the vasodepressor effect of bile constituents. Thus, bile acids suppress contractile activity in various vascular bed preparations, which include the rat vas deferens, rat portal vein, and the perfused isolated rat hind limb (46). This effect was observed with different types of bile acids (primary, conjugated, or secondary), and the concentrations used were similar to those observed clinically during obstructive jaundice (Figure 1). Likewise, the in vitro contractile response of arterial strips or rings taken from rats with obstructive jaundice is markedly suppressed (47).

Parenchymal liver damage due to obstructive jaundice may have an independent contributing role in the pathogenesis of the altered systemic hemodynamics. In patients with chronic liver disease, there is refractoriness of the peripheral vascular bed to exogenously administered vasoactive agents (48−50). Moreover, in spite of systemic hypotension, chronic liver disease is characterized by elevations in plasma and urine concentrations of norepinephrine (51), indicating once again an end-organ (i.e., vascular wall) unresponsiveness. This hemodynamic instability has been traditionally ascribed to the presence of large anatomical arteriovenous shunts. It has also been proposed that several circulating vasodilators that accumulate in this condition could play a role in diminishing the "fullness" of the arteriovenous tree. These vasodilators include bradykinin, substance P, vasoactive intestinal peptide (VIP), glucagon, prostacycline, and atrial natriuretic peptide. There is, however, no clear evidence of substantial selective involvement of any of these agents in the pathogenesis of hypotension in liver...
disease (52). Most recently, the endothelium-derived L-arginine product nitric oxide has been implicated in the pathogenesis of the diminished systemic vascular resistance in cirrhotic patients (see later).

In a recent study, Jacob et al. (53) have attempted to provide an insight into the cellular mechanism responsible for the blunted vascular response in experimental cholestasis. By using 3-day BDL rats, they presented both in vivo and in vitro evidence for a functional defect in the expression of α-1 adrenoceptors. Thus, blunted pressor responsiveness to noradrenaline, electrical stimulation, and selective α-1 agonists (methoxamine, phenylephrine) was observed in these animals as compared with sham-operated rats. Likewise, in aortic rings prepared from the BDL rats, they found blunted in vitro vascular reactivity to the same α-1 agonists. This defect seems to be selective for α-1 receptors because the response to α-2 agonists in BDL rats was normal. In their study, those investigators did not identify whether the α-1 receptor dysfunction was due to decreased binding of agonists to the receptor or due to a postreceptor defect (e.g., an altered phoshoinositide metabolic pathway). However, they make the interesting hypothesis that both bile acids and endotoxin, which accumulate in the plasma during obstructive jaundice, could be implicated in the modulated behavior of the vascular α-1 receptor (54,55).

All in all, it appears that the effects of obstructive jaundice on the peripheral vasculature, in humans and animals, are those of decreased vascular resistance with normal or low blood pressure and an exaggerated hypotensive response to volume depletion. These changes may, in part, be secondary to changes in vascular reactivity.

**Impaired Cardiac Performance in Obstructive Jaundice—the “Jaundiced Heart”**

The association of obstructive jaundice with bradycardia has been known for over a century (56). Many in vitro and in vivo studies have subsequently established the negative chronotropic and inotropic effects of bile acids (57–62). By exposing isolated atria of Wistar rats to cholic acid, Joubert demonstrated a dose-dependent negative chronotropic effect (61). It was felt that cholic acid was a functional antagonist of isoprenaline but that its mechanism of action was mechanically interfering with membrane function by forming a monolayer on the surface of the cell membrane. These effects were demonstrated at concentrations that were within the pathophysiologic range. This negative chronotropic effect of bile salts was also described by Bogin et al. (63) and by Enriquez de Salamanca and his group (64). Other studies have suggested that the negative chronotropic effect induced by bile acids is mediated through vagal stimulation and can be antagonized by atropine (62,64,65). In this regard, Dave and colleagues (65) observed that the bradycardiac influence of vagal stimulation of the isolated perfused frog heart could be reversed by sodium tauroglycocholate. On the other hand, the acetylcholine response was potenti ated by adding the salt to the medium. The responses to epinephrine, norepinephrine, and isoproterenol were not altered by these substances. More recently, our studies (66) have shown that, in addition to negative chronotropism, bile acids also exert a concentration-dependent negative inotropic effect on rat papillary muscle and isolated ventricular myocytes. This effect is attributed to a reduction in the duration of the action potential due to the suppression of the slow inward current of calcium.

In vivo studies have yielded conflicting results with regard to the effects of jaundice (choleemia) on left ventricular function. Species variability, different methodologies used for assessing cardiac function, and difficulties in distinguishing between the relative roles of jaundice versus parenchymal liver damage are among the reasons for this confusion. In BDL animals, cardiac output was found to be either normal (27), low (67), or increased (32). Some of these studies were done in animals that were anesthetized, which can have an independent effect on the heart. Also, assessing cardiac function by global cardiac output may not be sufficient to detect a latent or preclinical myocardial disease. Because most jaundiced animals and patients have peripheral vasodilatation and reduced left ventricular afterload, which could, by themselves, have a favorable effect on cardiac output, it is necessary to use more sensitive markers for left ventricular contractibility under these circumstances. To clarify this issue, Bina et al. (68) studied different markers of contractility in isolated ventricular muscles taken from BDL dogs (studies done 3 wk postoperatively) as compared with isolated hearts from sham-operated dogs. Contractility was assessed under basal conditions and after stimulation with the beta agonist isoproterenol. Although basal mechanical performance was spared in BDL dogs, there was a depressed contractile response to isoproterenol in BDL dogs as compared with the control animals (Figure 2). The contractility indices most markedly blunted in BDL dogs included: active tension, maximum rate of tension activation (+dT/dt), maximum rate of tension relaxation (−dT/dt), and twitch duration. Interestingly, the impaired cardiac performance in response to beta agonists was specific for these agents because contractile response to ouabain or to changes in the rate of stimulation (force-frequency relationship) was normal in hearts taken from BDL dogs. A similar cardiac beta-adrenoreceptor hypersensitivity has been also described in 4-wk BDL rats (69). In contrast, in a recent study (70) done on a 3-day BDL rats, (compared to sham operated animals), Jacob and his colleagues found impaired indices of basal cardiac contractility. However, responsiveness to norepinephrine and the beta receptor agonists isoproterenol and dobutamine was unaffected by BDL. These findings were obtained both in
vivo (the pithed rat preparation) and in vitro (isolated working heart preparation). Furthermore, in radio ligand-binding assays, the affinity and number of cardiac beta-adrenoreceptors in membranes from hearts of sham-operated and BDL rats were not significantly different from one another. The discrepancy between this study and the two other studies (68,69) could be ascribed to varying time intervals between the surgery (BDL) and the day of experiments (3 days versus 3 to 4 wk). Although the acute model is characterized by acute jaundice (cholema) and acute liver disease, the more chronic models are more kin to secondary biliary cirrhosis and portal hypertension. Thus, one can speculate that, with a shorter duration of BDL (70), sufficient time had not elapsed to allow down-regulation of the cardiac beta receptors.

In order to isolate the effect of jaundice (cholema) on cardiac function, independent of the role played by liver parenchymal disease itself, we studied left ventricular function in the in vivo trained and conscious dog model with CDCA (71). By using the noninvasive measurement of systolic time intervals (which assess left ventricular systolic function), we found that the pre-ejection period (signifying pressure development in the left ventricule during systole) was longer whereas the left ventricular ejection time (signifying stroke volume) was shorter in cholemic dogs compared with control animals. Also, the maximal rate of tension activation (dT/dt) was lower in cholemic dogs compared with control animals. Furthermore, isolated ventricular muscles taken from CDCA dogs show the same pattern as observed in isolated hearts from CBDL dogs, namely, normal basal mechanical performance with refractoriness to isoproterenol (68) (Figure 2). Taken together, the data reviewed here point to a jaundice-induced cardiac myopathy ("the jaundiced heart"). The cellular mechanism for this abnormality is unknown, but it may be linked to a depletion of intracellular glycogen and defective energy metabolism within the cardiac myocyte (72).

Clinical observations in patients with obstructive jaundice have established the negative chronotropic effect of bile acids (35,73). Moreover, the liver damage resulting from long-standing obstructive jaundice may have an adverse effect on cardiac function that is independent of the influence exerted by cholema. A support to this notion is derived from studies on cirrhotic patients (who usually have only minimal degree of jaundice and cholema). Although the cirrhosis associated with portal hypertension may not be identical to the clinical setting of liver damage in obstructive jaundice, it is conceivable that certain similarities do exist as far as the effect of liver disease on cardiovascular function.

Cirrhotic patients have been classically described as having "hyperkinetic circulation" characterized by tachycardia, cardiac enlargement, and high cardiac output (74,75). Also, echocardiographic studies suggest an increase in left ventricular performance in cirrhosis (76). Notwithstanding these findings, studies of global left ventricular function under these circumstances should be interpreted with caution because peripheral vasodilation and reduced left ventricular afterload (often found in patients with liver disease, as described above) can mask latent left ventricular failure. In fact, correction of hypotension with vasopressors, which increases the afterload of the heart, may precipitate pulmonary edema in cirrhotic patients (77). Similarly, an overzealous administration of colloid solutions to cirrhotic patients may also precipi-

Figure 2. Effect of isoproterenol on indices of cardiac contractility in normal and jaundiced dogs. (a) Active tension. (b) Maximum rate of tension activation (+dT/dt). Abscissa, molar concentrations of isoproterenol; ordinate, percent change in a given variable compared with control; closed circle, sham-operated dogs; open circle, CBDL dogs; triangle, CDCA dogs. For each twitch parameter, dose-response curves from the control and any jaundiced groups were compared by two-way analysis of variance (ANOVA). The P value for the ANOVA test is shown on the right-hand side of the figure. A t test was used to compare individual doses: \( * P < 0.01; \) \( ^{t}P < 0.05 \). Note the attenuation of the indices of contraction in myocardial tissue taken from CBDL and CDCA dogs. Reprinted by permission from Ref. 68.
tate pulmonary edema. Gould et al. (78) performed cardiac catheterization in 10 patients with cirrhosis who had a presystolic gallop. When exercising, all 10 patients showed an average increase in left ventricular end-diastolic pressure from 6.0 to 19.0 mm Hg (an increase of 216%). A striking increase was also noted in pulmonary artery pressure (24 to 47 mm Hg; +96%). This observation is another indication for the fact that, by challenging the cardiovascular system, one may unmask latent cardiac dysfunction in cirrhotic patients. A further insight into the pathogenesis of cardiac dysfunction in cirrhosis has been provided by Ramond et al. (79), who showed that these patients may have blunted positive inotropic and chronotropic responses to catecholamines because of the downregulation of myocardial β-adrenergic receptors. In conclusion, the current evidence indicates that obstructive jaundice is associated with impaired cardiac function. Retained bile acids as well as liver damage may contribute, in an independent manner, to negative chronotropic and inotropic effects. This, in turn, may play a role in the pathogenesis of “underfilling” of the circulation and susceptibility to acute renal failure in patients with obstructive jaundice.

EFFECT OF OBSTRUCTIVE JAUNDICE ON KIDNEY FUNCTION

When the natural excretory route of bile is blocked, the kidney becomes the main excretory organ for the retained bile substances. Given the multiple deleterious effects of bilirubin and bile salts on cell integrity and cell function (summarized in Ref. 80), it is conceivable that the prolonged exposure of the kidney to bile constituents will affect kidney function. Interpretation of the various studies related to changes in GFR or RBF in patients and animals with obstructive jaundice is fraught with major difficulties because of conflicting results (4.25–29,30,32,39,40, 44,67,80–88). Aside from interspecies variability, discrepancies between the different studies may be because of the use of anesthetics that are known to affect both RBF and GFR (19). Also, in different animal models, altered cardiovascular function in obstructive jaundice could have an independent adverse effect on kidney function.

Table 1 summarizes the main findings related to systemic blood pressure, GFR, and RBF in three animal models with BDL. By critically analyzing the data presented in Table 1, it appears that decreased renal perfusion exists either in the presence of normal systemic blood pressure (rats in late phase) or in the presence of altered systemic hemodynamics (dogs, baboons). Although systemic blood pressure in baboons is normal under basal conditions, there is an attenuated vasoconstrictor response to α-adrenergic stimulation in the vessels of the skeletal muscle (43). These studies also demonstrate that different vascular beds may possess different sensitivities to vasoactive agents. Thus, the attenuation of the vasopressor response of the peripheral vasculature in BDL baboons occurs in the face of an exaggerated vasoconstrictor response of cerebral and renal blood vessels (43).

Reduced RBF, which is common to all BDL species, mainly refers to cortical perfusion (i.e., redistribution of blood from superficial cortex to deep cortex and medulla). However, total RBF can be either normal or reduced, depending on the species and on the technique used to assess total RBF (e.g., clearance of paraminohippurate versus 133Xe washout or 85Sr-labeled microspheres). The compromised cortical perfusion in animals with BDL may underlie the susceptibility of these animals to acute renal failure during anoxia or hypotension.

It is noteworthy that, in spite of reduced renal perfusion in the animal models, GFR is relatively preserved, suggesting that obstructive jaundice exerts a modulatory role at the level of the efferent arteriole to increase intraglomerular hydrostatic pressure. Alternatively, vasodilator forces in the kidney (e.g., vasodilatory prostaglandins) could counterbalance the increased renal vascular reactivity associated with obstructive jaundice. Such a mechanism has been suggested by Zambraski and Dunn (89) and by Levy et al. (90). In these studies, after 4 to 6 wk of BDL in dogs, there was a significant increase in the renal production of prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2). RBF and GFR remained normal after BDL, but the administration of indomethacin caused a decrease in prostaglandin production, resulting in a marked decrease in both RBF and GFR.

The renal dysfunction associated with obstructive jaundice could be related either to altered systemic hemodynamics or to a direct nephrotoxic effect of bile. Most studies, however, were unable to demonstrate major renal dysfunction in response to exposure to bile, bile salts, or bilirubin. Thus, in dogs, both the direct infusion of bile into the renal artery and the systemic infusion of bile have been shown to result in increased urinary flow and sodium excretion without changing GFR or RBF (91–94). Moreover, acute (4-h) BDL in dogs (i.e., acute cholestasis without liver disease) actually increases GFR and RBF (94). Also, in dogs with CDCA (a “pure” cholemic model), GFR and RBF are preserved in the face of systemic hypotension (45), underscoring again the lack of a direct deleterious effect of bile on the kidney. The experimental data are buttressed by the clinical observation that, in spite of chronic hyperbilirubinemia and an increase in circulating bile acids, kidney function in patients with primary biliary cirrhosis is not affected until the very late stages of the disease (34). Likewise, jaundiced homozygous Gunn rats (glucuronyl transferase deficiency) manifest only subtle tubular damage while GFR remains unaltered (95).

Although bile and bilirubin may not be directly toxic, jaundice may potentiate ischemic injury to the kidney. Thus, whereas normal Sprague-Dawley rats can withstand 60 min of renal artery clamping without developing renal failure, irreversible acute renal
failure occurs when this maneuver is performed in CBDL rats (96–98). Gunn rats with CBDL that cannot form conjugated bilirubin (because of a genetic deficiency in glucuronyl transferase) do not develop acute renal failure after 60 min of clamping of the renal artery (97). This evidence would incriminate conjugated bilirubin rather than bile acids as the substance that potentiates the anoxic damage to the kidney.

Other investigators have found that the infusion of bile acids into normal rats followed by a period of renal ischemia of 30 min results in a reversible form of acute renal failure (99). Neither 30 min of ischemia alone nor the infusion of bile acids alone produced kidney failure. The infusion of conjugated bilirubin before the renal ischemia, in the hands of those investigators, did not result in acute renal failure (99). On the basis of those experiments, the authors felt that it is the bile acids, rather than conjugated bilirubin, that potentiates ischemic injury to the kidney (99). Another metabolic abnormality associated with obstructive jaundice, hypercholesterolemia, has also been considered as a possible cause for the increased renal vascular resistance seen in this condition (100).

From the foregoing review of the literature, it would appear that the high prevalence of postsurgery acute renal failure and mortality in patients with obstructive jaundice has its origin extrarenally. Thus, events occurring during surgery (hemorrhage, hypotension, anesthesia) may play in concert with jaundice and “arterial underfilling” (due to reduced peripheral vascular resistance and impaired cardiac function as described above) to compromise kidney function in the postoperative period.

**DIURETIC AND NATRIURETIC EFFECT OF BILE SALTS—A POTENTIAL CAUSE FOR HYPOVOLEMIA IN OBSTRUCTIVE JAUNDICE**

Thus far, direct determinations of intravascular volume in patients and animals with obstructive jaundice have yielded conflicting results (1,2,27,30,36,101,102). The lack of consensus in this regard mainly results from variations in the length of time after obstruction of the bile duct because it is clear that extracellular fluid volume may change profoundly over time. Also, confounding factors such as variations in fluid intake, vomiting due to cholemia, the use of diuretics, and liver disease itself may be responsible for the heterogeneity in blood volume results among the different studies.

Notwithstanding this confusion, accumulating evidence suggests that the retained bile acids in obstructive jaundice may have a diuretic and natriuretic effect, at least during the early stages of cholestatic jaundice. In 1966, Topuzlu and Stahl (91) described a decrease in proximal tubular Na⁺ absorption by infusing bile intravenously into dogs. Subsequent studies have shown (92,93) that the intrarenal infusion of bile or pure bile acids in dogs is associated with an increase in fractional Na⁺ excretion, urine flow, and K⁺ excretion without any change of inulin or p-aminomethylpuric acid clearances (Figure 3). Likewise, BDL in rats for 6 days resulted in increased Na⁺ excretion (103). In addition, the microperfusion of proximal tubules in rat kidney (in situ) with sodium taurocholate (100 μM) reduced fluid absorption by approximately 30%, which is believed to be due to the inhibition of the proximal tubular reabsorption of sodium (104).

The mechanism of the impaired tubular reabsorption of sodium by bile salts is not fully elucidated and may be related to a nontoxic detergent effect of bile acids causing direct membrane toxicity. However, Alon et al. (105) suggest a cyclooxygenase-dependent mechanism. Thus, bile acids infused intrarenally to dogs induce the production of PGE₂ in the kidney. Furthermore, indomethacin abolished both the natriuresis and the increase in renal PGE₂ synthesis associated with the intrarenal infusion of bile. Further insight into the cellular mechanism of bile acid-induced natriuresis has been provided by Sellinger et al. (106). By using brush border membrane vesicles from human kidney, those investigators have shown that the amiloride-sensitive, electroneutral Na⁺/H⁺ antiporter is significantly inhibited by sulfated bile acids at low concentrations (30 μM). Nonsulfated bile acids (e.g., taurocholic acid) required larger concentrations to exert an inhibitory effect on this transporter.

Because the Na⁺/H⁺ antiporter plays a fundamental role in proton secretion and reabsorption of Na⁺ in the proximal tubule, this in vitro finding of suppressed antiporter activity may be reconciled with the in vivo diuretic and natriuretic effect of bile salts. Sulfated bile acid derivatives are elevated in the plasma and urine of patients with obstructive jaundice (107). Also, the concentrations of bile acids used in that study were in the range of those expected in the proximal tubule (107), lending further credence to the physiologic meaning of this study.

Interestingly, clinical data seem to support the experimental evidence for the natriuretic property of bile salts. Thus, patients with severe obstructive jaundice (up to 40 mg/dL bilirubin) due to cholangiocarcinoma manifest increased urinary excretion of sodium (108). These patients have impaired renal ability to conserve sodium during sodium restriction. Furthermore, exaggerated natriuresis in response to volume expansion has been shown in patients with primary biliary cirrhosis, a condition characterized by marked cholestasis with retention of bile constituents in the circulation (34). Because of the slow progression of this disease, the liver architecture remains spared for many years. It is only after severe liver damage sets in and hypoalbuminemia develops (usually 10 to 20 yr after the onset of disease) that the patients will retain sodium and present with ascites. The renal handling of sodium in patients with severe bilirubinemia and cholelithiasis stands in sharp contrast to the handling of sodium in patients suffering from parenchymal liver disease (e.g., alcoholic cirrhosis) with minimal degree...
Figure 3. Effect of unilateral infusion of diluted bile on the flow of urine and on the rate of electrolyte excretion. Note the ipsilateral increase in the flow of urine and electrolyte excretion during the intrarenal infusion of bile. Intuions were: 0.9% NaCl (A), bile diluted 1:20 (B), bile diluted 1:10 (C), and 0.9% NaCl (D). Cross-hatched columns represent the ipsilateral (experimental) kidney, and open columns represent the contralateral (control) kidney. *P < 0.05 (versus Panel A); **P < 0.01 (versus Panel A). Results are expressed as means ±SD. V, urine flow; FE_{Na}, fractional excretion of sodium; U_{K}V, potassium excretion rate; C_{IN}, inulin clearance. Reprinted by permission from Ref. 92.

of jaundice. Under these circumstances, avid sodium retention by the kidney is the rule at a relatively early stage of the disease (109).

In contrast to the acute effect of bile acids on Na\(^+\) homeostasis, studies in dogs and rats with CBDL described increased Na\(^+\) and water absorption (25,28–30). In parallel with renal salt retention, CBDL dogs have a blunted natriuretic response to extracellular volume expansion (25). It is clear that CBDL used in the latter studies better describes the situation in chronic liver disease and portal hypertension. It is equally apparent, however, that cholema, per se, has diuretic and natriuretic properties, which serve as a potential cause for hypovolemia and prerenal disease in patients with obstructive jaundice.

ENDOTOXEMIA, LIVER DISEASE, AND OBSTRUCTIVE JAUNDICE

Systemic endotoxemia and bacteremia have been long recognized as markers of liver impairment. In 1941, Leach and Forbes (110) reported the ability of sulfonamides to protect against carbon tetrachloride–induced hepatic necrosis and death. This laboratory observation led to a number of studies implicating intestinal bacteria in the pathogenesis of both acute and chronic liver damage in the experimental animal. In 1964, Broitman and colleagues (111) not only showed that the cirrhosis induced by choline deficiency could be modulated by neomycin, but also that this protective effect was abolished by the addition of purified endotoxin to the drinking water of rats. From this, they concluded that the absorption of endotoxin (the lipopolysaccharide [LPS] outer wall of gram-negative bacteria) from the gastrointestinal tract contributed to the development of fibrosis and cirrhosis—at least in the experimental animal. Further progress was made by Nolan and Ali (112) when they showed that choline-deficient rats developed transaminase elevation together with histologic evidence of liver necrosis after the intraperitoneal injection of lipopolysaccharide at doses that were innocuous to rats fed an identical diet with added choline. Thus, not only did
Intestinal endotoxin appear to play a role in the development of the experimental cirrhosis, but liver injury appeared to render the animal unduly susceptible to the effect of endotoxin.

As opposed to the experimental studies, clinical observations relating endotoxia to liver disease are more contradictory. This discrepancy is related, in part, to the fact that interpretation of the Limulus lysate test (the assay used for the determination of circulating endotoxin levels; see Ref. 113) is fraught with major difficulties. This test has been found to be poorly reproducible, possibly because of the presence of serum inhibitors (114). Other problems relate to the use of different endotoxin standards with various degrees of purity. More recently, the development of a chromogenic assay for endotoxin has not only improved the sensitivity but also has permitted the quantitation of endotoxin measurements. Using this technique, several investigators were able to show that cirrhotic patients have significant portal and peripheral venous endotoxin concentrations as compared with healthy controls (115-117).

Endotoxin, which is normally released from the gut into the portal circulation, undergoes hepatic elimination in a two-step process that requires cooperation between Kupffer cells and hepatocytes. Kupffer cells trap endotoxin by a mechanism of nonspecific pinocytosis and modify it. This modification allows uptake by the hepatocyte via a mechanism yet to be defined. The hepatocyte, in turn, then both detoxifies and eliminates the modified endotoxin (118). In liver disease, these detoxification processes are impaired, which results in the "overspill" of endotoxin into the systemic circulation. The systemic endotoxia initiates a biologic cascade of multiorgan damage, clinically manifested as fever, metabolic acidosis, disseminated intravascular coagulation, hemodynamic instability, and organ dysfunction (119). Most of the cytopathic effects of endotoxin are thought to be the result of an intricate network of interaction between humoral and cellular factors. Thus, endotoxin-macrophage interaction leads to the activation of classic endocytic and detoxification functions and promotes the secretion of various mediators of the inflammatory response, including enzymes, reactive metabolites of oxygen, bioactive lipids, and monokines, mainly, interleukin-1, interleukin-6, and tumor necrosis factor (120,121). Potent vasoactive substances like prostaglandins, thromboxane, leukotrienes, and platelet-activating factor are secreted into the inflammatory milieu and contribute to regulate the microcirculation, vessel wall permeability, and platelet action. Oxygen radicals and proteases cause endothelial cell damage and tissue destruction and activate the coagulation cascade. Interleukin-1 and tumor necrosis factor produced by macrophages, monocytes, and endothelial cells act as proximal immune mediators of the inflammatory response. They, in turn, induce the release of multiple chemotoxins and promote cell-to-cell interactions and cell-tissue interaction.

The interplay between cellular factors and cellular mediators is also operative in the liver damage induced by endotoxin. In a murine model of chronic hepatic inflammation, generated by an injection of Corynebacterium parvum, the administration of LPS (endotoxin) results in progression to sudden hepatic necrosis. The liver damage is mediated by superoxide and hydroxyl radicals as well as by intravascular thrombosis (122,123). Interestingly enough, nitric oxide synthesis by hepatocytes and liver macrophages is stimulated by LPS (see later) and provides a protective function against endotoxin-induced liver injury (122-124). This modulatory rate of NO is attributable to reduced oxygen radical-mediated injury and the prevention of intravascular thrombosis triggered by LPS (123).

Endotoxin-mediated organ dysfunction probably plays an important role in the setting of extrahepatic biliary obstruction (125-127). Endotoxia occurs in 25 to 85% of patients with obstructive jaundice (128,129). There is considerable evidence that endotoxia is the underlying cause of some complications seen in this condition, e.g., renal failure, coagulation disorders, gastrointestinal hemorrhage, and depressed cellular immunity (for a review, see Ref. 130). Moreover, a relation exists between endotoxia and the outcome of jaundiced patients after surgery because all patients who died after surgery showed preoperative endotoxia (129).

Several studies, both clinical and experimental, have put special emphasis on the role of bile acids in the development of endotoxia during obstructive jaundice. Because this condition is characterized by low amounts of bile acids in the intestine combined with high serum bile acid levels, it has been shown that both phenomena can account for endotoxia during obstructive jaundice. Thus, the absence of bile acids in the gut allows enhanced absorption of endotoxin from the gastrointestinal tract. In addition, the high level of circulating bile acids in obstructive jaundice brings about impaired detoxifying function by Kupffer cells (131). On the basis of these data, it has been shown that in BDL rats who manifest portal and peripheral endotoxia on Day 7 after surgery, the incidence of this complication can be reduced significantly by the oral administration of the bile acid ursodeoxycholate (131). Moreover, postoperative morbidity and mortality of jaundiced BDL rats could be prevented by preoperative internal biliary drainage, a procedure that relocates bile salts back into the gastrointestinal tract (132,133). Likewise, it has been shown that in patients with obstructive jaundice, orally administered bile salts can protect the kidney. In this study, Cahill (134) has reported that 54% of patients with obstructive jaundice undergoing surgery had systemic endotoxia accompanied by a high incidence of postoperative renal impairment and that both the endotoxia and the renal dysfunction could be prevented by the administration of the bile salt sodium deoxycholate. He presented evidence to sup-
port the notion that the bile salt acted by absorbing endotoxin in the gastrointestinal tract rather than by any direct antimicrobial effect. On the other hand, studies with polymyxin B in jaundiced patients with obstructive liver disease have yielded inconsistent results (135). Polymyxin B binds and neutralizes endotoxin and thus is an antiendotoxin. A recent study from England reported the occurrence of endotoxinemia, its relationship to renal failure, and its response to polymyxin (129). Endotoxemia occurred in 68% of jaundiced patients who had increased likelihood of postoperative renal insufficiency and higher mortality than did patients without endotoxemia. Nevertheless, no significant improvement in renal function or decrement in endotoxemia was noted in the polymyxin B–treated group.

The sequence of events leading from endotoxemia to renal failure is poorly understood. Attempts at evaluating the renal effects of endotoxin are often confounded by the coexistence of hypotension, intravascular coagulation, and cardiovascular collapse. Several studies, however, have succeeded in clearly dissociating endotoxemia–induced renal dysfunction from hypotension and shock. Thus, a direct effect of endotoxin on renal function was originally suggested in 1970 from the observation that the injection of endotoxin into the renal artery of baboons decreased RBF before hypotension developed (136). Recently, several groups of investigators, using a bolus injection or a continuous infusion of endotoxin in rats (137), mice (138), sheep (139), or dogs (140), have demonstrated that hypotension was not necessary for GFR to decrease after exposure to endotoxin. In experimental models of nonhypotensive acute endotoxemia, light microscopic examination of the kidney is usually normal (141). When examined by electron microscopy, however, endotoxemic renal failure has been consistently associated at 1 to 3 h with ultrastructural changes demonstrating abnormalities and swelling of endothelial cells in renal arterioles and in glomerular and peritubular capillaries (137). These changes are apparent after the administration of a low-dose (100 μg/kg) Escherichia coli endotoxin and are consistent with early endothelial cell injury. These ultrastructural changes of the microvasculature are often associated with leukocyte sequestration in renal capillaries as well as intracapillary thrombosis (142).

In spite of this strong experimental background, the evidence remains equivocal for involving endotoxin in the pathogenesis of renal dysfunction associated with obstructive jaundice in human patients. Gatta and colleagues (143), in a careful study of systemic endotoxemia and renal function in cirrhosis, found no difference in the frequency of endotoxemia in patients with and without impaired RBF. Prospective studies are therefore needed on well-selected patient groups that directly address this issue by using sensitive, quantitative, and reproducible methods for measuring endotoxin. At the present, the mechanism and the sequence of events leading from endotoxemia to renal failure remain to be defined.

An interesting influence of endotoxemia, namely, the stimulation of NO in vascular tissue, has been implicated in the pathogenesis of systemic hypotension and other complications observed in liver disease and obstructive jaundice. This topic is reviewed in the next section. Figure 4 summarizes the cascade of presumed biologic events involved in the action of endotoxin during liver disease and obstructive jaundice.

NITRIC OXIDE, LIVER DISEASE, AND OBSTRUCTIVE JAUNDICE

Chronic liver disease (e.g., liver cirrhosis), as well as obstructive jaundice, is associated with decreased systemic vascular resistance and refractoriness to vasoconstrictor agents (49, 74). Mediation of these changes by the newly discovered endogenous vasodilator NO has recently received considerable attention. NO is a potent vasodilator synthesized from L-arginine by two distinct NO synthases in vessel walls. One enzyme is always present in the vascular endothelium of animals and humans, whereas it generates low NO concentrations to activate the soluble guanylate cyclase in vascular smooth muscle and regulates physiologic vascular tone, blood pressure, and tissue perfusion (144, 145). The second NO synthase is induced in the vascular endothelium and smooth muscle of animals and vascular smooth muscle cells of humans by endotoxin and some cytokines (146). In vitro studies show that the induction of this enzyme causes prolonged NO synthesis, which leads to sustained vasodilation and resistance to vasoconstrictors. In vivo studies in the dog and rat have shown that the vasodilation and decreased vascular responsiveness that occur in response to endotoxin or cytokines are mediated by NO synthesis (147, 148). Moreover, the induction of NO synthase with the increased production of NO may also explain the peripheral vasodilation that occurs in response to endotoxin infusion in humans (149) or in patients with septic shock (150).

Given the high incidence of endotoxemia in liver disease and obstructive jaundice (discussed in the previous section), it was proposed that high endotoxin levels in these conditions trigger the induction of vascular NO synthesis, thereby leading to systemic hypotension (151). Several lines of indirect evidence, in fact, seem to implicate NO in the hemodynamic profile associated with liver disease. In cirrhotic humans, significantly elevated urinary cGMP levels (a second messenger and biologic marker for NO) were detected even before the onset of ascites (152). Similarly, serum, nitrite, and nitrate levels (used as surrogates for NO) were found to be elevated in cirrhotic patients (153). The patients with ascites manifested higher nitrite and nitrate levels than did cirrhotic patients without ascites. A recent case report described an elevation in blood pressure in response to
methylene blue infusion (an inhibitor of guanylate cyclase and cGMP production) in a patient with liver disease due to alcoholic cirrhosis and severe hypotension resistant to pressor agents (154). Rats with portal hypertension due to CCL4-induced cirrhosis manifested enhanced sensitivity to the pressor effect of a structural analog of l-arginine (Nw-nitro-L-arginine) that blocks NO biosynthesis. Thus, after the administration of this agent, arterial pressure significantly rose in the cirrhotic rats but not in conscious control rats (155). Taken together, these data support the contention that an increased systemic release of NO in cirrhosis contributes to the decrease in systemic vascular resistance present in this condition.

Although most studies on NO in liver disease were done in cirrhotic patients, it is conceivable that NO also plays a role in the altered hemodynamics observed in obstructive jaundice. Given the close association of endotoxia with obstructive jaundice (128,129), the role of bile acids in the pathogenesis of endotoxia (131), and the link between endotoxin and NO production, one would assume that NO is responsible for the arterial hypotension observed in obstructive jaundice. Thus far, this hypothesis has not been tested either in experimental models of jaundiced animals (CBDL or CDCA) or in patients with cholestatic jaundice. It is clear, at this point, that more studies are needed to evaluate the role of NO in the hemodynamic disturbances associated with either cirrhosis or obstructive jaundice. Studies should include a large number of patients and use specific inhibitors of inducible NO synthase combined with measurements of both systemic and renal hemodynamic indices. Until such studies are available, it would be somewhat premature to establish a pathophysiologic importance for NO in these conditions.

Aside from its effects on hemodynamics, NO may also mediate some of the hepatocellular abnormalities associated with chronic liver disease or obstructive jaundice. It has been suggested that high endotoxin levels associated with these conditions, activate Kupffer cells, which in turn release several cytokines such as interleukin-1 and tumor necrosis factor. These products of endotoxin-triggered Kupffer cells may mediate a decrease in hepatocyte protein synthesis by an NO-dependent mechanism (156–158). The NO originates in liver cells (hepatocytes) after the induction of NO synthase in response to the cytokines produced by Kupffer cells. This was further substantiated by in vitro studies showing that endotoxin added to cultured hepatocytes and Kupffer cells, but not to hepatocytes alone, induced a profound decrease in hepatocyte protein synthesis without inducing hepatocellular death (158,159). The Kupffer cell–mediated inhibition of hepatocyte protein synthesis is associated with the production of nitrates, nitrites, and citrulline and is blocked by l-arginine analogs, suggesting that the production of NO from l-arginine is required (158). Northern blot analysis of hepatocyte albumin mRNA levels shows that NO has no effect on the relative abundance of hybridizable albumin mRNA (160), indicating that NO inhibits hepatocyte protein synthesis.
synthesis through an undefined translational or post-translational mechanisms. It is hypothesized that NO formation in endotoxemic states (sepsis, liver disease, obstructive jaundice) is involved in the decreased albumin synthesis seen in some patients with cirrhosis or in the impaired synthesis of coagulation factors found in liver diseases or obstructive jaundice.

The treatment of experimental animals with endotoxin or certain hepatotoxic drugs is associated with the intrahepatic accumulation of inflammatory macrophages thought to promote hepatic damage through the release of toxic secretory products. Because NO is one product of activated macrophages, it is possible that NO formed by activated macrophages may mediate endotoxin- or drug-induced liver damage. In fact, in an in vivo murine model of endotoxin-induced hepatic necrosis with known increased hepatocellular production of NO (122,124), increased NO production was found to protect the liver from damage. In this model, the inhibition of NO synthesis with an L-arginine analog decreased the endotoxin-induced increase in NO synthesis and markedly increased hepatic injury (122–124). The hepatic damage induced by suppressing NO production during endotoxia could be reduced by treating mice with superoxide dismutase and desferoxamine, scavengers of superoxide and hydroxyl radicals, respectively (123), suggesting that, during an endotoxin insult to the liver, NO may alleviate the liver damage by acting as an antioxidant. In contrast, other evidence suggests that NO may interact with reactive oxygen intermediates to form more toxic species. Thus, the reaction of NO with superoxide anion can produce the peroxynitrite anion, which can decompose to generate a strong oxidant with reactivity similar to hydroxyl radical (161,162). Whether NO acts to attenuate or potentiate tissue injury from reactive oxygen intermediates, it clearly plays an important role in conditions where reactive oxygen intermediates mediate hepatotoxicity. These conditions include endotoxia, such as observed in liver disease and obstructive jaundice, ischemia-reperfusion injury in hepatic allografts, drug-induced hepatotoxicity, and immune-mediated liver damage.

In conclusion, the L-arginine–NO pathways activated by endotoxia seem to have a wide spectrum of biologic effects in patients with parenchymal liver disease or in patients with cholestatic jaundice. The role of NO in the pathogenesis of the multisystemic disease in these patients is summarized in Table 2.

Interestingly, although some of its effects are harmful (e.g., reduced systemic vascular resistance, decreased albumin synthesis in liver) other NO effects may be beneficial (e.g., protecting the liver from oxidant injury by oxygen radicals). Because of this kind of diverse action attributable to NO, the potential use of NO synthesis inhibitors has recently been subjected to critical evaluation. Because endogenous NO protects the intestinal mucosa and liver against the toxic effects of endotoxin and because of its modulatory role on hepatic blood flow, it is clear that the nonspecific inhibition of NO synthase could have harmful effects on liver function. Furthermore, changes in endogenous NO could lead to the impairment of immune function and neurologic damage (163). As to the treatment of hypotension induced by endotoxin and NO, although some experimental and clinical studies (147–150) suggest that NO synthase inhibitors may elevate blood pressure in septic shock, these studies are preliminary at most. In fact, in rats with septic shock, the use of a high dose of NO synthase inhibitor (as opposed to a lower dose) worsened the hypotension, suggesting that complete inhibition of NO synthesis may be harmful (164). Thus, many obstacles need to be overcome (e.g., determination of optimal dose, mode of administration, and further toxicologic studies) before NO synthase inhibitors such as L-arginine analogs can be applied for routine clinical use. Perhaps the therapeutic future lies in the development of NO synthase blockers that inhibit only the NO synthase of a target cell, e.g., the vascular smooth muscle, while leaving other cells intact.

### TABLE 2. Spectrum of biologic effects of NO on systemic hemodynamics and hepatocellular function

- NO mediates systemic hypotension in liver disease and obstructive jaundice.
- NO modulates hepatic arterial blood flow.
- NO produced by Kupffer cells and hepatocytes in response to endotoxin inhibits hepatocyte protein synthesis.
- NO from activated macrophages may mediate endotoxin- or drug-induced hepatotoxicity.
- NO binds to cytochrome P450 enzymes and may alter enzyme activity and affect drug-induced hepatotoxicity.
- NO may act as an antioxidant to protect liver from oxidative injury.
- NO may produce highly reactive species (e.g., peroxynitrite) and accentuate oxidative liver injury.
to 25\% by internal biliary drainage. External biliary drainage did not significantly alter mortality. These findings are consistent with the theory that endotoxemia caused by the absence of bile salts in the intestine (a condition corrected by internal but not by external biliary drainage) is at least partially responsible for the high incidence of renal failure and mortality associated with obstructive jaundice. Several reports (134) showing that the preoperative administration of sodium deoxycholate to jaundiced patients prevents systemic and portal endotoxemia and also prevents postoperative renal dysfunction support this theory (168). At present, the use of one or more antiendotoxin therapeutic measures (biliary drainage, bile acids, antibiotics, lactulose) remains an unresolved issue and awaits further confirmation by well-designed controlled studies (130,169).

Patients with obstructive jaundice are prone to the development of hypotension both during and after surgery and may have a blunted vascular response to blood loss. Some of these patients may also suffer from impaired myocardial function. Hence, the maintenance of circulating extracellular volume is the mainstay of treatment and prophylaxis in jaundiced patients undergoing surgery. Williams et al. (3) noted that operative mortality declined if preoperative blood transfusions were given. Because a low hematocrit has been shown to be a significant risk factor in this population, normalization of the hematocrit is advisable. In addition, careful preoperative evaluation and both intraoperative and postoperative monitoring of fluid status and cardiac performance should be performed. Because both animals with BDL and human subjects with cirrhosis respond to nonsteroidal anti-inflammatory drugs with a marked decrease in both RBF and creatinine clearance, these drugs should be avoided. Finally, Dawson (16,96) has demonstrated the beneficial effects of mannitol administration in both animal and human subjects. Rats made jaundiced by BDL and then subjected to renal ischemia developed renal failure with a high mortality rate (9 of 14 animals). However, if mannitol was administered before renal ischemia, renal function was preserved and no deaths occurred (96). Similarly, jaundiced dogs subjected to hemorrhage had a transient but marked decrease in GFR that could be avoided by the prehemorrhage administration of mannitol (81). In human subjects, Dawson (16), in a nonrandomized study, was the first to advocate the use of mannitol immediately before the operation and for the first 2 to 3 postoperative days to prevent the decline in kidney function in patients with obstructive jaundice. The beneficial action of mannitol may result from several mechanisms. As an osmotic diuretic, it causes volume expansion, diuresis, and natriuresis. It also maintains RBF at low perfusion pressures and prevents endothelial cell swelling and tubular obstruction. Since Dawson's report, his method became standard practice in jaundiced patients. However, this therapeutic modality has not been adequately subjected to critical analysis, despite the high incidence of acute renal failure reported even with the use of mannitol (130). In fact, a recently reported prospective and randomized study (170) showed that mannitol did not improve the postoperative renal function in patients who were already impaired before surgery and it worsened that of patients who had normal creatinine clearances before surgery. The mean preoperative creatinine clearance of patients receiving mannitol was 71 mL/min, which dropped to 57 mL/min after surgery ($P = 0.037$). In the no-mannitol group, the mean preoperative creatinine clearance was 64 mL/min, which dropped to 54 mL/min after surgery; the difference was not statistically significant. On the basis of experimental evidence showing that rabbits with CBDL develop an appreciable reduction in extracellular water and intravascular volume (171), it has been suggested that severe disturbances of body fluid compartments may be the basic mechanism underlying kidney dysfunction in obstructive jaundice (even before surgery). Therefore, further water depletion induced by the osmotic action of mannitol may prove detrimental under these conditions. Despite various flaws in the study by Gubern et al. (170), the importance of perioperative fluid replacement in jaundiced patients cannot be overemphasized. The value of mannitol and its relative role vis-à-vis volume replenishment alone are still to be proved.

**SUMMARY**

The current evidence, mainly derived from experimental models, indicates that jaundice alone (i.e., independent of liver parenchymal disease) affects the integrity of the cardiovascular function. These effects are (1) reduction in peripheral vascular resistance, which results in systemic hypotension; (2) depression of myocardial performance; and (3) an initial and profound natriuresis and diuresis that may lead to volume depletion. Furthermore, most of the experimental data suggest that neither bilirubin nor bile acids have a direct nephrotoxic effect, and therefore, renal complications in experimental obstructive jaundice are mainly due to prerenal factors. Because most acute renal failure cases in patients with obstructive jaundice have been encountered in a postsurgical setting, it is conceivable that, in these patients, prolonged exposure of the kidney to bile constituents plays in concert with events taking place during the operation (hypotension, hemorrhage, endotoxemia, anesthesia) to cause severe hemodynamic perturbation and acute renal failure in the postsurgical state.

In addition to the deleterious effects of bile acids on the kidney and the circulation, it is clear that factors related to the liver parenchymal damage associated with obstructive jaundice may have an independent contribution to the pathogenesis of "arterial underfilling," which will further predispose these patients to prerenal failure and eventually to acute tubular necrosis. The role of cholemia vis-à-vis liver disease in
Figure 5. Schematic drawing of probable mechanisms whereby “cholemic” factors and parenchymal liver disease interact to produce renal dysfunction in obstructive jaundice. Renal failure can be observed during jaundice (cholemia) with minimal liver damage as well as in parenchymal liver disease associated with only a minimal degree of jaundice. Both conditions are associated with a combination of prerenal factors that, in turn, may lead to acute tubular necrosis (ATN). Hepatorenal syndrome (HRS) stands out as a separate entity that is associated with advanced stages of parenchymal liver disease (e.g., cirrhosis) and that is caused by an idiopathic hypoperfusion of the renal cortex. As explained in the text, although predominant “cholemic” conditions (e.g., PBC) are associated with exaggerated natriuresis, when severe liver damage supervenes, avid salt retention takes place with the attendant clinical features of ascites and peripheral edema. PBC, primary biliary cirrhosis; PVR, peripheral vascular resistance; LV, left ventricle; CO, cardiac output.

the pathogenesis of hemodynamic dysfunction and renal failure is depicted schematically in Figure 5. Clearly, the peripheral and renal hemodynamic effects of “surgical” jaundice (i.e., obstructive jaundice) are much more marked than that of “medical” jaundice associated with cirrhosis. This difference can be attributed to a higher prevalence and severity of endotoxemia in obstructive jaundice and the deleterious effects of endotoxin on both the peripheral vasculature and the renal microcirculation. In addition, the elevated levels of circulating bile acids in “surgical” jaundice contribute to a more severe hemodynamic perturbation by a direct effect on the systemic circulation, by a cardiodepressor effect, and probably by a hypovolemic (i.e., diuretic) effect.

Preventive measures based on the appreciation of the underlying pathogenetic mechanisms should focus on the vigilant management of fluid status. Clearly, prevention remains the key to the treatment of surgical acute renal failure in patients with obstructive jaundice.

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