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Bile acids and cardiovascular function in cirrhosis

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Abstract

Cirrhotic cardiomyopathy and the hyperdynamic syndrome are clinically important complications of cirrhosis, but their exact pathogenesis is still partly unknown. Experimental models have proven the cardiotoxic effects of bile acids and recent studies of their varied receptor-mediated functions offer new insight into their involvement in cardiovascular dysfunction in cirrhosis. Bile acid receptors such as farnesoid X-activated receptor and TGR5 are currently under investigation as potential therapeutic targets in a variety of pathological conditions. These receptors have also recently been identified in cardiomyocytes, vascular endothelial cells and smooth muscle cells where they seem to play an important role in cellular metabolism. Chronic cholestasis leading to abnormal levels of circulating bile acids alters the normal signalling pathways and contributes to the development of profound cardiovascular disturbances. This review summarizes the evidence regarding the role of bile acids and their receptors in the generation of cardiovascular dysfunction in cirrhosis.

KEYWORDS

bile acids, cholestasis, cirrhosis, cirrhotic cardiomyopathy, farnesoid X-activated receptor, hemodynamics, ursodeoxycholic acid

1 | INTRODUCTION

In patients with cirrhosis the course of the disease is determined by the development of severe complications due to the altered structure and metabolic function of the liver. Patients can develop splanchnic and arterial vasodilatation leading to an increase in heart rate and cardiac output defining the "hyperdynamic circulatory state", as well as a chronotropic and inotropic cardiac incompetence termed "cirrhotic cardiomyopathy".¹ This profound cardiovascular dysfunction contributes to multiorgan failure in decompensated cirrhosis but its' underlying pathogenesis is not fully understood. Exploration of the therapeutic opportunities presented by bile acid (BA) modulation in

cholestatic disorders as well as in nonalcoholic fatty liver disease, obesity, diabetes and inflammatory bowel disease has imposed a new paradigm of bile acids as a signalling and metabolic crossroad.² Thus, there is an abundance of data on the role of altered BA homeostasis in diseases ranging from metabolic syndrome to tumorigenesis to cirrhosis.

Although both the cardiotoxic effect of BAs and the existence of a hyperdynamic syndrome in cirrhotic patients have been known for some time, there is relatively little data on the impact of BAs on cardiovascular function in the setting of chronic liver disease. The aim of this review was to provide a survey of the current evidence regarding the action of BAs on receptors and pathways relevant to the development of cardiovascular disturbances in cirrhosis.

2 | BILE ACIDS AND THEIR METABOLISM

Bile acids are products of the tightly regulated metabolism of cholesterol by the liver. The cholic (CA) and chenodeoxycholic acid (CDCA)

Abbreviations: BA, bile acid; BK_{Ca}, large conductance calcium-dependent potassium channels; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; eNOS, endothelial nitric oxide synthase; FXR, farnesoid X-activated receptor; ICP, intrahepatic cholestasis of pregnancy; LCA, lithocholic acid; NFκB, nuclear factor κB; NO, nitric oxide; OCA, obeticholic acid; PBC, primary biliary cholangitis; Pgc1α, peroxisome-proliferator-activated receptor γ co-activator; PXR, pregnane X receptor; S1PR2, sphingosine-1-phosphate receptor-2; UDCA, ursodeoxycholic acid; VDR, vitamin D receptor.

also known as “primary bile acids” are exclusively synthesized in hepatocytes under enzymatic control with 7 α -hydroxylation by CYP7A1 as the main pathway and rate-limiting step.³ Once formed they are conjugated via an amide bond with an amino acid to increase hydrophilia. The amphipathic glyco- or tauroconjugates are then secreted through canalicular bile-salt export pumps into the bile canaliculi and contribute to hepatocyte excretion and bile formation. Interprandially bile is stored in the gallbladder from where it is expelled into the small intestine during meal ingestion. Once it reaches the intestinal lumen bile mixes with the gastric chyme and emulsifies fat and fat-soluble vitamins required for proper nutrient digestion and absorption. Ninety-five per cent of the BAs secreted are then reabsorbed in the terminal ileum via the apical sodium-dependent bile transporter present in the brush border membrane of the enterocytes.⁴ The remainder are converted into “secondary bile acids”: deoxycholate (DCA) and lithocholate (LCA) and less than 1% to ursodeoxycholate (UDCA) by anaerobic bacteria in the colon and are either passively absorbed or excreted in the faeces. The absorbed BAs are delivered to the liver where some are actively transported back into hepatocytes closing the loop of the so-called “enterohepatic circulation” (Figure 1). BAs that reach the colon can be absorbed but 5% are lost in faecal output, while most of the BAs reaching the kidneys are reintroduced in circulation.⁵

The alteration of BA pool size and composition is a consequence of the disturbed metabolism in cirrhosis but it also contributes to the progression of liver disease. There is now increasing evidence of a causal relationship between reduced faecal BA concentrations, the gut microbiome and systemic inflammation.^{6,7} The low input and conversion of primary BAs in the colon encountered in advanced cirrhosis leads to dysbiosis characterized by an alteration of the equilibrium between the main bacterial species normally inhabiting the large intestine.⁸ Overgrowth of intestinal bacteria and increased gut permeability due to the insufficient antimicrobial function of a depleted BA pool is followed by bacterial translocation and a potent inflammatory response that can determine decompensation of liver disease.⁹ In a recent observational prospective study, increased BA levels correlated with acute decompensation on admission of cirrhotic patients independently of sex, age and MELD score.¹⁰

Carefully regulated feedback loops that promote a stable BA pool have been identified in the last decades. The most important regulatory pathway is dependent on the Farnesoid X-activated receptor (FXR) expressed in the nucleus of both terminal ileum enterocytes and hepatocytes. FXR can reduce the BA pool by inhibiting the main synthetic CYP7A1-regulated pathway either directly or through fibroblast growth factor 19 as well as by lowering the hepatocyte portal uptake of BAs through sodium-taurocholate cotransporting polypeptide.¹¹

In cholestatic syndromes, serum BA concentration rises due to backflow or inefficient hepatocellular uptake illustrating a functional defect in bile formation at the level of the hepatocyte or impairment in bile secretion and flow. The accumulation of highly cytotoxic hydrophobic BAs¹² in the hepatocytes induces up-regulation and recruitment of alternative export pumps at the basolateral membrane in an attempt to evacuate the toxic molecules out of the cell and into the circulation with subsequent renal excretion offering some relief.¹³

Key points

- Cardiovascular dysfunction is prevalent in chronic cholestatic syndromes and cirrhosis.
- Bile acids directly and reversibly affect cardiac function in experimental models of cholestasis and cirrhosis.
- Through action on specific receptors bile acids influence metabolism, function, growth and survival of cardiomyocytes, vascular endothelial cells and smooth muscle cells.
- The similar pathogenetic mechanisms described in cardiovascular dysfunction in cirrhotic patients argue for the role of bile acids in the development of cirrhotic cardiomyopathy.

Cholestasis is encountered in numerous hepatic and systemic disorders^{14,15} and is a particularly common feature of cirrhosis. Based on Dame Sheila Sherlock's¹⁶ initial observations of increased serum BAs in liver disease, further efforts in the 1970s¹⁷⁻¹⁹ established that up to a 100-fold increase in concentrations is encountered in cirrhosis. Hence, cirrhotic patients can have serum concentrations well above 100 $\mu\text{mol/L}$,^{20,21} whereas the normal range of bile acids in fasting human adults is 2-15 $\mu\text{mol/L}$ depending on age and gender.²² Furthermore, there also appears to be a shift towards lower ratios of the trihydroxy to dihydroxycholic acids as well as glycine to taurine conjugates. So far, however, the lack of significant diagnostic or prognostic benefit has discouraged the adoption of serum BA measurement as part of the routine work-up in patients with liver disease.

3 | BILE ACID RECEPTORS IN CARDIAC AND VASCULAR CELLS

The discovery in 1995 of a new type of nuclear hormone receptor, the Farnesoid X-activated receptor,²³ and the search for its natural ligand led to the surprising conclusion that endogenous BAs were also potent signalling molecules that regulate cholesterol metabolism and their own synthesis.²⁴ FXR is activated by hydrophobic BAs: CDCA followed by LCA, DCA and CA and is essential to the regulation of the BA pool. Further studies have revealed other BA-responsive elements: nuclear receptors (pregnane X receptor-PXR,²⁵ vitamin D receptor-VDR²⁶), G-protein coupled receptors (muscarinic receptors – M₂, M₃, TGR5, sphingosine-1-phosphate receptor-2-S1PR²⁷), calcium-activated potassium channels and $\alpha 5\beta 1$ integrin.²⁸ These receptors are primarily expressed by gastrointestinal tissues but some have also recently been identified in cardiomyocytes, endothelium and vascular smooth muscle cells,^{29,30} which has led to speculation on possible cardiovascular effects of bile acids.

Ligand-bound nuclear receptors undergo conformational changes and dimerization to interact with specific DNA regions and induce gene transcription. FXR is currently the best characterized BA-responsive nuclear receptor and studies have shown its' role in

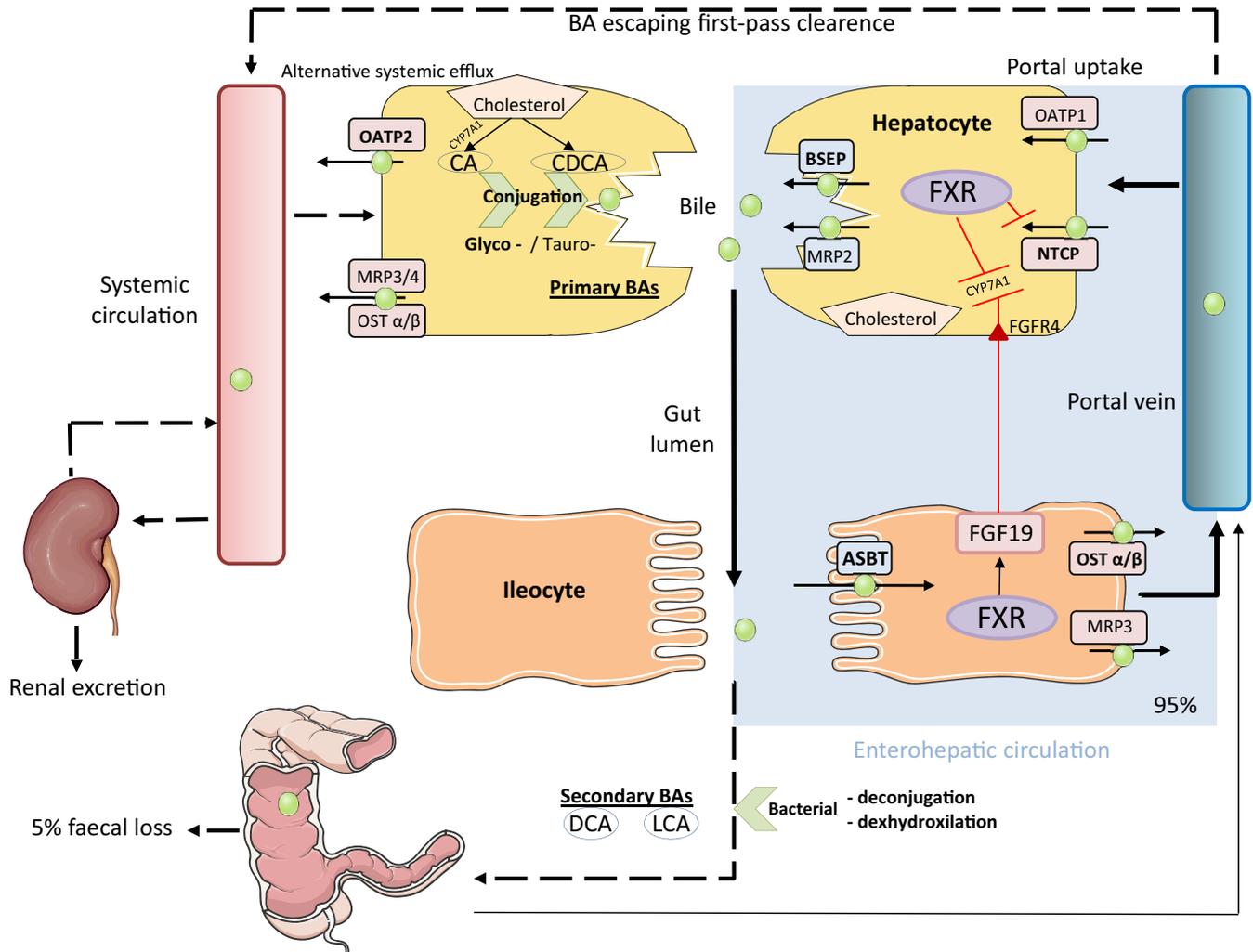


FIGURE 1 Bile acid metabolism. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are synthesized from cholesterol via a main pathway controlled by the rate-limiting enzyme CYP7A1. After conjugation with glycine or taurine they are excreted via the canalicular bile-salt export pump (BSEP) to form bile. 95% of bile acids (BA) are absorbed actively upon reaching the terminal ileum through the apical sodium-dependent bile-salt transporter (ASBT). They are excreted through organic solute transporter α and β dimer (OST α/β) located on the basolateral enterocyte into the portal circulation from where they are absorbed by hepatocytes via the sodium-taurocholate cotransporting polypeptide (NTCP) and organic anion transporters (OATP1). BAs reaching the colon are deconjugated and dehydroxylated by bacteria and form “secondary BAs” (mainly deoxycholic acid – DCA and lithocholic acid – LCA) which can be absorbed or pass into stool. The Farnesoid X-activated receptor (FXR) reduces BA synthesis by inhibiting CYP7A1 directly or through fibroblast growth factor 19 (FGF19) and lowers hepatocyte portal uptake of BAs through NTCP. MRP2, Multidrug resistant associated protein; OATP, Organic anion transporter protein

regulation of bile acid homeostasis, glucose and lipid metabolism, energy expenditure and inflammation. The finding that synthetic FXR ligands can inhibit interleukin-1 β -induced inflammatory responses in rat aortic smooth muscle cells pleads for the antiatherogenic potential of FXR agonists.³¹ The putative mechanism of this effect is the tethering transrepression of nuclear factor κ B (NF κ B) by the activated FXR with subsequent antagonization of this proinflammatory pathway.³² Using an automated high-throughput luciferase assay, Bijmans et al.³³ identified the glucocorticoid mometasone furoate as a potent inhibitor of the TNF α -induced transcriptional activity of NF- κ B. Showing that the proinflammatory cascade can be selectively inhibited without undue simultaneous influence on metabolic target genes is an important step in designing an FXR-targeted drug with anti-inflammatory properties.

This finding is extremely promising in the setting of our current knowledge of the pathogenesis of cirrhotic cardiomyopathy. Valuable work produced by Lee and his group in the last decade has convincingly established a pathogenetic link between bacterial translocation or endotoxemia and increased activity of an endocannabinoid-TNF α -NF κ B axis leading to reduced cardiac contractility in animal models.^{34,35} Study of TNF α knockout bile duct ligated mice offered insight into the complex interplay between the effects of local endocannabinoid and TNF α release and cardiac inotropism.³⁶ Bile duct ligated animals showed depressed cardiac function and increased expression of TNF α and NF κ B while treatment with anti-TNF α antibodies significantly improved cardiomyocyte contractility. There is also new evidence supporting the role of FXR in regulating vascular contractile response and blood pressure. In a recent study, treatment with CDCA

for 8 weeks of spontaneously hypertensive rats resulted in vasorelaxation and lower blood pressure and this correlated with a significant reduction in NF κ B activity in the mesenteric arteries.³⁷

Using cultured cardiomyocytes Pu et al. demonstrated that FXR is expressed in cardiac cells and that its' activation causes significant apoptosis through mitochondrial death signalling. They also verified their findings in an *in vivo* mouse model of myocardial ischaemia/reperfusion injury and concluded that FXR signalling could be involved in several cardiac diseases related to cardiomyocyte growth and apoptosis.³⁸ The indications that FXR may lower plasma triglyceride levels, regulate peripheral insulin sensitivity and protect against atherosclerosis,³⁹ make a very strong case for current attempts at therapeutic intervention on this receptor in patients suffering from metabolic syndrome. While PXR and VDR play important parts in BA and drug metabolism and detoxification, less is known of their effects on vascular homeostasis.⁴⁰ Green et al.⁴¹ studied the effect of vitamin D(3) on sarcomere shortening and relaxation in adult rat myocytes and described an acute decrease in peak shortening coupled with an increase in contraction rate, but only accelerated relaxation persisted under chronic stimulation. This rapid nongenomic response could be due to a membrane-associated VDR that regulates calcium influx into the cardiomyocytes resulting in modulation of diastolic function.⁴²

Bile acids can also functionally interact with membrane receptors and activate intracellular effector cascades. Discovery of a structural similarity between tauroolithocholate and acetylcholine led to interest in the interaction between BAs and muscarinic receptors, with reports revealing an antagonistic effect of DCA on M₂ and M₃ receptors also expressed in cardiac tissue.⁴³ In this study, Raufman et al. compared the effect of BAs to other muscarinic blockers on Chinese hamster ovary cells expressing rat M₃ receptors and found that DCA and its' conjugates act as muscarinic antagonists at levels normally encountered in human bile. Such an effect would result in a reduction in intracellular levels of cyclic adenosine monophosphate which negatively influences chronotropism.

Observations related to the reduced cell-mediated immunity and macrophage functions in cholestasis led to the identification of a novel cell-surface-based signalling pathway for BAs: the G-protein coupled TGR5 identified in macrophages but also in the heart, skeletal muscle, spleen, kidney, liver, small intestine and placenta.⁴⁴ The deleterious effect of prolonged exposure of immune cells to increased levels of BAs indicates that they may be a mediator of the increased risk of infectious complications and endotoxemia frequently encountered in cirrhosis. TGR5 seems to be integral to the control of inflammasome NLRP3 activation by BAs, a process required to develop the proinflammatory response to pathogen-associated molecular patterns.⁴⁵ While its' exact effect is still debated due to contradictory results in different experimental models, there is substantial evidence supporting the action of CDCA on the TGR5-NLRP3 axis.^{38,46} Another pathway by which BAs may contribute to the pathogenesis of hyperdynamic circulation in cirrhosis was proposed by Fiorucci et al. who showed that LCA but not CDCA activates endothelial TGR5 to increase cystathionin γ -lyase-dependent generation of vasodilatory hydrogen sulphide.⁴⁷ TGR5 activation by BAs is also involved in metabolic switching from fatty acid

to glucose oxidation in cardiac cells as well as increasing energy expenditure in brown adipose tissue,⁴⁸ a function which is intriguing considering the role played by cachexia in the outcome of cirrhotic patients.

Another G-protein coupled receptor that has proven sensitive to BAs is the sphingosine-1-phosphate receptor-2. Conjugated BAs activate S1PR2 which acts through ERK1/2 and AKT signalling pathways to regulate hepatic glucose and lipid metabolism.⁴⁹ The interaction between BAs and sphingosine-1-phosphate receptors is worthy of research due to the involvement of S1PR-mediated pathways in hepatic myofibroblast motility and liver fibrogenesis⁵⁰ as well as angiogenesis and vascular cell maturation.⁵¹

Bile acids have also been shown to increase the activity of large conductance calcium-dependent potassium channels (BK_{Ca}) located in smooth muscle cells. Dopico et al.⁵² speculate that the reversible BA-induced systemic vasodilation seen in hepatobiliary diseases could be due, at least in part, to activation of BK_{Ca} and subsequent relaxation of vascular smooth muscle cells. LCA was also shown to induce vasodilation and a 30% increase in blood flow in cerebral resistance arteries in an endothelium-independent fashion but this effect was abrogated in BK β -1 subunit knockout mice models, underlining the role of this subunit of potassium channels in BA-dependent activation of ion flow.⁵³ Since vasodilation and increased flow are essential components of the hyperdynamic syndrome, these findings argue for a receptor-mediated BA involvement in the persistence of this haemodynamic complication of cirrhosis.

4 | BILE ACIDS AND CARDIOVASCULAR FUNCTION

4.1 | Cardiac effects

The initial observation of a deleterious effect of bile on the cardiac function dates back to the 19th century. Intravenous injection of BAs in animal specimens induced profound bradycardia and, in high doses, even cardiac arrest despite heart denervation.⁵⁴ Further studies confirmed a direct arrhythmogenic response of the heart to exposure to supraphysiological levels of BAs as such encountered in cholestasis. Joubert demonstrated a dose-dependent negative chronotropic effect of cholic acid,⁵⁵ but it took several years until the precise cellular mechanism was elucidated. Working on papillary muscle and isolated ventricular myocytes Binah et al.⁵⁶ reported that sodium taurocholate decreased the slow inward sodium and calcium current and slightly increased the outward potassium current, thus reducing action potential duration, inotropism and chronotropism.

A lot of interesting work in the field of bile acid effects on cardiac tissue is a direct consequence of observations regarding the high rate of foetal complications and stillbirths associated with intrahepatic cholestasis of pregnancy (ICP).⁵⁷⁻⁵⁹ Starting from reports of foetal arrhythmias in obstetric cholestasis Williamson and Gorelik proposed that impaired foetal cardiomyocyte function leading to intra-uterine death could be due to the high levels of BAs present in patients with ICP.⁶⁰ Their initial report revealed that taurocholate altered calcium dynamics which led to loss of synchronous beating of cardiomyocytes.

The same group showed that taurocholic acid was responsible for reduced contractility and pacemaker activity⁶¹ while ursodeoxycholic acid protected against reentrant arrhythmias by modulating potassium conductance.^{62,63}

Due to the difficulties of conducting studies in the setting of ICP, such conclusions are mainly based on cell-cultures and animal models with few studies looking into the arrhythmogenic effects of BA in humans.⁶⁴ Rainer et al.⁶⁵ showed that taurocholic acid-induced concentration-dependent arrhythmia in human atrial myocardium and noted an association between atrial fibrillation and higher serum levels of nonursodeoxycholic bile acid conjugates and low levels of ursodeoxycholic acid conjugates in 250 patients. This reinforces the concept that bile acid composition and not only the increased concentration is important.⁶⁶

The accumulating evidence of the bile acid alteration of cardiac function in cholestasis has led to the hypothesis that BAs may play a major role in the pathogenesis of cardiomyopathy in cholestatic liver diseases.⁶⁷ Based on evidence of their negative inotropic and chronotropic effects, Gazawi et al.⁶⁸ showed that BAs also adversely affect cardiac β -adrenoceptor density and affinity and membrane fluidity, modifications which have also been described in cirrhotic cardiomyopathy. A comprehensive summary of the various factors that mediate the effects of BAs on cardiovascular tissues from experimental animal models has been presented by Khurana et al.⁶⁹ However, despite identification of several BA-sensitive receptors (FXR, VDR, TGR5, M₂) in cardiomyocytes, proof of their function is mainly indirect and a definitive pathogenetic mechanism has not yet been formulated.

4.2 | Vascular effects

The abnormally high levels of bile acids in the circulation encountered in cholestatic and chronic liver disease also have a direct effect on the function of endothelial and vascular smooth muscle cells with potential haemodynamic consequences.

Creation of a choledochocaval anastomosis in dogs resulted in a decrease in mean arterial pressure and peripheral vascular resistance but with preserved mean cardiac index and plasma volume.⁷⁰ Bile duct ligation was shown to reduce the vascular smooth muscle contractile response to noradrenaline with DCA being the most potent inhibitor.⁷¹ Pak et al.⁷² elegantly tried to identify the pathogenetic mechanisms by pharmacologically blocking membrane pumps, ion channels, adrenoceptors and sensory afferent nerves in rat isolated portal venous and superior mesenteric arterial specimens. Incremental doses of BAs induced vasorelaxation irrespective of blocking agents or denudement of the endothelium showing that the action is probably mediated through inhibition of calcium entry through membranary channels. This is highly influenced by the type of bile acid and indeed it seems that hydrophobic and lipophilic BAs are more likely to induce vasorelaxation.⁷³ The authors speculated on the mechanism by which bile acids accomplish this effect and concluded that it must be through direct interaction with components of the cellular membrane.

Again, the discovery and characterization of previously unknown bile acid receptors changed our understanding of how BAs induce vasodilation. Attention turned towards FXR due to its' recent identification in vascular endothelial and smooth muscle cells. Because of its' function as a transcription factor, it was to be expected that activated FXR regulates vasomotricity by altering the expression of vasoactive molecules and other receptors. Studies have shown that it can downregulate endothelin-1 and upregulate endothelial nitric oxide synthase (eNOS) in endothelial cells,^{74,75} modulate angiotensin-II receptor expression and inhibit vascular smooth muscle cell inflammation and migration.⁷⁶ After proving the functionality of FXR in pulmonary endothelial cells He et al.⁷⁴ demonstrated that activation by CDCA results in a decreased expression of endothelin-1 mRNA in a concentration-dependent manner. Since endothelin-1 is the most potent known vasoconstrictor its' repressed expression due to BAs could be an important contributor to the systemic vasodilation present in cirrhosis. The same group later proposed the existence of a FXR-responsive element in the promoter region of eNOS, the activation of which resulted in upregulation of eNOS and subsequent increase in production of the vasodilatory nitric oxide (NO).⁷⁵ S1PR2 is another BA-sensitive receptor found on vascular smooth muscle cells involved in NO signalling, but it acts by inhibiting the inducible nitric oxide synthase and thus lowering local NO levels in vascular injury.⁷⁷⁻⁷⁹

4.3 | Lessons learnt from therapy: ursodeoxycholic acid and obeticholic acid

Further evidence of the impact of BAs on cardiovascular function can be inferred from reports of ursodeoxycholate in experimental models as well as human studies. Since its' introduction in clinical practice UDCA has mainly been used in the treatment of primary biliary cholangitis^{80,81} and intrahepatic cholestasis of pregnancy. UDCA is a highly hydrophilic bile acid that improves biological parameters and histological features and delays progression to cirrhosis and the time to liver transplantation and was, until recently, the only approved therapy for primary biliary cholangitis (PBC).^{82,83} The mechanism of action has long been a matter of debate, but it is beyond a doubt that UDCA is a potent signalling molecule which modulates cholangiocytic bicarbonate secretion and intracellular calcium availability but also activates various kinases resulting in antiapoptotic and anti-inflammatory effects.⁸⁴⁻⁸⁶

The first exploration of the cardiohaemodynamic impact of UDCA in patients with cirrhosis was predicated on its' suspected diuretic and natriuretic properties compared to hydrophobic bile acids. Bomzon's group administered therapeutic doses of UDCA for 1 month to patients with PBC and postnecrotic cirrhosis and used blood pressure, heart rate, two-dimensional and pulsed Doppler echocardiography to measure cardiac function. They reported a decrease in diastolic volume in PBC patients and slightly lowered cardiac output in postnecrotic cirrhotic patients, with no change in heart rate or blood pressure.⁸⁷ It is worth noting that only half of the patients with PBC were cirrhotic while the postnecrotic viral hepatitis B or C patients all had significantly lower mean arterial blood pressure at baseline.

The same hypothesis was tested in patients with refractory ascites, half of them with TIPS, in the hope that UDCA would reduce vasodilation and improve renal sodium handling. Radionuclide angiography and venous occlusion plethysmography were used to ascertain central blood volume and total forearm blood flow respectively. There was no change in these systemic haemodynamic parameters, heart rate or mean arterial pressure during or after the end of the treatment, but the authors noted a decrease in sodium clearance and weight gain in all patients, concluding that UDCA led to sodium retention.⁸⁸

More recent studies have yielded similarly conflicting results. Thus, Schiedermaier et al.⁸⁹ reported a decrease in diastolic blood pressure but not portal flow in a small human cross-over study, while Yang et al.⁹⁰ described a reduction in portal pressure due to diminished intrahepatic resistance in a rat model. A nitric oxide-delivering derivative of UDCA was also shown to ameliorate portal hypertension without affecting arterial pressure.⁹¹

The impact on cardiac function has not been well studied but there is evidence that UDCA exerts limited but positive effects on peripheral blood flow in heart failure,⁹² prevention of ischaemia-reperfusion injury and apoptosis,⁹³ as well as acute cardiac rejection in the post-transplant setting.⁹⁴

The limited effect of UDCA in cholestatic conditions led to the search for new therapeutic agents.⁹⁵ Obeticholic acid (OCA) was synthesized from CDCA as a selective potent FXR agonist with anticholestatic properties.⁹⁶ It was hoped that OCA might supersede UDCA and represent an alternative for patients with primary biliary cholangitis not responding to first-line treatment. Cautiously optimistic improvement in composite endpoints was noted in two randomized, double-blind, placebo-controlled trials after 12 months of treatment^{97,98} which has led to the accelerated FDA approval of OCA for treatment of PBC.⁹⁹ Studies are also underway in primary sclerosing cholangitis, nonalcoholic steatohepatitis,¹⁰⁰ severe alcoholic hepatitis, portal hypertension and bile acid-induced diarrhoea.

Recently, there have been several exciting reports regarding the effect of obeticholic acid on the portal circulation. In both cholestatic and noncholestatic cirrhotic rat models, OCA improved ileal barrier function, reduced bacterial translocation and gut immune cell infiltration.¹⁰¹⁻¹⁰³ Verbeke et al.¹⁰⁴ showed that cirrhotic rats receiving OCA had a mean portal pressure 15%-21% lower than controls without a decrease in mean arterial pressure, thus suggesting a liver-specific effect of OCA most probably due to increased intrahepatic eNOS activity. This lack of effect on the systemic circulation does not seem to indicate obeticholic acid use in the setting of cirrhotic cardiomyopathy, but systemic haemodynamic effects with a longer treatment period are conceivable and FXR modulation could turn out to be the "molecular master switch" for cirrhosis progression.¹⁰⁵ Some evidence of the therapeutic capabilities of OCA on extrahepatic vasculature comes from a model of induced pulmonary hypertension in which OCA treatment counteracted fibrosis and endothelial/mesenchymal transition and exerted cardiopulmonary protective effects.¹⁰⁶ Whether similar benefits can be expected in reducing the deleterious effects of hyperdynamic syndrome or even portopulmonary hypertension in cirrhosis is debatable.

5 | BILE ACIDS AND THEIR RELATIONSHIP WITH CIRRHOTIC CARDIOMYOPATHY

A profound and chronic state of cardiovascular dysfunction has been a well-known manifestation of decompensated cirrhosis for more than 60 years.¹⁰⁷ Cirrhotic patients develop arterial vasodilation and redistribution of the circulating blood volume with ensuing central hypovolaemia caused by increases in hepatic vascular resistance and splanchnic pooling of blood.¹⁰⁸ The identification of this veritable hyperdynamic syndrome encouraged further study of the cardiac effects of advanced liver disease. The pattern of cardiac functional and structural alterations noted irrespective of aetiology or severity of cirrhosis developed into a novel concept named "cirrhotic cardiomyopathy". The currently accepted definition of this complication of cirrhosis requires evidence of systolic and/or diastolic dysfunction, the presence of electromechanical disturbances and changes in levels of serological markers of cardiomyocyte injury in the absence of concurrent cardiac pathology.¹⁰⁹ This generally entails 2D echocardiography, electrocardiography and measurement of pro-brain natriuretic peptide or Troponin levels, however, more advanced and accurate techniques such as tissue Doppler imaging, speckle tracking and cardiac magnetic resonance imaging are increasingly being used.^{110,111} While the best diagnostic algorithm and cut-off for the various parameters are still under evaluation, cirrhotic cardiomyopathy has been shown to be clinically relevant in this population of fragile patients.¹¹²⁻¹¹⁷ Stressful events that further alter the haemodynamic balance such as insertion of TIPS, liver transplantation or sepsis provoke the transformation of the normally latent cardiac dysfunction into overt heart failure with severe systemic consequences such as the development of hepatorenal syndrome.^{118,119} Reversal of cardiac dysfunction is normally seen in the first 6-12 months after liver transplantation.¹²⁰

Various vasoactive substances and pathways have been shown to be involved in the pathogenesis of cardiovascular dysfunction in cirrhosis.¹²¹ In experimental models of cirrhosis, cardiomyocytes evince reduced membrane fluidity, perhaps due to a direct action of bile acids,⁶⁸ which leads to altered β -adrenergic receptor function and density.¹²² An inadequate response to adrenergic stimulation is one of the main features that define our current understanding of cirrhotic cardiomyopathy. A blunted response to muscarinic M_2 and M_3 receptors located in cardiac as well as vascular endothelial cells has also been noted in cirrhosis¹²³ and this is in accordance with the described effect of DCA on such receptors.⁴³ The main role of membrane receptor-signalling regards regulation of intracellular potassium and calcium concentrations which impacts the duration of the action potential and thus inotropism and lusitropism.¹²⁴

Recent advances in characterizing the metabolism and actions of nitric oxide have led to a deeper understanding of the importance of this molecule in the pathogenesis of the hyperdynamic syndrome in cirrhosis.³⁴ NO is synthesized in endothelial cells and cardiomyocytes and is involved in vasodilation, inotropic and chronotropic cardiac impairment through a variety of mechanisms. The increased formation of NO in cirrhosis may be due to bacterial translocation with endotoxemia that results in macrophage activation and increased expression

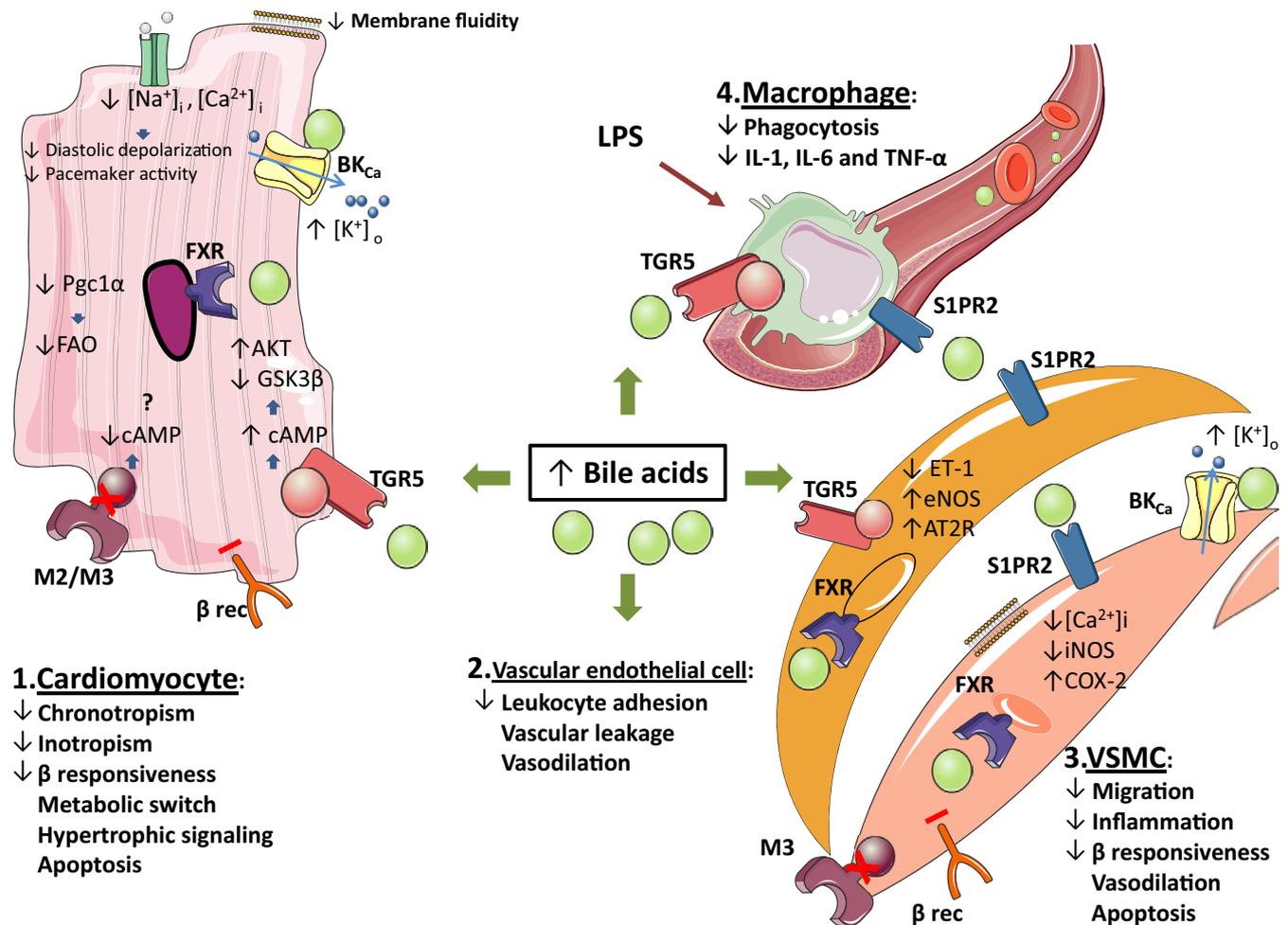


FIGURE 2 The effects of bile acids on the main cellular pathways involved in cardiovascular homeostasis. Elevated bile acid (BA) levels affect the function and metabolism of cardiomyocytes (CM), vascular endothelial cells, VSMC (vascular smooth muscle cells) and circulating macrophages. BAs open large conductance calcium-dependent potassium channels (BK_{Ca}) on CM and VSMC resulting in increased outward potassium ($[K^+]_o$) current.⁵² Membrane fluidity is also directly reduced as are sodium and calcium entry, leading to decreased action potential duration, decreased chronotropism and inotropism and an increased risk of arrhythmias.^{55,56} BAs are antagonists of muscarinic receptors (M2, M3) located on CM and VSMC but they also affect β -adrenoceptor (β -rec) membrane density and responsiveness.^{43,68,121} Receptors like TGR5 and sphingosine-1-phosphate receptor-2 (S1PR2) activate metabolic switching due to reduced peroxisome-proliferator-activated receptor γ co-activator (Pgc1 α) expression and altered protein kinase function (AKT, GSK3 β).^{131,132} BA action is responsible for vasodilation through reduction in endothelin-1 expression (ET-1) and modulation of inducible (iNOS) and endothelial (eNOS) nitric oxide synthase.^{74,75,77} BAs also affect inflammatory response to circulating bacterial lipopolysaccharides (LPS).^{8,9} COX-2, Cyclooxygenase; AT2R, angiotensin II receptor; FAO, fatty acid oxidation; cAMP, cyclic adenosinemonophosphate

of tumour necrosis factor α .¹²⁵ Carbon monoxide, endocannabinoids and inflammatory cytokines also play a role as vasoactive and cardio-depressant agents in this setting.^{126,127}

This variety of molecules with different and often opposite actions argues for the existence of multiple and complex pathways to cardiovascular dysfunction in cirrhosis, precluding a unique pathogenetic agent (Figure 2). It is intriguing that so many of the aforementioned pathways have recently been shown to be influenced or regulated by bile acids. Initial in vitro and in vivo studies also suggest that BAs could be involved in splanchnic hyperaemia and circulatory dysfunction leading to the hyperdynamic syndrome.¹²⁸ However, so far, there have been few studies specifically aimed at defining the interactions between bile acids and cardiovascular function in cirrhosis.

By incubating isolated heart mitochondria with BAs at toxicologically relevant concentrations, Ferreira proved that hydrophobic BAs significantly alter mitochondrial bioenergetics in conditions similar to those encountered in cholestasis.¹²⁹ Zavecs and Battarbee have shown that acute exposure of cardiac muscle to cholic acid mimics several characteristics of cardiac dysfunction observed in cirrhotic rat models including depressed β -adrenoceptor-mediated inotropism and decreased depolarization-dependent calcium entry. Furthermore, replacing lipophilic BAs with UDCA reduces cardiac impairment.¹³⁰ By obtaining similar results in cirrhotic and noncirrhotic portal vein stenosis models, their results suggest that bile acids themselves are significant factors in the genesis of cirrhotic cardiomyopathy.

Further proof of this relationship was provided by Desai et al.¹³¹ by comparing RNA and protein expression in heart tissue from a model of biliary fibrosis with cardiomyocyte cell cultures treated with taurochenodeoxycholic or lithocholic acid. The authors documented similar myocardial hypertrophic signalling reminiscent of cirrhotic cardiomyopathy in both cases.

Recently, the same group elegantly demonstrated that high serum BA levels were associated with increased ejection fraction and shortening fraction of the left ventricle but lower heart rate.¹³² Furthermore, they demonstrated that the foetal gene expression of hypertrophic signals as well as electrocardiographic and ultrasonographic features of cardiomyopathy resolve with reversal of liver injury. The authors proposed a new term “cholecardia” to describe the cardiodepressant effects of BAs and they used a double knockout model (*Fxr*^{-/-}; *Shp*^{-/-}) to show similarities between experimental severe bile acid overload and human cirrhotic cardiomyopathy. Analysis of the metabolic switch from fatty acid to glucose oxidation encountered in cardiomyocytes exposed to bile acids led to the conclusion that reduced peroxisome-proliferator-activated receptor γ co-activator (*Pgc1 α*) expression affects cardiac performance. Both overexpression of *Pgc1 α* in cardiomyocytes and administration of BA-binding cholestyramine reduced the detrimental effects of hydrophobic BAs on cardiac function. These results convincingly argue for a direct and reversible effect of bile acids on cardiomyocytes.¹³³

6 | CONCLUSION

Experimental models continue to improve and they have significantly increased our understanding of the relationship between bile acids and cardiovascular dysfunction, but they do not perfectly mirror the clinical experience of cirrhotic cardiomyopathy. The current wealth of data generated by the recent interest in FXR modulation of metabolism and its' therapeutic possibilities would indicate a major role for this receptor in the pathogenesis of cirrhotic cardiomyopathy. However, when considering that the cardiovascular and metabolic profile encountered in cirrhosis has not been perfectly replicated in experimental models so far, the information we have is still lacking. Future efforts should be dedicated to deciphering the complex interactions between bile acids and their various receptors. In addition, energy should also be directed towards assessment of the concentration and composition of the bile acid pool in various populations and their relationship with cardiovascular dysfunction in cirrhosis.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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