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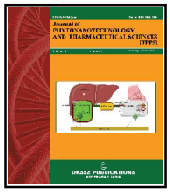

Review Article : Open Access

Bile duct ligation in rat: Induction of cirrhotic cardiomyopathy and impact on cellular pathways of bile acid on cardiovascular risk factors

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Abstract

Liver cirrhosis is associated with two conditions: Primary sclerosing cholangitis and primary biliary cholangitis. They raise the risk of heart dysfunction. Bile acid binds to G-protein-coupled plasma membrane receptors such as TGR5 and muscarinic receptors in addition to nuclear receptors such as farnesoid (FXR) and pregnane (PXR) xenobiotic receptors. The identification of bile acid receptors in cardiovascular tissue has spurred research into the connection between bile acid metabolic issues and heart disease. Fifty percent of individuals with liver cirrhosis have cirrhotic cardiomyopathy, which is caused by a combination of bile acids, cardiac hypertrophy, cardiomyocyte apoptosis, and aberrant heart hemodynamic conditions. It has been shown that a useful model of biliary cholestasis is bile duct ligation (BDL), which induces oxidative damage and fibrosis in rats. Different cholesterol levels are the outcome of chronic cholestasis. interferes with normal signaling pathways, which causes serious cardiovascular issues to arise. The data supporting bile duct ligation and the involvement of bile acids and their receptors in the development of cardiovascular dysfunction associated with cirrhosis are compiled in this study.

1. Introduction

1.1 Bile acids

The liver produces bile acids (BAs) as a byproduct of cholesterol breakdown, which are then discharged into the duodenum. These substances traverse the small intestine and undergo degradation by intestinal microorganisms. The mesenteric and portal veins return them to the liver after they are efficiently reabsorbed by specific transporters in the ileum (Dawson, 2016). It is now shown that BAs interact with nuclear and cell wall receptors as signaling molecules (Yang *et al.,* 2024). Bioactive compounds (BAs) that engage with these receptors are postulated to have a role in regulating their biosynthesis, maintaining glucose and energy equilibrium, and performing other essential functions related to cardiovascular health. The chemical regulates channel conductivity and calcium dynamics in sinoatrial and ventricular heart muscle cells by interacting with nuclear receptors, comprising farnesoid (FXR) and pregnane (PXR) xenobiotic receptors, and additionally with G-protein-coupled receptors such as TGR5 and muscarinic receptors. Moreover, it influences vascular tone *via* either endothelium-dependent or independent mechanisms. These interactions aim to reduce heart rate (Hao *et al.,* 2024; Zhao *et al.,* 2024; Groenen *et al.,* 2024; De Aguiar Vallim and Edwards, 2009). Therefore, understanding the interactions between BAs and cardiovascular tissues should provide a fresh mechanistic understanding of their regulatory role.

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1.2 Bile acid synthesis

Bile acids (BAs) are generated in the liver by a multi-enzymatic process that involves the catabolism of cholesterol. The rate of this process is mostly determined by the first conversion mediated by the cytochrome P450 enzyme CYP7A1. Following this, the liver integrates the two primary bile acids, namely cholic acid (CA) and chenodeoxycholic acid (CDCA), with either taurine or glycine ions. The intestinal microbiota produces secondary bioactive substances, namely deoxycholic acid (DCA) and lithocholic acid (LCA), during the process of food absorption. These compounds are then discharged into the gastrointestinal system. The secondary bile acids are then deconjugated and dehydroxylated by 7-alphadehydroxylase (Kiriyama and Nochi, 2021). After being reabsorbed in the stomach, the majority of BAs were transported back to the liver *via* the portal vein. Because BAs are naturally amphipathic, the degree of hydrophobicity depends on how their amino acids are conjugated. Conjugated BAs lose some of their membrane permeability as they grow more hydrophilic, which reduces their potential for cytotoxicity. Additionally, they are involved in the beginning and maintenance of bile flow, the absorption of fat from the gastrointestinal tract, and the process of lipid solubilization within the gastrointestinal tract and bile (Minoretti and Emanuele, 2024).

1.3 Bile acid metabolism

Animals differ in a wide range of morphological and metabolic traits related to BAs. They are only created by the way that human hepatocytes metabolize cholesterol. Figure 1 illustrates the presence of two main bile acids in the human body, namely chenodeoxycholic acid (CDCA) and catholic acid (CA). The bacterial 7-dehydroxylase

enzyme in the small intestine converts a fraction of these molecules into the secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA). Tertiary bioactive compounds (BAs), such as ursodeoxycholic acid (UDCA), are formed by further bacterial and hepatic modifications. Multidrug resistance proteins and the bile salt export pump (BSEP) allow hepatocytes to release BAs. Enterocytes employ ASBT in their apical membranes to digest BAs. After that, the ileal BA binding protein moves BAs across cells and releases them into the small intestine's portal circulation (Lu *et al.,* 2024).

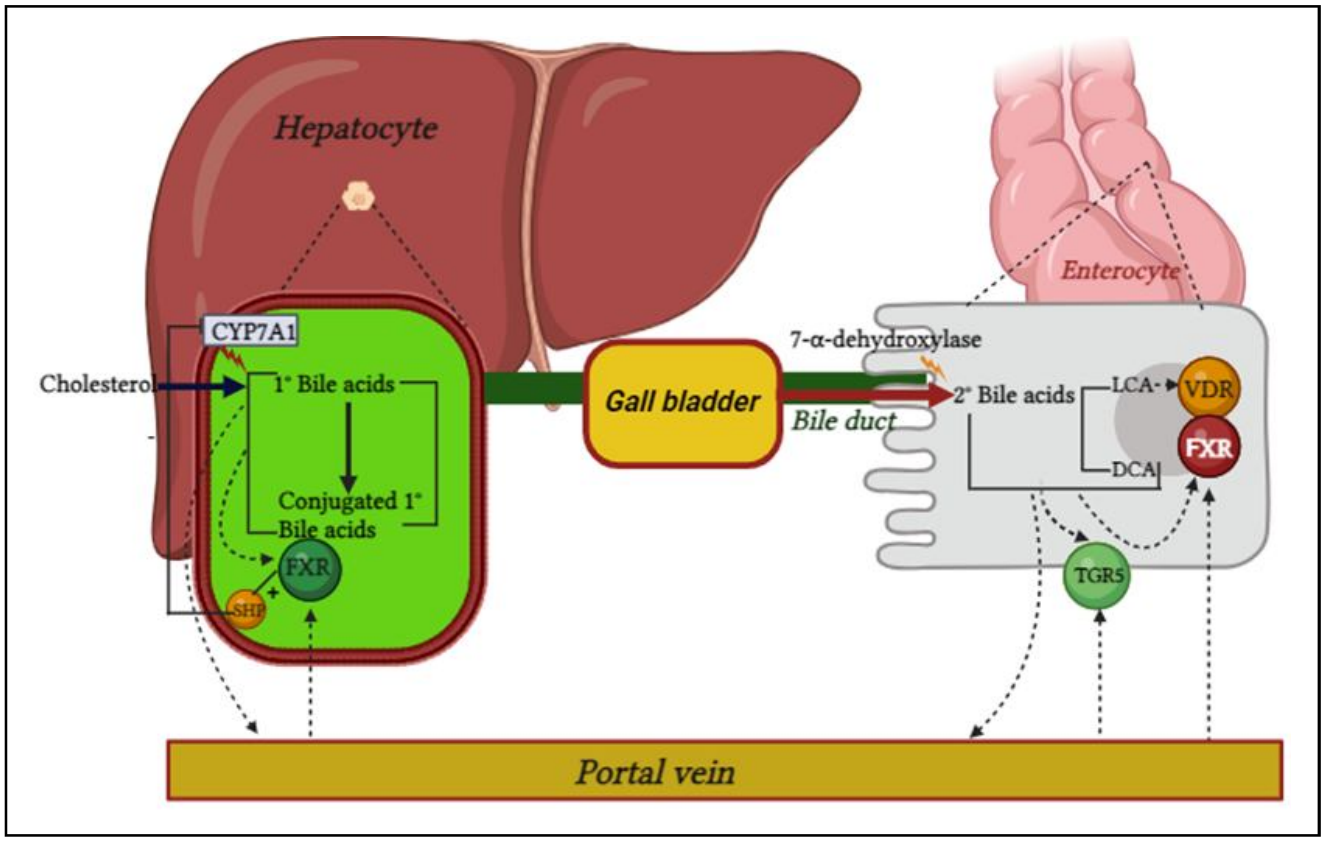

Figure 1: Synthesis and signaling of bile acids (BAs): Primary BAs are produced and conjugated in the liver, while secondary BAs are formed by deconjugation and dehydroxylation in the gut. The nucleus-based activation of the enterocyte-expressed G protein-coupled receptor (TGR5) and the Farnesoid X receptor (FXR) by primary and secondary BA ligands, as well as the nucleus-based activation of the vitamin D receptor (VDR) by LCA, are the two main pathways through which their signaling occurs.

2. Role of bile acid receptors in the heart

The expression of receptors involved in BA signaling in cardiovascular tissue has been established by the suggested mechanism of action shown in Figure 2 (Zhang *et al.,* 2021). The vasculature has been shown to express the nuclear BA receptor farnesoid-X receptor (FXR), which mostly binds to primary BAs. The activation of proteins specific to the vasculature takes place upon the activation of the FXR. FXR alters arterial stress and elevates lipid profiles to prevent atherosclerosis. FXR plays a protective effect against atherosclerosis by altering arterial stress and raising lipid profiles (Chiang and Ferrell, 2022).

2.1 Deteriorating liver conditions are linked to compromised cardiovascular health

According to reports, patients with liver disease had better cardiac and hemodynamic outcomes, such as reduced vascular resistance and increased cardiac output (Brankovic *et al.,* 2023). It is known that in these people, bile acid concentrations increase. Further studies on cirrhotic patients and the fact that bile acid levels are noticeably elevated after liver failure lend credence to the idea that bile acid plays a role in the process of cardiac dysfunction (Boeckmans *et al.,* 2024; Wang and Chen, 2008).

Cirrhotic cardiomyopathy (CC) is characterized by anatomical alterations, abnormalities in the heart's electrophysiology, and dysfunction in both the diastolic and systolic phases (Liu *et al.,* 2023). Fifty percent of cases of hepatic cirrhosis are thought to develop CC (Shah *et al.,* 2009). Diastolic dysfunction may arise from left ventricular hypertrophy, a morphological abnormality that has been discovered in individuals to varied degrees of severity, according to a research done on cirrhotic patients. When compared to non-cirrhotic controls, an increase in QT interval duration is the most obvious electrophysiological abnormality observed in CC patients (Kalluru *et al.,* 2022).

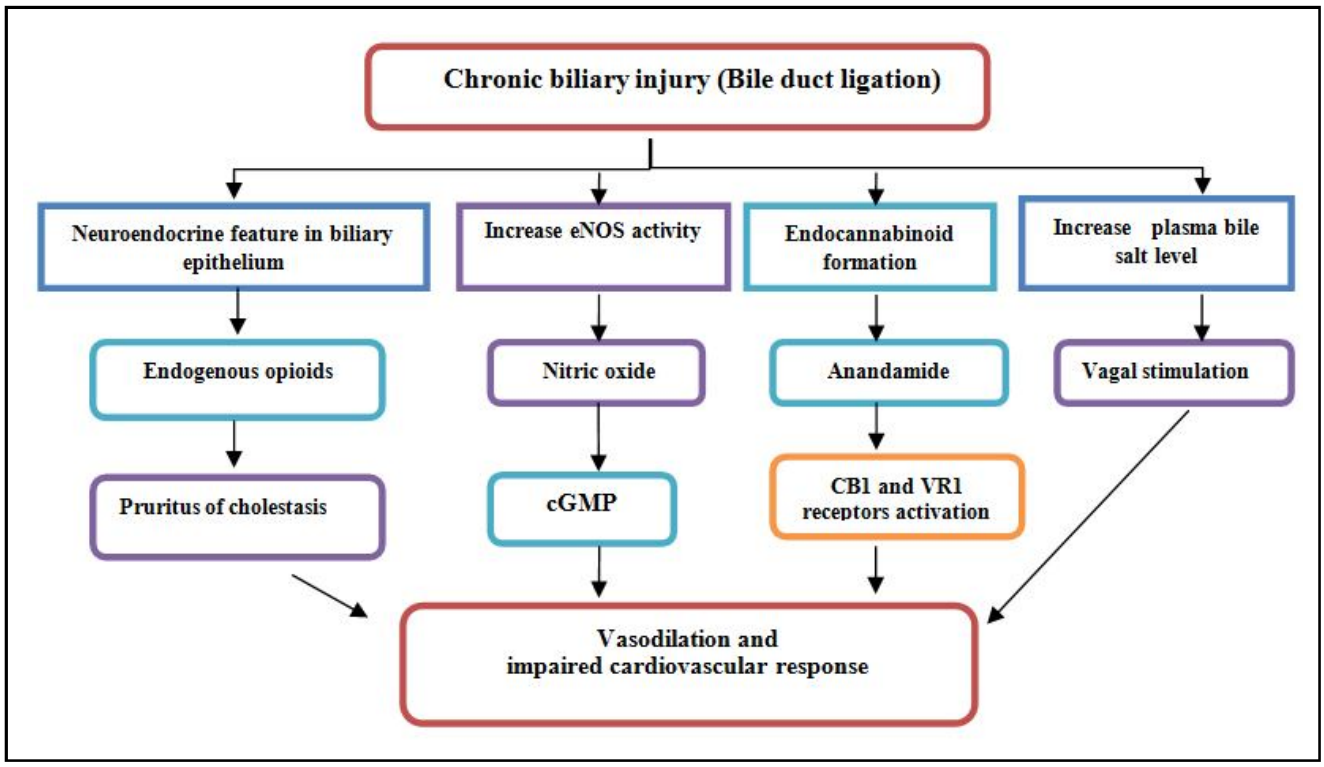

Figure 2: An illustration of how bile acids, endocannabinoids, nitric oxide, and endogenous opioids contribute to circulatory abnormalities in obstructive cholestasis.

2.2 The condition of cirrhosis has the potential to lead to the onset of cirrhotic cardiomyopathy

There is evidence that BAs have a major influence on CC development, even if many other variables are considered to have played a role as shown in Figure 3. Laboratory studies in intact animals as well as *in vitro* systems have shown the connection between cardiac dysfunction or CC and BA metabolism (Myers *et al.,* 2024). Oxidative stress has been linked to bile acid-induced oxidative stress and peroxidation of lipids in the liver, which is distinguished by an aberrant clumping of the extracellular matrix, or ECM, proteins. Cirrhosis-related cardiomyopathy (CC) is characterized by structural defects, systolic and diastolic unsteadiness, morphological alterations, and cardiac electrophysiological impairments (Dash *et al.,* 2023). Lipid peroxidation resulted in increased levels of apoptosis and malondialdehyde in the hearts, along with reduced activities of glutathione peroxidase and catalase. Moreover, by producing stellate cells, oxidative stress aggravates liver fibrosis (Zardi *et al.,* 2010). The evolution of CC is attributed to a number of factors, including electrophysiological abnormalities, a longer QT interval, diversion of cardiomyocytes' contraction response to electrical stimulation, and inability to respond to certain pharmacological stimuli. In fact, the latter signal permits a ventricular repolarization delay that might result in ventricular arrhythmia. A prolonged QT interval is linked to a higher risk of sudden death and mortality due to the predisposition for arrhythmias (Zambruni *et al.,* 2006).

2.3 Cirrhotic cardiomyopathy mechanisms are made possible by bile duct ligation

An excellent illustration of biliary cholestasis in animals is bile duct ligation (BDL), which has been demonstrated to increase oxidative damage and fibrosis in rats (Cesari *et al.,* 2015; Ghonem *et al.,* 2015). In addition to additional organ damage, the BDL rat exhibits cholestasis, raised levels of hepatic and circulatory ADMA, and heightened levels of systemic oxidative stress. Severe hemodynamic abnormalities, including elevated cardiac output, hypotension, and baseline bradycardia, are commonly observed in rats exposed to BDL. It is probable that BAs directly contribute to the pathophysiology of these parameters since they reverse the symptoms of cholestyramine, an intestine BA sequestrate (Tokaç *et al.,* 2013; Reddy and Urooj, 2018). Despite the numerous and intricate pathophysiologies of CC, experimental research into some of the underlying processes has been made possible by manually constricting the bile duct. By inducing mouse and rat models of what is now recognized as CC, BDL enables researchers to investigate the connection between the related cardiovascular function and BA metabolism. When administered an inhibitor of the apoptotic Fas system, an antibody against FasL, BDL rats exhibited substantial elevations in systolic and diastolic activity as well as apoptotic markers such poly ADP-ribose polymerase (PARP). When cardiomyocytes were isolated from their artificial relatives, this impact vanished. According to these findings, BDL may cause myocardial apoptosis, which may thereafter cause coronary heart disease (Sokolovic *et al.,* 2013). Further research has clarified NO's function in cardiomyocyte apoptosis. Higher rates of apoptosis and morphological problems are seen in the hearts of BDL mice; these features were all exacerbated when NO synthase was inhibited in these animals, suggesting that it acts as a mediator (Alam *et al.,* 2023). With reduced production of the contractile inhibitory agent tumour necrosis factor (TNF) in BDL rats, diastolic and systolic dysfunction was recovered, and oxidative stress was reduced (Yang *et al.,* 2012) (Figure 3). Rat cirrhosis caused by BDL reduces the heart mitochondria's capacity to produce ATP and use oxygen (Nam *et al.,* 2014).

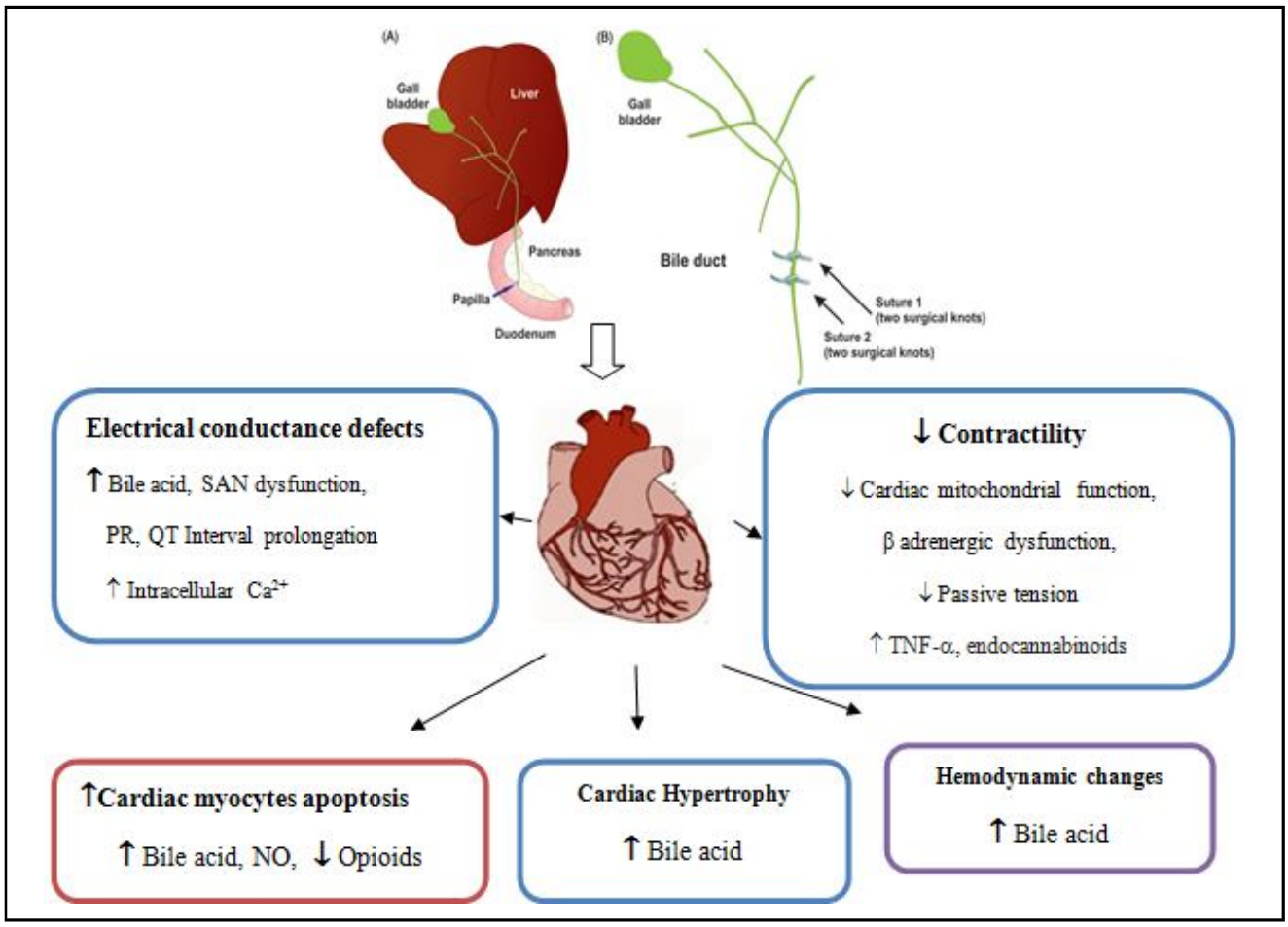

Figure 3: A schematic representation of the pathogenesis of cirrhotic cardiomyopathy (CC).

2.4 Heart failure results from exposing the heart to bile acids, which are rather hydrophobic

Growing data suggests that bile acids modify cardiac function in cholestasis, lending credence to the concept that bile acids are a major player in the development of cardiomyopathy in cholestatic liver diseases (Shafaroodi *et al.,* 2010). Inotropic and chronotropic actions negatively impact membrane fluidity, density, and affinity of cardiovascular α-adrenoceptors (Liu *et al.,* 2012). Bile acid may alter the energetics of mitochondria, causing a reduction in the respiratory part of mitochondria and perhaps the membrane. As a consequence, numerous aquaphobic BAs, including CDCA, LCA, and DCA, can be detected cardinally (Shulpekova *et al.,* 2022). Less of an impact was shown by the moderately hydrophilic BAs TDCA (taurodeoxycholic acid), GUDCA (glycoursodeoxycholic acid), and GCDCA (glycochenodeoxycholic acid). With the least evidence of mitochondrial toxicity and the highest hydrophilicity of all the BAs tested, GUDCA stood out (Kemp *et al.,* 2008). CC and BAs investigated the crucial steps. Feeding of DDC causes an increase in ventricular dysfunction markers, which in turn causes a decrease in cardiac (heart) mass and rate as well as an expansion in the releasing fraction. These two outcomes were linked to an increase in circulating BA levels. In mice, cholanaemia and biliary fibrosis were seen concurrently. Moreover, the quantity of BA was associated with the part of genes that regulate how fatty acid (DFA) breaks down while under stress (Ferreira *et al.,* 2005).

Lipoproteins and cholesterol have a major role in the development of plaque and the lesions linked to atherosclerosis (LDL and HDL). If the body uses increased BA synthesis as a main route for eliminating cholesterol, then increased BA production by UDCA may play a large role in avoiding atherosclerosis. Research has demonstrated the potential advantages of UDCA in reducing LDL and increasing HDL levels (Moezi and Dehpour, 2013; Gazawi *et al.,* 2000). Experimental animal models provide a detailed description of the several processes by which BAs impact cardiovascular tissues (Zhang *et al.,* 2023; Desai *et al.,* 2015).

2.5 Factors exert vasodilation and impaired cardiovascular function

High blood bile acid levels, as observed in cholestatic and chronic liver disease, have a major influence on the activity of endothelium and vascular smooth muscle cells. This might have hemodynamic consequences (Sauerbruch*et al.,* 2021). It is increasingly probable that bile acids, nitric oxide, opioid peptides, and endogenous cannabinoids may impact cardiovascular illnesses linked to obstructive cholestasis. The most effective inhibitor of noradrenaline's contractile effect on vascular smooth muscle is diclofenac (DCA), which is produced *via* bile duct ligation (Bouscarel *et al.,* 1995). Anandamide-induced relaxation in the mesenteric vascular beds is augmented, according to the involvement of endocannabinoids in

cholestasis (Poupon *et al.,* 1993). In the mesenteric beds of rats with bile duct ligation or without surgery, acute naltrexone medication had no effect on anandamide-induced vasorelaxation, most likely because of diminished cannabinoid receptor activity. Furthermore, increased nitric oxide synthesis might be the source of cholestasis-induced vascular hyperresponsiveness to anandamide (Khurana *et al.,* 2011). Isolated samples from the rats' portal veins and superior mesenteric arteries showed evidence of pathogenetic involvement when tested with pharmaceutical inhibitors of ion channels, adrenoceptors, membrane pumps, and sensory afferent neurons. Vasorelaxation was observed in response to progressive concentrations of BAs, irrespective of endothelium completeness or inhibiting medications. This suggests that the mechanism underlying the effect is the inhibition of calcium penetration through membranary channels (Nowiñski *et al.,* 2023). The chemical structure of the bile acid plays a major role in this; hydrophobic and lypophilic bile acids seem to be more prone to induce vasorelaxation (Utkan *et al.,* 1996).

Due to its most recent finding in smooth muscle cells and vascular endothelium, FXR has drawn a lot of interest (Wei *et al.,* 2020). As a transcription factor, it was previously believed that activated FXR affects vasomotricity by changing the synthesis of various receptors and vasoactive chemicals. Scientists have shown that endothelial cells have the ability to raise eNOS levels and reduce endothelin-1 levels (Ghatage *et al.,* 2024). Regulate angiotensin-II receptor expression to inhibit inflammatory response and vascular smooth muscle cell migration (Utkan *et al.,* 1996). Following the revelation that FXR is flexible in pulmonary endothelial cells (He *et al.,* 2006). When an FXR-responsive element in the eNOS promoter region is activated, it results in the enhancement of eNOS expression and an increased synthesis of the vasodilator nitric oxide (NO) (Voiosu *et al.,* 2017). Additionally, S1PR2, a bile acid-sensitive receptor involved in NO signaling, suppresses the action of inducible nitric oxide synthase in vascular smooth muscle cells, thus reducing NO levels in the context of vascular injury (Zhang *et al.,* 2023; Li *et al.,* 2008). Since both cardiomyocytes and endothelial cells produce nitric oxide (NO), research into its metabolism and dynamics has improved our knowledge of its function in the development of hyperdynamic syndrome in cirrhosis. It is associated with many pathways that promote inotropy, chronotropic cardiac dysfunction, and vasodilation (Roy *et al.,* 2023; Zhang *et al.,* 2008). In cirrhosis, the elevation in NO production may stem from bacterial translocation leading to endotoxemia, which activates macrophages and boosts the output of tumor necrosis factor (Violi *et al.,* 2023). Endocannabinoids, inflammatory cytokines, and carbon monoxide all affect vasodilation and cardio-depression (Nakajima *et al.,* 2000; Khurana *et al.,* 2012; Machida *et al.,* 2016).

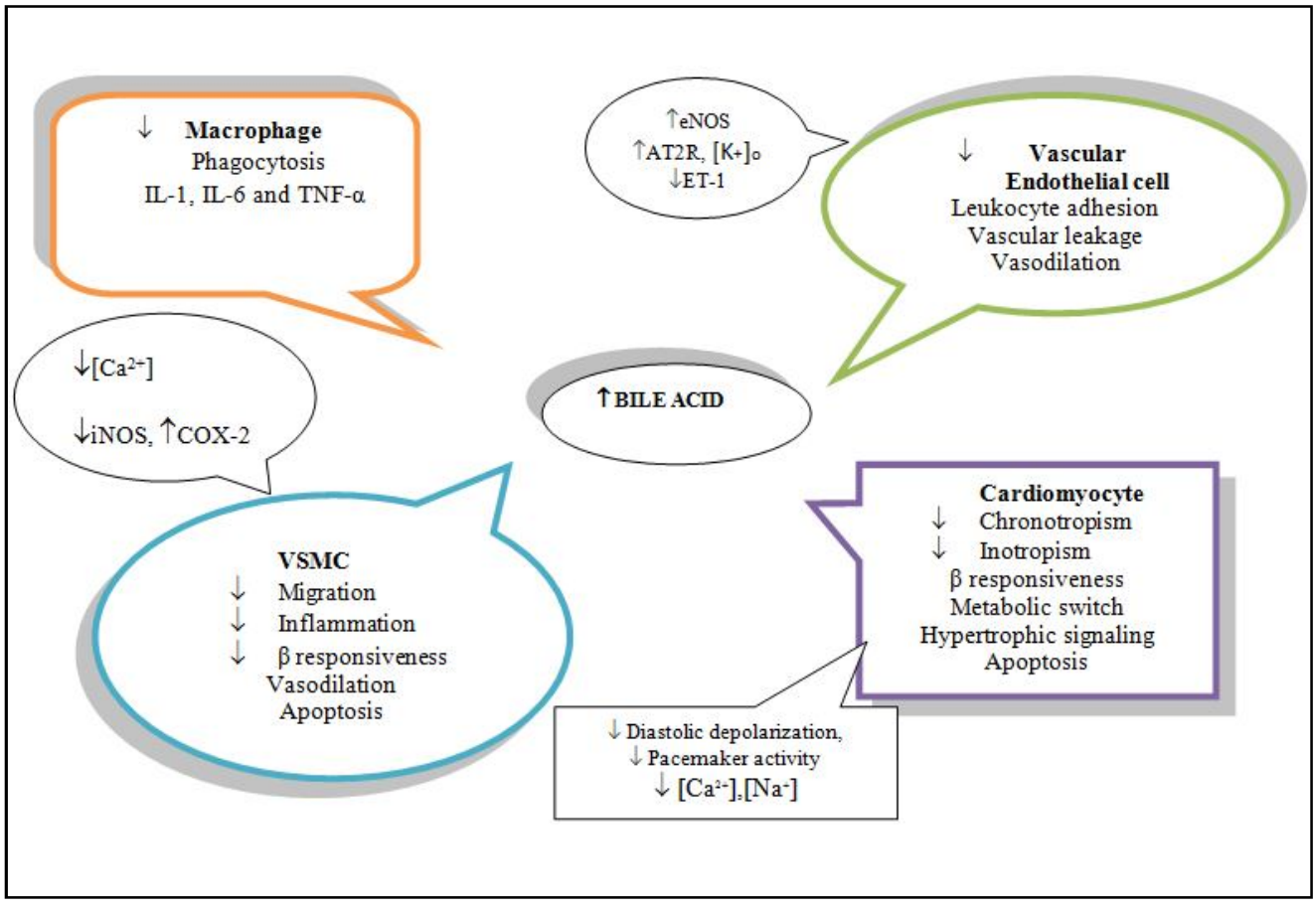

Figure 4: Bile acids have distinctive effects on the primary cellular processes that govern cardiovascular stability. High levels of bile acids (BAs) impact the operation and metabolic activities of cardiomyocytes (CM), vascular endothelial cells, vascular smooth muscle cells (VSMC), and circulating macrophages.

3. Cellular pathways involved in cardiovascular homoeostasis

The particular mechanisms by which bile acids impact the primary cellular mechanisms that preserve cardiovascular homeostasis. Increased levels of bile acids (BA) influence the metabolism and functionality of circulating macrophages, vascular smooth muscle cells, vascular endothelial cells, and cardiomyocytes (CM) (Figure 4) (Zhang *et al.,* 2023; Ruiz and Serradilla, 2015). In cirrhosis, several diverse mechanisms might lead to cardiovascular failure, aside from the presence of a single pathogenetic agent (Gaskari and Liu, 2015). By activating vascular smooth muscle cells (VSMC) and cardiomyocytes' (CM) large conductance calcium-activated potassium channels (BKCa), bile acids (BAs) increase the amount of potassium that is released into the surrounding environment (Ferreira *et al.,* 2005). A direct reduction in membrane fluidity as well as sodium and calcium entry results in a decrease in chronotropism and inotropism, a longer action potential, and an increased risk of arrhythmias (Ferreira *et al.,* 2005; Zavecz and Battarbee, 2010). As muscarinic receptor (M2, M3) antagonists, BAs influence the membrane density and responsiveness of α-adrenoceptor (α-rec) receptors on CM and VSMC (Bukiya *et al.,* 2007). As a result of an increase in the activity of protein kinases (AKT, GSK3) and a reduction in the expression of peroxisome-proliferator-activated receptor co-activator (Pgc1), receptors including TGR5 and sphingosine-1-phosphate receptor-2 (S1PR2) are activated, leading to changes in metabolism (Dicks *et al.,* 2024; Zardi *et al.,* 2010). BA activity modulates endothelial (eNOS) and inducible (iNOs) nitric oxide synthases, which reduces the production of endothelin-1 (ET-1) and causes vasodilation (Ward *et al.,* 2001; Desai *et al.,* 2010; Desai *et al.,* 2015). Bas also affects cyclic adenosine monophosphate, AT2R, COX-2, cyclooxygenase, circulating bacterial lipopolysaccharides (LPS), fatty acid oxidation, and inflammatory responses (He *et al.,* 2006; Li and al., 2008; Nakajima *et al.,* 2000). According to studies, both cardiomyocytes and endothelial cells generate NO (Kakiyama *et al.,* 2013; Ridlon *et al.,* 2015; Ayvaz *et al.,* 2013; Li *et al.,* 2007). It is also associated with inotropic, chronotropic, and vasodilation cardiac destruction *via* a number of different routes (Khurana *et al.,* 2005; Keitel *et al.,* 2007).

The increase in nitric oxide (NO) production seen in cirrhosis could be attributed to bacterial translocation leading to endotoxemia, which activates macrophages and elevates the expression of tumor necrosis factor (Gorelik *et al.,* 2004; Williamson *et al.,* 2001). Furthermore, carbon monoxide, endocannabinoids, and inflammatory cytokines also play crucial roles as vasoactive and cardiodepressant agents (Gorelik *et al.,* 2002; Bahrle *et al.,* 1998).

4. Conclusion

Research in rats with bile duct ligation (BDL)-induced oxidative damage and fibrosis is presented here as a unique paradigm for animal biliary cholestasis. Cholestasis, increased systemic oxidative stress, higher circulation and liver ADMA levels, and significant organ damage are all seen in this animal. Several substances, including bile acids, nitric oxide, opioid peptides, and endocannabinoids, are shown to play crucial roles in the development of circulatory difficulties related to obstructive cholestasis in studies that use bile duct-ligated rats as models of cirrhosis. We now know much more about the connection between bile acids and heart failure because of experimental models. Additionally, cardiomyocyte BA receptor discovery suggests that circulating BAs may have an effect on heart function. Also, cholestasis on its own may cause heart problems, which might play a role in the development of cirrhotic cardiomyopathy.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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