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Cardiac injury induced by obstructive jaundice: A comprehensive review

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Highlights

- Elevated bile acid concentrations impair myocardial structure and function by disrupting mitochondrial integrity and acting on TGR5 and FXR receptors.
- Endotoxins contribute to cardiovascular dysfunction by exacerbating systemic inflammation, primarily via NF-κB activation and increased levels of pro-inflammatory cytokines such as TNF-α.
- Reactive oxygen species alter cardiac electrophysiology by modulating L-type calcium channels and reversing Na^+/Ca^{2+} exchanger activity, leading to contractile dysfunction. Excessive nitric oxide disrupts vascular tone regulation.
- Autophagy is activated through the AMPK-mTOR-ULK1 signaling pathway, while apoptosis-driven myocardial injury is mediated by caspase activation and the Bax/Bcl-2 protein family.
- Appropriate preoperative management, anesthetic selection, and the application of traditional Chinese medicine can alleviate cardiac injury associated with obstructive jaundice.

Abstract

Obstructive jaundice can lead to systemic multi-organ complications, with the heart being one of the most critically affected organs. This review summarizes recent insights into the mechanisms of cardiac injury induced by obstructive jaundice, including bile acid toxicity, inflammatory responses, oxidative stress, nitric oxide dysregulation, endotoxemia, apoptosis, and autophagy. Currently, no specific treatment protocol exists for this condition. However, appropriate anesthetic choices, traditional Chinese herbal medicine, and optimized perioperative management have shown potential in mitigating myocardial damage. This review provides a detailed discussion of these aspects.

Keywords: Obstructive jaundice, cardiac injury, bile acids, mechanisms

Introduction

Obstructive jaundice (OJ) is a common clinical condition caused by partial or complete blockage of intrahepatic or extrahepatic bile ducts, most often due to bile duct stones, inflammatory hyperplasia, or tumors. These conditions lead to impaired bile drainage from the liver. In severe cases, patients with OJ develop jaundice, characterized by yellowing of the skin and eyes due to elevated bilirubin levels in the blood. OJ is associated with high morbidity and mortality rates. Previous studies have reported that the surgical mortality rate for patients with OJ can reach 18% and approximately 8%-10% of surgical patients develop acute renal failure, of whom 70–80% eventually succumb to the condition [1]. OJ can cause multi-organ damage, affecting the liver, kidneys, heart, intestines, brain, and immune system [2-4]. A

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comprehensive understanding of OJ is crucial for optimizing treatment and improving patient outcomes. To study OJ and its complications, various experimental models have been developed, among which bile duct ligation (BDL) is widely used to simulate OJ and related pathophysiological changes [5].

Cardiac injury is a significant complication of OJ, contributing to increased morbidity and mortality. OJ is associated with various cardiovascular abnormalities, including hypotension, bradycardia, QT interval prolongation, reduced adrenergic responsiveness, and a predisposition to hypovolemic shock and acute renal failure [6-9]. Cardiac dysfunction in patients with OJ is primarily characterized by reduced cardiac output, leading to decreased exercise capacity and an elevated risk of perioperative mortality [10]. The relationship between OJ and cardiac injury was first described by Green et al. in 1986 as the "Jaundiced Heart" and is now widely recognized as a clinical phenomenon [1, 11]. OJ is known to cause significant hemodynamic disturbances. In 1991, Lumlertgul et al. studied nine jaundiced patients and eight healthy volunteers, demonstrating that jaundiced patients exhibited a blunted myocardial contractile response to inotropic stimulation [12].

In recent years, researchers have proposed that heart dysfunction induced by chronic BDL models may be classified as cirrhotic cardiomyopathy, a condition often studied in mice subjected to bile duct ligation for 28 days or longer to induce liver cirrhosis [13].

This review aims to summarize the current understanding of the mechanisms underlying cardiac injury in OJ. Based on previous studies, OJ-induced cardiac damage is associated with bile acid toxicity, endotoxemia, inflammation, oxidative stress, apoptosis, and autophagy. Given the limited research in this area, further elucidation of these mechanisms is essential to developing preventive and therapeutic strategies for OJ-associated cardiac injury.

Mechanism of OJ in heart injury

Toxic effects of bile acids

Bile acids (BAs) are essential components of bile but can exert significant toxic effects when they accumulate in the bloodstream, particularly affecting the circulatory system and the heart [14]. Under normal physiological conditions, BAs are taken up through the basolateral membrane and exported via tubular efflux pumps. However, in OJ, bile flow is obstructed, leading to the accumulation of BAs in the blood and liver cells. As early as 1964, studies demonstrated that BAs inhibit adenosine triphosphatase (ATPase) activity, reduce oxygen consumption, and impair protein synthesis in the intestines of rats [15]. Some scholars have proposed that BA toxicity contributes to cardiac injury [16].

The earliest available literature indicates a study in 1909 indicated that the association between BAs and bradycardia was first described in 1863 and suggested that BAs could cause jaundice-associated bradycardia [17]. Later, in 1939 and 1940, Wakim, Essex, and Mann used a rabbit model and found that bile salts induced bradycardia, negative inotropism, and even cardiac arrest, confirming the cardiotoxic effects of BAs [18-20]. In 1983, Bogin et al. demonstrated in both in vitro and in vivo studies that BAs reduced the beating rate of cardiomyocytes in a concentration- and time-dependent manner [21].

Mitochondrial dysfunction plays a key role in BA-induced toxicity. Previous studies have confirmed that high BA concentrations impair mitochondrial structure and function [22]. When BA levels exceed the binding capacity of cytoplasmic binding proteins in hepatocytes, they induce apoptosis and necrosis by damaging mitochondria [23]. Similarly, cardiac mitochondria are highly susceptible to BA toxicity, particularly hydrophobic BAs, which exert potent harmful effects. In 1997, electron microscopy studies revealed that the myocardial mitochondria of male Sprague-Dawley rats exhibited swelling and a reduction in number 14 days after BDL. Furthermore, in rats that did not undergo BDL but received gastric intubation of sodium cholate, myocardial injury was observed when serum cholate levels reached concentrations equivalent to those in the BDL group, further confirming the toxic effects of BAs on the heart [16].

BAs impair myocardial contractile responses to positive inotropy by disrupting cardiomyocyte metabolism, membrane integrity, and ion transport mechanisms. Additionally, they interfere with calcium homeostasis by affecting the uptake and release of calcium from the sarcoplasmic reticulum, leading to reduced mitochondrial function and impaired cardiac performance in the presence of high BA concentrations [24]. An in vitro study conducted in 1987 using Sprague-Dawley rat papillary muscles and isolated ventricular myocytes evaluated myocardial contractility, action potentials, and membrane currents [25]. It was found that taurine-conju-

gated bile acids interact with muscarinic M2 receptors, reducing intracellular cyclic adenosine monophosphate levels and exerting a negative chronotropic effect on cardiomyocytes [26].

BAs have also been shown to shorten ventricular action potential duration, reduce inward ionic currents, and enhance outward potassium currents. These alterations may contribute to negative inotropic effects and abbreviated action potentials [25]. Furthermore, high BA concentrations damage cardiomyocytes by activating the G protein-coupled receptor 5 and the farnesoid X receptor. Cell-based studies have demonstrated that hydrophobic BAs, such as chenodeoxycholic acid, activate farnesoid X receptor in cardiomyocytes, promoting inflammation and apoptosis. Additionally, excessive BAs reduce fatty acid oxidation in cardiomyocytes, potentially leading to cardiac insufficiency [27, 28].

Endotoxin

Endotoxin, also known as lipopolysaccharide (LPS), is a major component of the cell wall in Gram-negative bacteria and exhibits strong immunogenicity and toxicity [29, 30]. The high incidence of postoperative complications in patients with OJ is significantly influenced by endotoxemia [31].

In an experimental rabbit model of OJ, serum total bilirubin, transaminase, and endotoxin levels were measured on days 2, 5, 8, and 13 post-surgery. The results showed that rabbits in the OJ group had a higher frequency of endotoxemia in both the portal vein and systemic circulation compared to the sham-operated group [32]. Patients with OJ are prone to endotoxemia, primarily due to increased absorption of endotoxins from the intestinal lumen and reduced clearance by the liver reticuloendothelial system [32]. In OJ, endotoxemia exacerbates organ injury through excessive endotoxin release [33].

Endotoxins contribute to vascular damage by intensifying systemic inflammation. Studies have shown that the inflammatory response, primarily driven by the activation of the nuclear factor kappa B (NF-κB) signaling pathway and the upregulation of inflammatory cytokines such as tumor necrosis factor-alpha, plays a crucial role in endotoxin-induced myocardial injury [34]. During endotoxemia, LPS interacts with toll-like receptor 4 on immune and non-immune cells, leading to toll-like receptor 4 upregulation and NF-κB pathway activation. This results in increased expression of phosphorylated NF-κB and phosphorylated I-kappa-B-alpha, which further induces the overexpression of pro-inflammatory cytokines, including interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha, ultimately leading to myocardial injury [35]. In addition, LPS not only activates NF-κB but also triggers the NOD-like receptor protein 3 inflammasome, leading to the cleavage of Gasdermin D into its active N-Gasdermin D form. This activation promotes the cleavage of caspase-1 and increases the levels of interleukin-1 beta, interleukin-18, and reactive oxygen species (ROS), ultimately inducing pyroptosis in cardiomyocytes [36].

Furthermore, endotoxins stimulate macrophages to generate reactive free radicals and release lysosomal enzymes, which contribute to myocardial cell damage [37]. LPS also induces oxidative stress, further exacerbating myocardial injury and impairing cardiac contractility. Therefore, endotoxin plays a critical role in OJ-related cardiac injury.

Oxidative stress

Oxidative stress is an imbalance between the production of ROS and the endogenous antioxidant defense mechanisms, leading to redox dysregulation [38]. Previous studies have demonstrated that OJ induces systemic oxidative stress in multiple organs, including the heart, liver, kidneys, brain, lungs, blood, and intestines [39-44]. Due to their hydrophobic nature, bile acids disrupt membrane stability and impair organelle structure and function, particularly in mitochondria. This disruption results in increased oxygen free radicals and lipid peroxidation products, thereby disturbing redox homeostasis. Additionally, toxic bile acids activate membrane-associated proteins, such as nicotinamide adenine dinucleotide phosphate oxidases, which catalyze ROS production [45]. In 2009, Cruz and Shafarood used a BDL mouse model to demonstrate significant oxidative damage in cardiac tissue, characterized by elevated levels of malondialdehyde and nicotinamide adenine dinucleotide phosphate, along with reduced activity of antioxidant enzymes such as catalase and glutathione peroxidase [46, 47].

Bile acids also induce endoplasmic reticulum oxidative stress, leading to the release of calcium ions (Ca^{2+}) into the cytoplasm. The increased intracellular Ca^{2+} concentration further stimulates mitochondria to overproduce ROS, exacerbating oxidative stress [48]. ROS can enhance Ca^{2+} influx through L-type calcium channels and reverse the function of the Na^{+}/Ca^{2+}

exchanger, causing excessive Ca^{2+} inflow and Na^{+} outflow, which severely disrupts cardiac electrophysiology. Additionally, excessive ROS inhibit sarcoplasmic reticulum calcium ATPase activity, resulting in Ca^{2+} overload, reduced calcium sensitivity of myofilaments, and ultimately impaired cardiac contractile function [49].

Cardiac myocytes are rich in mitochondria, the primary source of ROS. Under pathological conditions, toxic bile acids directly interfere with mitochondrial respiratory complexes and the electron transport chain, leading to excessive ROS production. This disrupts the balance of proteins involved in mitochondrial fusion and fission, inducing apoptosis. The ROS generated by mitochondria, known as mitochondrial ROS, damage mitochondrial DNA and lipids, impair myocardial energy metabolism, and contribute to cardiomyocyte apoptosis and heart failure [50, 51].

Moreover, ROS activate inflammatory pathways, promoting the infiltration of inflammatory cells and the release of inflammatory mediators [52]. Excessive ROS production also triggers lipid peroxidation of myocardial cell membranes, leading to structural and functional damage, culminating in apoptosis and necrosis of cardiomyocytes. In summary, these findings suggest that oxidative stress plays a crucial role in OJ-induced cardiac injury.

Inflammation

Inflammation is the body's immune defense mechanism against injury, infection, and other harmful stimuli [53]. An increasing number of studies suggest a strong association between inflammation and cardiovascular diseases, with inflammation playing a critical role in conditions such as myocardial infarction and heart failure [54]. In OJ, inflammatory injury has also been observed in cardiac tissue. In 2021, Ommati et al. reported that the most prominent lesion in the cardiac tissue of BDL rats was inflammation [55].

Excessive oxygen free radicals and other ROS can activate immune cells and trigger inflammatory pathways such as NF-κB, c-Jun N-terminal kinase, and activator protein 1, ultimately leading to an inflammatory response [56, 57]. Biliary obstruction and bile deficiency are key pathological events that compromise gut barrier integrity. When OJ patients develop gut barrier dysfunction, elevated endotoxin levels in the portal and systemic circulation trigger a systemic inflammatory response. This leads to the release of cytokines and proinflammatory mediators such as tumor necrosis factor-alpha and interleukin-6 into the bloodstream, exacerbating systemic and cardiac inflammation [58]. These findings indicate that inflammation plays a significant role in OJ-induced cardiac injury.

Nitric oxide

Nitric oxide (NO) is a potent vasodilator synthesized by vascular endothelial cells. It induces vasodilation by activating guanylate cyclase, thereby increasing intracellular cyclic guanosine monophosphate levels [59]. Excessive NO production has been implicated in cardiovascular dysfunction, including decreased vascular responsiveness to adrenergic receptor agonists and the induction of bradycardia in OJ animal models [8, 9].

In OJ, endotoxins activate vascular smooth muscle cells and macrophages, leading to excessive NO production [60]. This disrupts the balance between vasodilation and vasoconstriction, resulting in persistent vasodilation, reduced blood pressure, and impaired coronary perfusion [61]. In 2005, researchers isolated thoracic aortas from rats and mice and precontracted the vessels with phenylephrine before examining the effects of acetylcholine and taurine-conjugated deoxycholic acid in the presence or absence of a nitric oxide synthase inhibitor and lithocholic acid (a bile acid). Their findings confirmed that the vasodilatory effects of bile acids were NO- and endothelium-dependent [62].

Moreover, NO contributes to cardiomyocyte apoptosis by regulating multiple signaling pathways [63]. In BDL mice, intraperitoneal injection of L-NAME (a non-selective nitric oxide synthase inhibitor) reduced myocardial NO levels, improved cardiac structural abnormalities, and decreased cardiomyocyte apoptosis [47]. These findings suggest that NO plays a crucial role in the pathogenesis of jaundice-related cardiac injury and may exacerbate myocardial damage under pathological conditions.

Autophagy

Autophagy is a highly conserved cellular process that delivers cytosolic components to lysosomes for degradation and recycling. The term "autophagy," derived from the Greek words for "self-eating," was first introduced by Deter in 1967 [64, 65]. Autophagy plays a critical role in maintaining cardiac structure and function. Previous studies have demonstrated its involvement in various cardiac diseases, including diabetic cardiomyopathy, doxorubicin-induced

cardiomyopathy, myocardial ischemia, heart failure, and genetic cardiomyopathy [66-70]. By clearing misfolded proteins, damaged mitochondria, and other organelles, autophagy contributes to the preservation of normal cardiac function [71]. Additionally, research has suggested that autophagy plays a significant role in organ injury, including liver and intestinal damage, in OJ [72, 73].

In 2024, Wang et al. investigated myocardial injury induced by common bile duct ligation in rats. Their study showed that under OJ conditions, cardiac tissue exhibited increased levels of autophagy markers, such as light chain 3-II and Beclin-1 [74]. Furthermore, cholestasis inhibits autolysosome formation. Cholesterol 7α-hydroxylase catalyzes the conversion of cholesterol into bile acids, which subsequently activate the nuclear receptors farnesoid X receptor and intestinal fibroblast growth factor, both of which suppress autophagy-related transcriptional genes [75].

In the late stages of OJ, decreased connexin 43 expression leads to excessive autophagy activation through the adenosine monophosphate-activated protein kinase-mammalian target of rapamycin-unc-51-like autophagy activating kinase 1 signaling pathway, further exacerbating myocardial injury [74]. Additionally, bile acids upregulate p62 and Beclin-1 expression, thereby enhancing autophagy. The phosphatidylinositol 3-kinase-Beclin complex recruits the autophagy-related 12-autophagy-related 5 complex and autophagy-related 16 multimers. These proteins, along with microtubule-associated protein light chain 3, promote the formation of autophagic vesicles [76].

These findings highlight the significant role of autophagy in cardiac injury caused by OJ. However, studies investigating the involvement of autophagy in OJ-induced cardiac injury remain limited. Nevertheless, current evidence suggests that autophagy is a key mechanism underlying jaundice-associated cardiac dysfunction and warrants further investigation.

Apoptosis

Apoptosis is a key mechanism of programmed cell death. The term “apoptosis” was first introduced by Kerr et al. in 1972 to describe a distinct form of morphological cell death [77]. To date, numerous studies have demonstrated the role of apoptosis in various cardiac diseases, including myocardial infarction, heart failure, coronary artery disease, myocardial ischemia, ischemia/reperfusion injury, and diabetic cardiomyopathy [78-80]. Recent research has also indicated that OJ induces cardiomyocyte apoptosis [81]. Apoptosis is mediated through two major pathways: the intrinsic and extrinsic pathways [82]. The intrinsic pathway is triggered by factors such as ischemia, hypoxia, oxidative stress, DNA damage, and toxic drugs effects [83]. In contrast, the extrinsic pathway is typically activated by death receptor superfamily ligands, such as tumor necrosis factor-alpha [84, 85].

In 2010, BDL mouse experiments demonstrated positive TUNEL staining in myocardial tissue from cholestatic mice on day 3, indicating increased apoptosis [47]. In 2014, Abbasi et al. further confirmed an increased number of apoptotic cardiomyocytes in a rat model of bile duct ligation, supporting the role of apoptosis in the pathogenesis of the “Jaundiced Heart” [86]. That same year, Nam et al. investigated the apoptotic pathways involved in myocardial apoptosis in BDL mice after two weeks [87]. They intravenously injected CD178 [Fas ligand (FasL)] monoclonal antibodies via the caudal vein at day 12 post-BDL and found that FasL antibody treatment significantly improved myocardial contractility in BDL mice. Their study also demonstrated that the Fas receptor, a member of the TNF superfamily, recruits the adaptor protein Fas-associated death domain- and caspases upon trimerization, forming a multiprotein complex. This process leads to the recruitment of caspase-8, initiating a cascade that ultimately activates caspase-3 and caspase-7, thereby triggering the extrinsic apoptosis pathway [87].

B-cell lymphoma-2 (Bcl-2) associated X protein and Bcl-2 are key members of the Bcl-2 protein family and play crucial roles in apoptosis, particularly in the intrinsic pathway. Bcl-2 associated X protein, a pro-apoptotic protein, induces mitochondrial outer membrane permeabilization, leading to the release of pro-apoptotic factors such as cytochrome c into the cytoplasm. This, in turn, activates cytosolic signaling pathways, recruiting caspase recruitment domain proteins to caspase-9, ultimately triggering apoptosis through caspase activation and resulting in cell death [88]. In 2021, Moheimani et al. demonstrated that in BDL rats, activation of caspases, along with the involvement of Bcl-2 associated X protein and Bcl-2 family proteins, plays a central role in myocardial apoptosis [89]. These studies collectively confirm that apoptosis is a key mechanism in myocardial injury induced by BDL.

Current treatment influencing factors

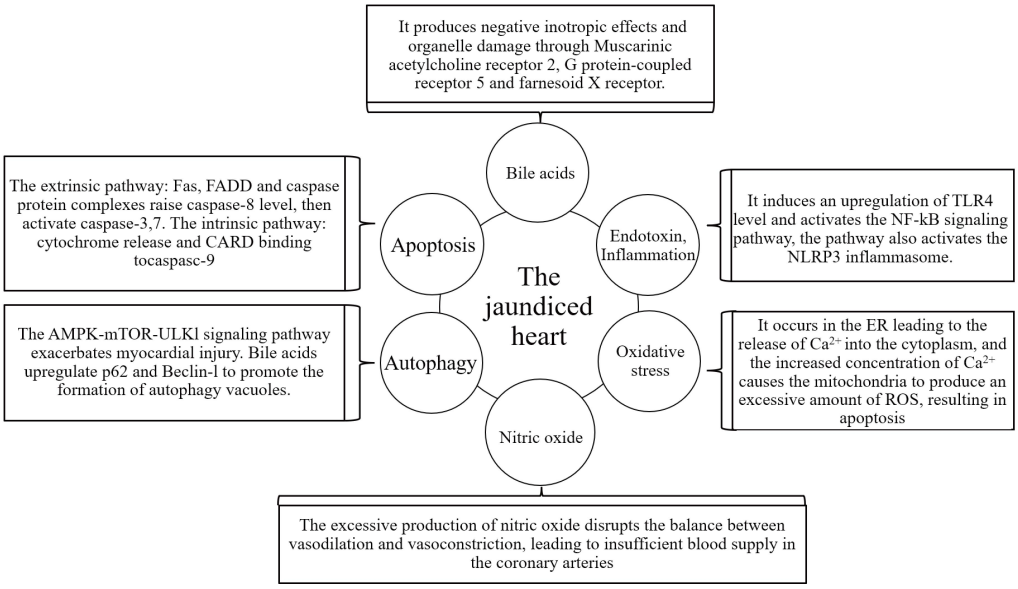

Figure 1. Illustration of the mechanisms of cardiac injury in obstructive jaundice. TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor (NLR) family pyrin domain-containing 3; ER, endoplasmic reticulum; AMPK, Adenosine monophosphate-activated protein kinase; m-TOR, mammalian target of rapamycin; ULK1, Unc-51 like autophagy activating kinase 1; Fas, Fas cell surface death receptor; FADD, Fas-associated protein with death domain.

Currently, there are no well-established preventive measures for cardiac injury in OJ. In this review, we summarize treatment-related factors that may influence the prognosis of OJ-induced cardiac injury.

Selection of anesthetic drugs

Patients with OJ undergoing anesthesia experience significant fluctuations in mean arterial pressure before and after induction, making them more susceptible to hypotension or bradycardia. Additionally, the incidence of delayed postoperative awakening in OJ patients is higher than in non-OJ patients [90]. Therefore, careful selection of anesthetic agents is crucial.

Propofol, a widely used intravenous anesthetic, has cardiovascular depressant effects. In a study using male Sprague-Dawley rats with BDL models, researchers found that myocardial function was impaired in the BDL group. Low to moderate concentrations of propofol did not further impair cardiac function, whereas high doses significantly reduced myocardial performance [91]. Thus, propofol should be administered with caution in OJ patients, with careful dose adjustment and continuous cardiac monitoring to prevent excessive myocardial suppression. Interestingly, propofol has also been found to protect vascular endothelial cells by significantly reducing H_2O_2-induced caspase-3 activity, thereby inhibiting apoptosis and exerting a cardioprotective effect [92].

Etomidate, another commonly used anesthetic, has also been studied in the context of OJ. However, its relationship with OJ-related cardiac injury remains poorly understood. Song et al. compared 20 OJ patients with 20 non-OJ patients and found that the OJ group required lower doses of etomidate than the control group [93]. These findings suggest that different anesthetic agents may have varying effects on OJ patients. Anesthetic selection should be carefully considered to avoid exacerbating cardiac injury in this population.

Traditional Chinese medicine (TCM)

TCM has shown has shown potential in preventing cardiac injury in OJ. Alam et al. proposed that the combination of lupeol and naringin effectively alleviates myocardial injury in BDL rats. This combination enhances antioxidant enzyme activity (superoxide dismutase, catalase, and Glutathione), scavenges free radicals, and reduces oxidative stress, thereby protecting cardiomyocytes. Additionally, it inhibits NF-κB/p65 expression, suppressing inflammatory responses and further preventing myocardial damage [94].

Astragalus, a well-known TCM herb, has been studied for its cardioprotective effects. Astragaloside Ⅳ, a bioactive compound found in Astragalus roots, has been shown to reduce isoproterenol-induced myocardial injury by decreasing cytoplasmic Ca^{2+} levels. Additionally, it

lowers malondialdehyde levels while increasing superoxide dismutase activity, suggesting that its antioxidant properties may contribute to its cardioprotective effects [95].

Perioperative impact

Optimizing preoperative assessment, intraoperative management, and postoperative care can improve patient prognosis and reduce mortality. Preoperative biliary drainage helps lower bilirubin levels, mitigate cardiotoxic effects, and enhance cardiovascular function. During surgery, patients with OJ are prone to hypovolemia, necessitating aggressive fluid therapy to maintain adequate circulating blood volume. Additionally, due to the high incidence of cardiovascular depression in these patients, continuous cardiovascular monitoring is essential. Cardiovascular support medications should be administered as needed to stabilize blood pressure and heart rate [96].

Future research

A 2024 study on OJ rats revealed that elevated bile acid levels, in conjunction with increased LPS concentrations, induce pyroptosis and exacerbate hepatic injury [97]. Extensive evidence has demonstrated the role of pyroptosis in various forms of myocardial injury [98]. However, few studies have investigated the role of pyroptosis in OJ-induced cardiac injury. Whether pyroptosis occurs in the myocardium of patients with OJ remains an open question, warranting further research.

Current research on cardiac injury in OJ remains limited, and many areas require further exploration. Omics technologies, with their high-throughput and high-sensitivity capabilities, enable dynamic monitoring of endogenous small-molecule metabolites. By systematically analyzing metabolic changes under physiological and pathological conditions, omics research can provide valuable insights into the complex mechanisms underlying OJ-induced cardiac injury.

Conclusion

OJ can lead to multiple systemic complications, with the heart being one of the most affected organs. The clinical manifestations of OJ-induced cardiac injury are diverse, significantly impacting patients' quality of life and prognosis. Early identification and intervention are crucial for improving patient outcomes.

The toxic effects of bile acids, inflammation, oxidative stress, endotoxemia, NO dysregulation, apoptosis, and pyroptosis all contribute to OJ-related cardiac injury. As illustrated in **Figure 1**, these mechanisms are interconnected. Bile acids and endotoxins can directly trigger inflammatory responses or exacerbate inflammation by increasing oxidative stress. Apoptosis and autophagy are often induced by bile acid toxicity, while abnormal regulation of these processes, combined with severe inflammatory responses, leads to myocardial cell damage.

This review summarizes current research on the mechanisms of cardiac injury in OJ. Furthermore, it proposes potential therapeutic strategies and research directions for future studies.

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References

[1] Green J, Better OS. Systemic hypotension and renal failure in obstructive jaundice-mechanistic and therapeutic aspects. J Am Soc Nephrol 1995;5(11):1853-1871.

[2] Sheen JM, Chen YC, Tain YL, et al. Increased circulatory asymmetric dimethylarginine and multiple organ failure: bile duct ligation in rat as a model. Int J Mol Sci 2014;15(3):3989-4006.

[3] Krones E, Pollheimer MJ, Rosenkranz AR, et al. Cholemic nephropathy - Historical notes and novel perspectives. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1356-1366.

[4] Pavlidis ET, Pavlidis TE. Pathophysiological consequences of obstructive jaundice and perioperative management. Hepatobiliary Pancreat Dis Int 2018;17(1):17-21.

[5] Mariotti V, Strazzabosco M, Fabris L, et al. Animal models of biliary injury and altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1254-1261.

[6] Williams RD, Elliott DW, Zollinger RM. The effect of hypotension in obstructive jaundice. Arch Surg 1960;81:334-340.

[7] Tajuddin M, Tariq M, Bilgrami NL, et al. Biochemical and pathological changes in the heart following bile duct ligation. Adv Myocardiol 1980;2:209-212.

[8] Namiranian K, Samini M, Mehr SE, et al. Mesenteric vascular bed responsiveness in bile duct-ligated rats: roles of opioid and nitric oxide systems. Eur J Pharmacol 2001;423(2-3):185-193.

[9] Mani AR, Nahavandi A, Moosavi M, et al.

Dual nitric oxide mechanisms of cholestasis-induced bradycardia in the rat. Clin Exp Pharmacol Physiol 2002;29(10):905-908.
[10] Junejo MA, Siriwardena AK, Parker MJ. Peripheral oxygen extraction in patients with malignant obstructive jaundice. Anaesthesia 2014;69(1):32-36.
[11] Green J, Beyar R, Sideman S, et al. The "jaundiced heart": a possible explanation for postoperative shock in obstructive jaundice. Surgery 1986;100(1):14-20.
[12] Lumlertgul D, Boonyaprapa S, Bunnachak D, et al. The jaundiced heart: evidence of blunted response to positive inotropic stimulation. Ren Fail 1991;13(1):15-22.
[13] Uhlig M, Hein M, Habigt MA, et al. Cirrhotic Cardiomyopathy Following Bile Duct Ligation in Rats-A Matter of Time? Int J Mol Sci 2023;24(9):8147.
[14] Zhang Z, Lv T, Wang X, et al. Role of the microbiota-gut-heart axis between bile acids and cardiovascular disease. Biomed Pharmacother 2024;174:116567.
[15] Parkinson TM, Olson JA. INHIBITORY EFFECTS OF BILE ACIDS ON ADENOSINE TRIPHOSPHATASE, OXYGEN CONSUMPTION, AND THE TRANSPORT AND DIFFUSION OF WATER-SOLUBLE SUBSTANCES IN THE SMALL INTESTINE OF THE RAT. Life Sci (1962) 1964;3:107-112.
[16] Mu YP, Peng SY. Relation between bile acids and myocardial damage in obstructive jaundice. World J Gastroenterol 1997;3(3):174-176.
[17] King JH, Stewart HA. EFFECT OF THE INJECTION OF BILE ON THE CIRCULATION. J Exp Med 1909;11(5):673-685.
[18] Joubert P. Cholic acid and the heart: in vitro studies of the effect on heart rate and myocardial contractility in the rat. Clin Exp Pharmacol Physiol 1978;5(1):9-16.
[19] Wakim KG, Essex. Mann FC. The effects of whole bile and bile salts on the perfused heart. Am Heart J 1939;171-175.
[20] Wakim KG, Essex. Mann FC. The effects of whole bile and bile salts on the innervated and the denervated heart. Am Heart J 1940;486-491.
[21] Bogin E, Better O, Harari I. The effect of jaundiced sera and bile salts on cultured beating rat heart cells. Experientia 1983;39(11):1307-1308.
[22] Spivey JR, Bronk SF, Gores GJ. Glycochenodeoxycholate-induced lethal hepatocellular injury in rat hepatocytes. Role of ATP depletion and cytosolic free calcium. J Clin Invest 1993;92(1):17-24.
[23] Palmeira CM, Rolo AP. Mitochondrially-mediated toxicity of bile acids. Toxicology 2004;203(1-3):1-15.
[24] Ferreira M, Coxito PM, Sardão VA, et al. Bile acids are toxic for isolated cardiac mitochondria: a possible cause for hepatic-derived cardiomyopathies? Cardiovasc Toxicol 2005;5(1):63-73.
[25] Binah O, Rubinstein I, Bomzon A, et al. Effects of bile acids on ventricular muscle contraction and electrophysiological properties: studies in rat papillary muscle and isolated ventricular myocytes. Naunyn Schmiedebergs Arch Pharmacol 1987;335(2):160-165.
[26] Sheikh Abdul Kadir SH, Miragoli M, Abu-Hayyeh S, et al. Bile acid-induced arrhythmia is mediated by muscarinic M2 receptors in neonatal rat cardiomyocytes. PLoS One 2010;5(3):e9689.
[27] Vasavan T, Ferraro E, Ibrahim E, et al. Heart and bile acids - Clinical consequences of altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis 2018;1864(4 Pt B):1345-1355.
[28] Jia W, Li Y, Cheung KCP, et al. Bile acid signaling in the regulation of whole body metabolic and immunological homeostasis. Sci China Life Sci 2024;67(5):865-878.
[29] Foster DM, Kellum JA. Endotoxic Septic Shock: Diagnosis and Treatment. Int J Mol Sci 2023;24(22):16185.
[30] Nguyen M, Gautier T, Masson D, et al. Endotoxemia in Acute Heart Failure and Cardiogenic Shock: Evidence, Mechanisms and Therapeutic Options. J Clin Med 2023;12(7):2579.
[31] Yorganci K, Baykal A, Kologlu M, et al. Endotoxin challenge causes a proinflammatory state in obstructive jaundice. J Invest Surg 2004;17(3):119-126.
[32] Papakostas C, Bezirtzoglou E, Pitiakoudis M, et al. Endotoxinemia in the portal and the systemic circulation in obstructive jaundice. Clin Exp Med 2003;3(2):124-128.
[33] Song JG, Cao YF, Sun YM, et al. Baroreflex sensitivity is impaired in patients with obstructive jaundice. Anesthesiology 2009;111(3):561-565.
[34] Tang F, Liu D, Wan F, et al. Ameliorative effect of anisodamine (654-1/654-2) against myocardial dysfunction induced by septic shock via the NF-κB/NLRP-3 or the PI3K-AKT/NF-κB pathway. Phytomedicine 2024;123:155277.
[35] Wang SM, Liu GQ, Xian HB, et al. LncRNA NEAT1 alleviates sepsis-induced myocardial injury by regulating the TLR2/NF-κB signaling pathway. Eur Rev Med Pharmacol Sci 2019;23(11):4898-4907.
[36] El-Sisi AEE, Sokar SS, Shebl AM, et al. Octreotide and melatonin alleviate inflammasome-induced pyroptosis through inhibition of TLR4-NF-κB-NLRP3 pathway in

hepatic ischemia/reperfusion injury. Toxicol Appl Pharmacol 2021;410:115340.
[37] Scott-Conner CE, Grogan JB. Serum and cellular factors in murine obstructive jaundice. Surgery 1994;115(1):77-84.
[38] Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol 2011;301(6):H2181-2190.
[39] Tsai LY, Lee KT, Liu TZ. Evidence for accelerated generation of hydroxyl radicals in experimental obstructive jaundice of rats. Free Radic Biol Med 1998;24(5):732-737.
[40] Assimakopoulos SF, Vagianos CE, Patsoukis N, et al. Evidence for intestinal oxidative stress in obstructive jaundice-induced gut barrier dysfunction in rats. Acta Physiol Scand 2004;180(2):177-185.
[41] Assimakopoulos SF, Vagianos CE, Zervoudakis G, et al. Gut regulatory peptides bombesin and neurotensin reduce hepatic oxidative stress and histological alterations in bile duct ligated rats. Regul Pept 2004;120(1-3):185-193.
[42] Ara C, Karabulut AB, Kirimlioglu H, et al. Protective effect of resveratrol against renal oxidative stress in cholestasis. Ren Fail 2005;27(4):435-440.
[43] Chroni E, Patsoukis N, Karageorgos N, et al. Brain oxidative stress induced by obstructive jaundice in rats. J Neuropathol Exp Neurol 2006;65(2):193-198.
[44] Tieppo J, Vercelino R, Dias AS, et al. Evaluation of the protective effects of quercetin in the hepatopulmonary syndrome. Food Chem Toxicol 2007;45(7):1140-1146.
[45] Orozco-Aguilar J, Simon F, Cabello-Verrugio C. Redox-Dependent Effects in the Physiopathological Role of Bile Acids. Oxid Med Cell Longev 2021;2021:4847941.
[46] Cruz A, Tasset I, Ramírez LM, et al. Effect of melatonin on myocardial oxidative stress induced by experimental obstructive jaundice. Rev Esp Enferm Dig 2009;101(7):460-463.
[47] Shafaroodi H, Ebrahimi F, Moezi L, et al. Cholestasis induces apoptosis in mice cardiac cells: the possible role of nitric oxide and oxidative stress. Liver Int 2010;30(6):898-905.
[48] Che Y, Xu W, Ding C, et al. Bile acids target mitofusin 2 to differentially regulate innate immunity in physiological versus cholestatic conditions. Cell Rep 2023;42(1):112011.
[49] van der Pol A, van Gilst WH, Voors AA, et al. Treating oxidative stress in heart failure: past, present and future. Eur J Heart Fail 2019;21(4):425-435.
[50] Goicoechea L, Conde de la Rosa L, Torres S, et al. Mitochondrial cholesterol: Metabolism and impact on redox biology and disease. Redox Biol 2023;61:102643.
[51] Viola HM, Hool LC. Targeting calcium and the mitochondria in prevention of pathology in the heart. Curr Drug Targets 2011;12(5):748-760.
[52] Kim JA, Montagnani M, Koh KK, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113(15):1888-1904.
[53] Duodu P, Sosa G, Canar J, et al. Exposing the Two Contrasting Faces of STAT2 in Inflammation. J Interferon Cytokine Res 2022;42(9):467-481.
[54] Suetomi T, Miyamoto S, Brown JH. Inflammation in nonischemic heart disease: initiation by cardiomyocyte CaMKII and NLRP3 inflammasome signaling. Am J Physiol Heart Circ Physiol 2019;317(5):H877-H890.
[55] Ommati MM, Amjadinia A, Mousavi K, et al. N-acetyl cysteine treatment mitigates biomarkers of oxidative stress in different tissues of bile duct ligated rats. Stress 2021;24(2):213-228.
[56] Sul OJ, Ra SW. Quercetin Prevents LPS-Induced Oxidative Stress and Inflammation by Modulating NOX2/ROS/NF-kB in Lung Epithelial Cells. Molecules 2021;26(22):6949.
[57] Yin X, Zhuang X, Luo W, et al. Andrographolide promote the growth and immunity of Litopenaeus vannamei, and protects shrimps against Vibrio alginolyticus by regulating inflammation and apoptosis via a ROS-JNK dependent pathway. Front Immunol 2022;13:990297.
[58] Assimakopoulos SF, Scopa CD, Vagianos CE. Pathophysiology of increased intestinal permeability in obstructive jaundice. World J Gastroenterol 2007;13(48):6458-6464.
[59] Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991;337(8744):776-778.
[60] Jolobe OM. Role of endotoxin and nitric oxide in the pathogenesis of renal failure in obstructive jaundice. Br J Surg 1997;84(12):1747.
[61] Gray GA, Schott C, Julou-Schaeffer G, et al. The effect of inhibitors of the L-arginine/nitric oxide pathway on endotoxin-induced loss of vascular responsiveness in anaesthetized rats. Br J Pharmacol 1991;103(1):1218-1224.
[62] Khurana S, Yamada M, Wess J, et al. Deoxycholyltaurine-induced vasodilation of rodent aorta is nitric oxide- and muscarinic M(3) receptor-dependent. Eur J Pharmacol 2005;517(1-2):103-110.
[63] Razavi HM, Hamilton JA, Feng Q. Modulation of apoptosis by nitric oxide: implications in myocardial ischemia and heart failure. Pharmacol Ther 2005;106(2):147-162.

[64] Ohsumi Y. Historical landmarks of autophagy research. Cell Res 2014;24(1):9-23.
[65] Deter RL, De Duve C. Influence of glucagon, an inducer of cellular autophagy, on some physical properties of rat liver lysosomes. J Cell Biol 1967;33(2):437-449.
[66] Chen Y, Shi S, Dai Y. Research progress of therapeutic drugs for doxorubicin-induced cardiomyopathy. Biomed Pharmacother 2022;156:113903.
[67] Dewanjee S, Vallamkondu J, Kalra RS, et al. Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Ageing Res Rev 2021;68:101338.
[68] Ding X, Zhu C, Wang W, et al. SIRT1 is a regulator of autophagy: Implications for the progression and treatment of myocardial ischemia-reperfusion. Pharmacol Res 2024;199:106957.
[69] Li A, Gao M, Liu B, et al. Mitochondrial autophagy: molecular mechanisms and implications for cardiovascular disease. Cell Death Dis 2022;13(5):444.
[70] Choi JC, Muchir A, Wu W, et al. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. Sci Transl Med 2012;4(144):144ra102.
[71] Sciarretta S, Maejima Y, Zablocki D, et al. The Role of Autophagy in the Heart. Annu Rev Physiol 2018;80:1-26.
[72] Zhang X, Zhang F, Zhang C, et al. miRNA-125b Signaling Ameliorates Liver Injury Against Obstructive Jaundice-Induced Excessive Fibrosis in Experimental Rats. Yonsei Med J 2021;62(5):453-460.
[73] Zhang X, Peng B, Zhang Y, et al. Biliary Drainage Reduces Intestinal Barrier Damage in Obstructive Jaundice by Regulating Autophagy. Contrast Media Mol Imaging 2022;2022:3301330.
[74] Wang X, Liao P, Dong H, et al. Reduced Cx43 Expression Induces Autophagy through Activation of the Ampk-Mtor-Ulk1 Signaling Pathway in the Common Bile Duct Ligation Rat Heart. Shock 2024;62(3):386-397.
[75] Rochette L, Dogon G, Rigal E, et al. Lipid Peroxidation and Iron Metabolism: Two Corner Stones in the Homeostasis Control of Ferroptosis. Int J Mol Sci 2022;24(1):449.
[76] Kang R, Zeh HJ, Lotze MT, et al. The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 2011;18(4):571-580.
[77] Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972;26(4):239-257.
[78] Ouyang C, You J, Xie Z. The interplay between autophagy and apoptosis in the diabetic heart. J Mol Cell Cardiol 2014;71:71-80.
[79] Jose Corbalan J, Vatner DE, Vatner SF. Myocardial apoptosis in heart disease: does the emperor have clothes? Basic Res Cardiol 2016;111(3):31.
[80] Dong Y, Chen H, Gao J, et al. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. J Mol Cell Cardiol 2019;136:27-41.
[81] Zhao N, Shao Z, Xia G, et al. Protective role of the CD73-A2AR axis in cirrhotic cardiomyopathy through negative feedback regulation of the NF-κB pathway. Front Immunol 2024;15:1428551.
[82] Lossi L. The concept of intrinsic versus extrinsic apoptosis. Biochem J 2022;479(3):357-384.
[83] Danial NN, Korsmeyer SJ. Cell death: critical control points. Cell 2004;116(2):205-219.
[84] Kalkavan H, Green DR. MOMP, cell suicide as a BCL-2 family business. Cell Death Differ 2018;25(1):46-55.
[85] Liu X, Kim CN, Yang J, et al. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. Cell 1996;86(1):147-157.
[86] Abbasi A, Joharimoqaddam A, Faramarzi N, et al. Opioid receptors blockade modulates apoptosis in a rat model of cirrhotic cardiomyopathy. Ann Med Health Sci Res 2014;4(3):404-409.
[87] Nam SW, Liu H, Wong JZ, et al. Cardiomyocyte apoptosis contributes to pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated mice. Clin Sci (Lond) 2014;127(8):519-526.
[88] Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol 2020;21(2):85-100.
[89] Moheimani HR, Amiriani T, Alizadeh AM, et al. Preconditioning and anti-apoptotic effects of Metformin and Cyclosporine-A in an isolated bile duct-ligated rat heart. Eur J Pharmacol 2021;893:73807.
[90] Yang LQ, Song JC, Irwin MG, et al. A clinical prospective comparison of anesthetics sensitivity and hemodynamic effect among patients with or without obstructive jaundice. Acta Anaesthesiol Scand 2010;54(7):871-877.
[91] Ren HM, Yang LQ, Liu ZQ, et al. In vivo and ex vivo effects of propofol on myocardial performance in rats with obstructive jaundice. BMC Gastroenterol 2011;11:144.
[92] Wang B, Luo T, Chen D, et al. Propofol reduces apoptosis and up-regulates endothelial nitric oxide synthase protein expression in hydrogen peroxide-stimulated human umbilical vein endothelial cells. Anesth Analg 2007;105(4):1027-1033, table of contents.
[93] Song JC, Sun YM, Zhang MZ, et al. The etomidate requirement is decreased in

patients with obstructive jaundice. Anesth Analg 2011;113(5):1028-1032.

[94] Alam F, Kharya AK, Srivastav RK, et al. Synergetic Effect of Lupeol and Naringin Against Bile Duct Ligation Induced Cardiac Injury in Rats via Modulating Nitrite Level (eNos) and NF-kB /p65 Expression. Drug Res (Stuttg) 2023;73(1):23-29.

[95] Shahzad M, Shabbir A, Wojcikowski K, et al. The Antioxidant Effects of Radix Astragali (Astragalus membranaceus and Related Species) in Protecting Tissues from Injury and Disease. Curr Drug Targets 2016;17(12):1331-1340.

[96] Wang L, Yu WF. Obstructive jaundice and perioperative management. Acta Anaesthesiol Taiwan 2014;52(1):22-29.

[97] Shen X, Zhang X, Li K, et al. Combined bacterial translocation and cholestasis aggravates liver injury by activation pyroptosis in obstructive jaundice. Heliyon 2024;10(16):e35793.

[98] Toldo S, Mauro AG, Cutter Z, et al. Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2018;315(6):H1553-H1568.