Journal of Science and Technology
ISSN: 2456-5660 Volume 8, Issue 12 (Dec -2023)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2023.v8.i12.pp256- 275*

Cardiac Complications Induced by Biliary Diseases: Clinical Manifestations, Pathogenesis, and Treatment Strategies for Cholecardia Syndrome

D.Dhachinamoorthi[1], M.Rajan[2], A. Purnima Devi[3], L. Ramachandra Reddy[4]

1. Professor, Department of pharmaceutics, QIS College of pharmacy, Ongole, A.P
2. Professor, Department of pharmacognosy, QIS College of pharmacy, Ongole, A.P
3.Assistant Professor, Department of pharmacology, QIS College of pharmacy, Ongole, A.P
4.Assistant Professor, Department of pharmacognosy, QIS College of pharmacy, Ongole, A.P

To Cite this Article

D.Dhachinamoorthi, M.Rajan, A. Purnima Devi, L. Ramachandra Reddy**, "Cardiac Complications Induced by Biliary Diseases: Clinical Manifestations, Pathogenesis, and Treatment Strategies for Cholecardia Syndrome "** *Journal of Science and Technology, Vol. 08, Issue 12- Dec 2023, pp256-275*

Article Info

Received: 28-10-2023 Revised: 05-12-2023 Accepted: 15-12-2023 Published: 27-12-2023

ABSTRACT

Among the most prevalent digestive disorders are gallbladder and biliary diseases (GBDs). As people's diets have changed and medical diagnostic technology has advanced steadily, links between GBDs and several other organs have progressively come to light. Cholecardiasyndrome, which targets the heart as a major target for GBD problems, has received particular attention. Nevertheless, there is currently no comprehensive study on the pathophysiology and accompanying clinical symptoms. Arrhythmia, myocardial damage, acute coronary syndrome, and heart failure are all prevalent in the general population, according to this study, which included the most current reports of cholecardia syndrome types. Additionally, the clinical diagnostic rate of Alagille syndrome linked to gene mutation and intrahepatic cholestasis of pregnancy (ICP) is rising. Thus, more information was provided on the underlying pathophysiology, which included aberrant bile acid secretion, gene mutation, translocation, and deletion (JAG1, NOTCH2, ABCG5/8, and CYP7A1), nerve reflex, and autonomic neuropathy. In order to support clinical diagnosis and treatment, the clinical medication and potential treatment measures represented by ursodeoxycholicacid were finally summarized.

. Corresponding author: D.Dhachinamoorthi
Mail: d.d.moorthy@gmail.com

1. Introduction

One of the most prevalent digestive disorders is gallbladder and biliary diseases (GBDs), which includes gallstones, cholecystitis, and other biliary disorders. Globally, the diagnosis, operation success rate, and prognosis associated with GBDs have improved dramatically because to the ongoing advancements in ultrasonography and laparoscopic procedures [1]. The human body has a whole system of circulating materials, and when one organ malfunctions, it often results in issues for other organs. Most people think that

there is a connection between the ERCP, endoscopic retrograde cholangiopancreatography; GBDs, gallbladder and biliary diseases; ECG, electrocardiogram; BDL, bileduct ligation; LBBB, left bundle branch block; PBC, primary biliary cirrhosis; HRV, heart rate variability; SRS, stress reflex sensitivity; CBDL, chronic bile duct ligation; AVB, complete atrioventricular block; PFIC, or progressive familial intrahepatic cholestasis; GD, or gallstone; LDL, or low-density lipoprotein; ICP, or intrahepatic cholestasis of pregnancy; DDC, 3, 5-diethoxycarbonyl-1, 4-dihydro-collidine; CHD, or coronary heart disease; GP, or gallbladder polyps; QT-disp,QT dispersion parameter; QTc,CorrectedQTInterval;MPI,Myocardialfunctionindex;LMPI,Leftventricularmyocardialfunctionchangeindex;MOD-MPI,Modifiedmyocardialfunctionindex;AGS,Alagillesyndrome;BA,BileAcid;Tbil,TotalBilirubin;AMY,Amylase;EC31,Lipase;ALT,AlanineAminotransferase;CRP,C-reactiveprotein;WBC,WhiteBloodCell;AST,Aspartate Aminotransferase; PCT, Procalcitonin; MAP, Mean Arterial Pressure; TGF-β, Transforming Growth Factor-β; CI, Cardiac Index; TPR, Total PeripheralResistance;TPRI,TPRIndex;HDL,High-DensityLipoprotein;LVEF,LeftVentricularEjectionFraction;LV,LeftVentricular;Bil,Bilirubin;NT-proBNP,N-terminalpro–brain natriuretic peptide; Lp a, Lipoproteins (a); E/A, E wave /A wave peak velocityratio; CK, Creatine Kinase; GGT, Glutamyl Transpeptidase; AMA-M2, Anti-Mitochondrial Antibody M2; FACS, Fluorescence-Activated Cell Sorted; Dbil, Direct Bilirubin; Ibil, Indirect Bilirubin; TBA, Total Bile Acid; ALP, Alkaline Phosphatase;CHE,Cholinesterase;UDCA,Ursodeoxycholic;TC,TotalSerumCholesterol;TG,Triglyceride;CA, CholicAcid;CMs,CardiacMyocytes;IRT,IsovolumetricRelaxation Time; ICT, Isovolumetric Contraction Time; LMPI, Left Ventricular Modified Myocardial Performance Index; LVET, Left Ventricular Ejection Time; SR,Torsional Shortening Ratio; HRV, Heart Rate Variability; PAP, Pulmonary Artery Pressure; PVR, Pulmonary Vascular Resistance. * The first affiliated hospital of Dalian Medical University, Laboratory of Integrative Medicine, No. 222, Zhongshan Road, Dalian116011, China, is the address of the corresponding authors.

Pharmaceutical Research, Y. Lital, 199(2024)107006 Because of their intimate physiological relationship, the liver and gallbladder cannot be separated. As a result, a number of hepatobiliary disorders, including cholestatic hepatitis and primary biliary cirrhosis (PBC), have gained significant attention. It's also important to note that as dietary patterns have changed and medical diagnostic technology has advanced steadily, links between the gallbladder and other organs have progressively come to light. Among them, the heart has emerged as a crucial target for GBD problems that cannot be disregarded. In 1931, Tennant et al. used autopsy to discover a strong positive association between gallbladder disease and arteriosclerotic heart disease [2]. Additionally, gallbladder illness may set off reflexes that lead to arrhythmias, angina pectoris discomfort, and alterations in the electrocardiogram (ECG) [3]. However, these phenomena typically vanished when GBDs healed. Trinkle et al., for instance, described a case of gallstone-induced obstructive jaundice with QRS prolongation on ECG. Following cholecystectomy, the ECG abnormalities vanished [4]. The term "cholecardia" was first used by Desaietal. to refer to cardiac malfunction brought on by an excess of bile acid till 2017 [5].

The connection between cholelithiasis and cardiovascular disease has received a lot of attention since it is one of the most prevalent clinical gallbladder illnesses. Large prospective cohorts have shown that cholelithiasis raises the risk of ischemic heart disease, even if the causal link between the two has not been established. This correlation is independent of conventional cardiovascular risk factors [6,7]. Cholecardia symptoms can arise in a variety of hepatobiliary surgical procedures in addition to pathological conditions. The most common procedure that causes coronary heart disease syndrome is endoscopic retrograde cholangiopancreatogy (ERCP), a common surgical procedure used primarily to treat acute suppurative cholangitis, obstructive cholangitis, choledocholithiasis, advanced cholangiocarcinoma, and pancreatic head cancer. While not all patients will have actual myocardial ischemia after ERCP surgery, up

to 50% of patients may experience a cardiac arrhythmia syndrome, which is characterized by an ECG ST segment shift resembling myocardial ischemia [8,9]. A few hours after surgery, for instance, a patient receiving therapeutic ERCP had significant cardiogenic pulmonary edema, which is believed to be related to reduced myocardial blood supply [10]. In addition, ERCP therapy-induced Takotsubocardiomyopathy, sometimes referred to as stress cardiomyopathy, has been linked to left ventricular systolic failure without coronary artery disease [11]. The nerve reflex between the gallbladder and the heart is often used to explain the aforementioned behavior. Gallbladder irritation causes nerve reflexes that slow the heartbeat, lower blood pressure, and in extreme situations, cardiac ischemia or cardiac collapse. However, more research is necessary to determine if there are several mechanisms that explain the connection between gallbladder and cardiac complications in various GBDs. We discovered via comprehensive literature review that several forms of cardiac injury may develop over the course of GBD sickness. Among them, GBDs have the potential to directly induce arrhythmia, myocardial ischemia, and Takotsubo cardiomyopathy. However, based on GBDs, individuals who already have coronary heart disease and myocardial infarction may see their condition deteriorate. Additionally, its pathophysiology is linked to disorders of the body's circulation and metabolism of several organic compounds, especially the metabolism of bile acids. Supportive care is the primary treatment of choice at this time. Because of the variety of illness categories, therapeutic medications have certain selectivity and limits. In order to better patient prognosis and provide fresh concepts for its future clinical prevention and therapy, we have attempted to present and synthesize the kinds, pathophysiology, and treatment of cholecardia syndrome holistically in this study.

2. CardiaccomplicationsofGBDs

The initial development of cardiac abnormalities (without a history of cardiovascular illness) or the accumulation of cardiac abnormalities after the onset of GBDs is referred to as cholecardia syndrome. A thorough review of the literature revealed that the most frequent cardiac dysfunctions brought on by GBDs under pathological settings include arrhythmia, myocardial injury, and coronary heart disease. In severe situations, these dysfunctions might progress to heart failure. Furthermore, it is important to mention that cholecythalopathy is more prevalent in two specific disorders, intrahepatic cholestasis of pregnancy (ICP) and Alagille syndrome. These diseases' etiology is linked to bile acid metabolism and gene mutations that are common in pregnancy and neonates. Arrhythmia and myocardial injury are the two primary cardiac abnormalities that may be directly induced by GBDs among the aforementioned cardiac problems. In order to aid in the clinical prevention of cholecardiasyndrome, this section will present a summary of the main forms of problems from the clinical to basic research mentioned above (Table 1). An irregular heartbeat One significant subtype of cardiovascular illness is arrhythmia. The primary reasons may be separated into acquired and hereditary variables. The latter might be divided into two categories: pathological and physiological causes. However, anatomical or functional alterations in other organs that are not limited to the heart may also result in arrhythmias. For instance, it is well recognized that one of the most frequent cardiac side effects of cholestatic liver illness is arrhythmia [15]. The three conditions that are brought on by GBDs will next be explained in turn: bradycardia, atrioventricular block, and alterations in heart rate variability (HRV).

Bradycardia One of the most prevalent signs of an arrhythmia is bradycardia. Bradycardia symptoms are often seen in individuals with cholecystitis or cholelithiasis as a consequence of GBDs. The idea of reflex bradycardia in patients with acute cholecystitis was initially documented by O'Reilly and Krauthamer and was termed Cope's sign [14], even if various indicators such ECG abnormalities are detected in 1971. In the meanwhile, a previous clinical research of cholelithiasis in individuals with familial hyperlipoproteinemia also found bradycardia. Of those with definite ECG evidence of myocardial injury, 39% had it, and 24% had sinus bradycardia [12]. Additionally, Twave inversion, which resembles myocardial ischemia, may show up in the patient's ECG during the physical examination [13]. Thus, it is commonly accepted that gallbladder illness (or intra-abdominal disease) is the source of bradycardia brought on by gallstones or acute cholecystitis, since it affects the cardiovascular system's neural reflexes [13,14]. Consequently, after gallbladder therapy, such as cholecystectomy, cardiovascular symptoms may lessen or go away [14]. It is noteworthy

that since the cardio-biliary reflex may be deceptive, doctors should take into account the potential of gallbladder illness (as well as intra-abdominal disease) while treating patients with acute coronary syndrome who have bradycardia, T-wave inversion, and ST-segment elevation [13]. Studies on animals have shown demonstrated that GBDs may induce bradycardia. Rats with bileduct ligation (BDL) showed significant bradycardia and hypotension, according to Hajrasouli et al. Moreover, these authors discovered that even a brief case of cholestasis might cause the lengthening of QT interphase [15]. However, under some situations, such as cardiac ischemia-reperfusion, which may be connected to autonomic alterations, short-term cholestasis may withstand generated arrhythmias. Consequently, an antiarrhythmicrole may result from increased cholinergic and reduced adrenergic tissue responsiveness during cholestasis.

Heartblock, which may be classified as either atrioventricular block or bundle branch block based on the various blocking sections, is the slowing or blocking of impulse conduction in any region of the heart conduction system. Acute cholecystitis, gallstones, cholangitis, and bradycardia all have the same potential to result in cardiac conduction abnormalities. Additionally, studies show that the two distinct forms of heart block do not seem to be independent when they have some degree of sequence [17]. At the same time, physicians must closely monitor the patient's condition due to the potential for delayed heart block [13]. Regardless of whether pain or gallstones are present, the cardiobiliary reflex is often thought to be the cause of heart block after other frequent reasons have been ruled out. Following therapy for the associated GBDs, the cardiac examination indicators—particularly the ECG—will often improve. The anterior biphasic T waves on the ECG, however, persisted after the patient had a laparoscopic cholecystectomy, according to a special case report by Steffen et al. [16]. Atypical Wellen's ECG, first documented in 1982 [30], is caused by high-gradenarrowing of the heart's anterior descending artery. After the patient's coronary arteries were examined, no pathological alterations were found, hence the ECG abnormalities were ultimately categorized as pseudo-Wellen's illness. In individuals with acute cholecystitis, this is also the first report of Wellen's ECG with intermittent left bundle branch block [16]. Heart rate variability changes (HRV)

After an acute myocardial infarction, heart rate variability (HRV), which is defined as the change in heart cycle variability, has been shown to be a strong independent predictor of mortality [31]. In the general population, there is an independent correlation between the rise in the risk of sudden cardiac death and the decline in HRV [19]. In contrast to bradycardia and heart block, individuals with primary biliary cirrhosis (PBC) who have at least one aberrant parameter in the temporal or frequency domain are more likely to have HRV alterations [18]. Additionally, while they are not exclusive to late stages, HRV abnormalities are linked to clinical symptoms, weariness, and itching [18,19]. The nitration of important proteins in heart tissue is primarily responsible for the aberrant cardiac chronotropic function that also manifested in BDL rats. Moreover, rat heart response may be restored to normal with separate therapies using N-acetylcysteine or L-NAME. Additionally, this offers a fresh concept for further studies on HRV alterations in human participants [20]. Damage to the heart Cirrhosis of the heart

One of the acknowledged significant complications of end-stage PBC is cirrhotic cardiomyopathy (CCM). However, it is also one of these severe complications of liver cirrhosis, which mostly present as aberrant electrophysiological function, decreased myocardial contractile responset stress, and/or diastolic dysfunction. Although the exact cause of CCM is unknown, prior research indicates that it may be connected to several forms of viral hepatitis. A growing number of research in recent years have shown that the pathophysiology of CCM is a consequence of multi-step and multi-factor interactions, among which the role of bile acids cannot be disregarded. The structure, function, and tissue properties of the heart were altered in the early stages of the disease, according to a new prospective research that examined early asymptomatic myocardial damage in PBC. Furthermore, in contrast to other recognized primary or secondary cardiomyopathies, "streaking" of these ptal walls is thought to be an unusual characteristic of myocardial fibrosis in PBC [21].

Regarding the basic study on CC, it was common practice to use mouse models that were established by chronic bile duct ligation or DDC feeding, which are unable to escape the impact of cholestasis. Remission of liver damage and repeated bile acid feeding may also ameliorate CCM [22]. Consequently, cholestasis causes cholecardiasyndrome.

complex. The most prevalent symptom in DDC-fed mice is biliary fibrosis, which is associated with QT prolongation and decreased heart rate [22, 23]. The degree of hyperbilirubinemia and cholestasis in these animals may be used to explain the heart's decline during biliary fibrosis. The ailment described as "icterus bradycardia" was first identified by Rohrig et al. in 1863 [32]. Additionally, in biliary cirrhosis brought on by BDL, hyperdynamic circulation and decreased cardiac contractility were seen [24–26]. Here, we hypothesize that hyperbilirubinemia and bile acids may accelerate the development of cardiac illness brought on by GBDs. Cardiachypertrophy
Cardiachypertrophy is an adaptive compensatory condition of the heart that is often brought on by cardiac coverload. Increases in the size rather than quantity of individual myocardial cells in the adult heart eventually lead to cardiac hypertrophy, which lowers ventricular wall pressure, preserves function and efficiency, and allows the heart to handle the increasing workload [33]. Cholestatic conditions such PBC, progressive familial intrahepatic cholestasis (PFIC), and biliary cirrhosis are often the etiology of dilated cardiomyopathy in GBDs [28,29,27]. ECG signs of Twave inversion may be seen in some PBC patients [28].
It is important to note that cholestatic illnesses may generate indirect and complicated ventricular hypertrophy in animal tests. For instance, to assess the effect of biliary cirrhosis on ventricular hypertrophy, animal models are often constructed by doubly ligating and disconnecting the main bile duct. Bile duct ligation, which simulates biliary obstruction, causes cirrhosis and portal hypertension, which in turn causes left ventricular hypertrophy in rats. CHD, or coronary heart disease

Coronary artery stenosis or occlusion is the cause of coronary heart disease, a kind of ischemic heart disease. Cholelithiasis has the strongest correlation with CHD among the GBDs. Gallstones and CHD were positively correlated, according to study published as early as 1985. Additionally, the authors noted that gallstones are more likely to be associated with an elevated risk of later coronary artery disease [34]. A growing number of research have shown the correlation between the incidence rate of cholelithiasis and CHD in recent years. Compared to individuals who never reported cholelithiasis, the overall incidence of CHD in the cholelithiasis group is about double. Furthermore, persons with cholelithi- asis have a greater risk of stroke and myocardial infarction [35–37]. Furthermore, the detrimental impact of gallstones on the risk of CHD may not be lessened by cholecystectomy [37]. As a result, even gallstone patients who are asymptomatic should have their CHD regularly assessed. However,it ispuzzlingthattheeffectofcholelithiasisonCHDmorbidityandmor- tality differentially. Patients with acute coronary syndrome have a significantly lower death rate when they have cholelithiasis [38].
Other GBD forms, such as gallbladder polyps (GP), PFIC, and PBC, can have a variety of cardiovascular effects. Similar to gallstones, GP is linked to a higher risk of CHD; however, after cholecystectomy, the risk decreased [39]. Similarly, PFIC patients are regarded as a high-risk category for cardiovascular illnesses associated with atherosclerosis [40]. Conversely, reduced Lp (a) levels may contribute to the heart protective effect, and the incidence of CHD in PBC patients is lower than anticipated [41]. Myocardial Stroke

Acute myocardial infarction is often brought on by acute and chronic ischemia and hypoxia in the coronary arteries, whose clinical manifestations of excruciating and ongoing retrosternal pain below the sternum cannot be fully alleviated by restorative medications. In the interim, patients may

suffer concomitant heart failure, shock, or arrhythmia when they are followed by increasing ECG alterations and increased serummyocardial enzyme activity, which may be fatal. Cholelithiasis interacts with myocardial infarction, which is the subsequent stage of coronary heart disease. As early as 1947, Oscar realized that the patient who had anterior myocardial infarction immediately after cholecystectomy and appen- dectomywasentitledtothefirstreportedcase[42]. In addition, PBC is not linked to a higher risk of stroke, myocardial infarction, or transient ischemic attack [43]. In a similar vein, people who have had myocardial infarction also have a markedly elevated incidence of gallstones [44]. As contemporary genetic research continues to advance, scientists have discovered that CYP7A1 gene variants may

contribute to elevated risk because of their impact on elevated LDL levels [45]. This offers compelling proof of the connection between myocardial infarction and cholelithiasis.
It is important to remember that biliary pancreatitis brought on by gallstones may also elicit ST segment elevation in the ECG, which is comparable to that seen in myocardial infarction [46]. While ST-segment elevation is uncommon in acute pancreatitis, other ECG abnormalities such as arrhythmia, abnormal conduction, and T-wave and QT interval changes are more frequent. In addition, hyperemia may often show as "myocardial infarction" in certain situations. In these circumstances, the use of hypothetical causes severe bleeding issues [46, 47]. In order to decide on the best course of treatment for individuals with biliary pancreatitis who exhibit ECG abnormalities, cardiovascular examination is advised.
Takotsubo cardiomyopathy, a kind of stress cardiomyopathy, is another uncommon cardiac condition linked to biliary pancreatitis. While normal coronary angiography satisfies the expression of acute nonischemic cardiomyopathy, patients may suffer symptoms similar to the acute myocardial infarction that the ST segment was increased. Leubner et al. reported a patient who was released from the hospital after a laparoscopic cholecystectomy and who acquired tacosubocardiomyopathy immediately after the beginning of gallstone pancreatitis [48]. Failure of the heart

The symptoms of left-sided pulmonary circulation congestion were the first manifestation of heart failure, which is the last stage of heart disease. In fact, when therapy is not provided efficiently and promptly, sepsis and cardiopulmonary failure have become the leading causes of mortality for the majority of cholelithiasis patients [49]. According to data from population surveys, people with cholelithiasis are far more likely than those without gallstones to develop coronary heart disease and heart failure. Additional age-stratified analysis revealed that individuals with cholelithiasis between the ages of 18 and 40 had a greater risk of cardiovascular disease than do older patients. Therefore, it is more effective to attribute a decreased risk of cardiovascular disease to gallstone avoidance in younger individuals [50]. Often, M2-type antimitochondrial antibodies are linked to PBC, a chronic progressive cholestatic liver disease. Some individuals withPBCareaccompaniedbypolymyositis. Consequently, chronic myocarditis is linked to the majority of reported cases of heart failure in PBC. This myocardial damage progressively worsens over time, leading to heart failure. This implies that there may be an immune-level connection between PBC and cardiac disease. Others pregnancy-related intrahepatic cholestasis (ICP)
Pregnancy-specific liver disease known as intrahepatic cholestasis of pregnancy (ICP) is characterized by impaired liver function, high total bile acid levels, or maternal pruritus. In terms of severity, intra-hepatic cholestasis is rather benign for women, but it may have major consequences for the baby, such as cardiac dysplasia and irregular heartbeats. Additionally, because of the limited examination methods,

ECG and Doppler testing are the primary methods used to identify fetal heart disease.
The QT and PR intervals are the primary indicators of abnormalities in ICP patients during an ECG test. The condition of ventricular repolarization is often reflected by the QTinterval and QTdispersion parameter (QT-Disp). The QT-Disp value, which may be utilized to differentiate between moderate and severe ICP, is dramatically altered in ICP patients when compared to normal pregnant women [51]. The QTC interval and ST segment did not, however, change significantly between the two groups. Consequently, the QTC interval itself may not be impacted by arrhythmia events in the ICP [52]. Furthermore, alterations in the embryonic cardiac conduction system are indicated by a significant difference in the fetal PR interval between healthy pregnant women and ICP patients [53]. MostICPfetusesexperienceoverallleftventriculardysfunction[54,55]. Additionally, the degree of diastolic or systolic dysfunction and the severity of heart failure may be assessed quantitatively using N-terminal pro BNP (NT-pro BNP). In the meanwhile, poor perinatal outcomes in ICP are linked to both high LMPI and MOD-MPI. In summary, there is a positive correlation between maternal total bile acid and NT-pro BNP and fetal cardiac abnormality. ICP embryonic cardiac injury may be mostly caused by elevated bile acid levels [56]. The Alagilles Syndrome Asaspecialtypeofcholecardiasyndromeandautosomaldominant

disease,Alagillesyndrome(AGS)involvesmultiplesystemsandresults insparseintrahepaticbileductsandabnormalitiesintheheart,bones,

eyes, face, and kidneys. In the meanwhile, one of the major contributors to babies' chronic cholestatic liver illness is AGS. The ventricular septal defect [57–61], atrial septal defect [58,59,61,62,63], pulmonary stenosis [58–60,62,63–65], patent ductus arteriosus [59,60], and right ventricular hypertrophy [57,64] are among the cardiovascular development abnormalities currently recognized to be caused by AGS. Furthermore, in children with impaired liver function, substantial diversity is seen in the clinical features and genetic analysis of AGS. Since not all patients fit the traditional diagnostic criteria, genetic testing is thus required to diagnose AGS [58]. 3. Pathogenesisofcholestaticheartdisease

Clinically, the primary pathogenic mechanism of cholecardiasyndrome is widely thought to be the nerve reflex between the gallbladder and the heart. But it's important to think about how GBD might result in cardiac complications without the need for surgery or other harmful materials like gallstones. The pathophysiology of cholecardiasyndrome from the viewpoints of bile acid, genes, and nerves was thoroughly examined in this part in an effort to provide fresh ideas for the investigation of GBD problems. Bile acid An essential part of bile that is an endogenous amphiphilic steroid is bile acid. Current fundamental medical research has

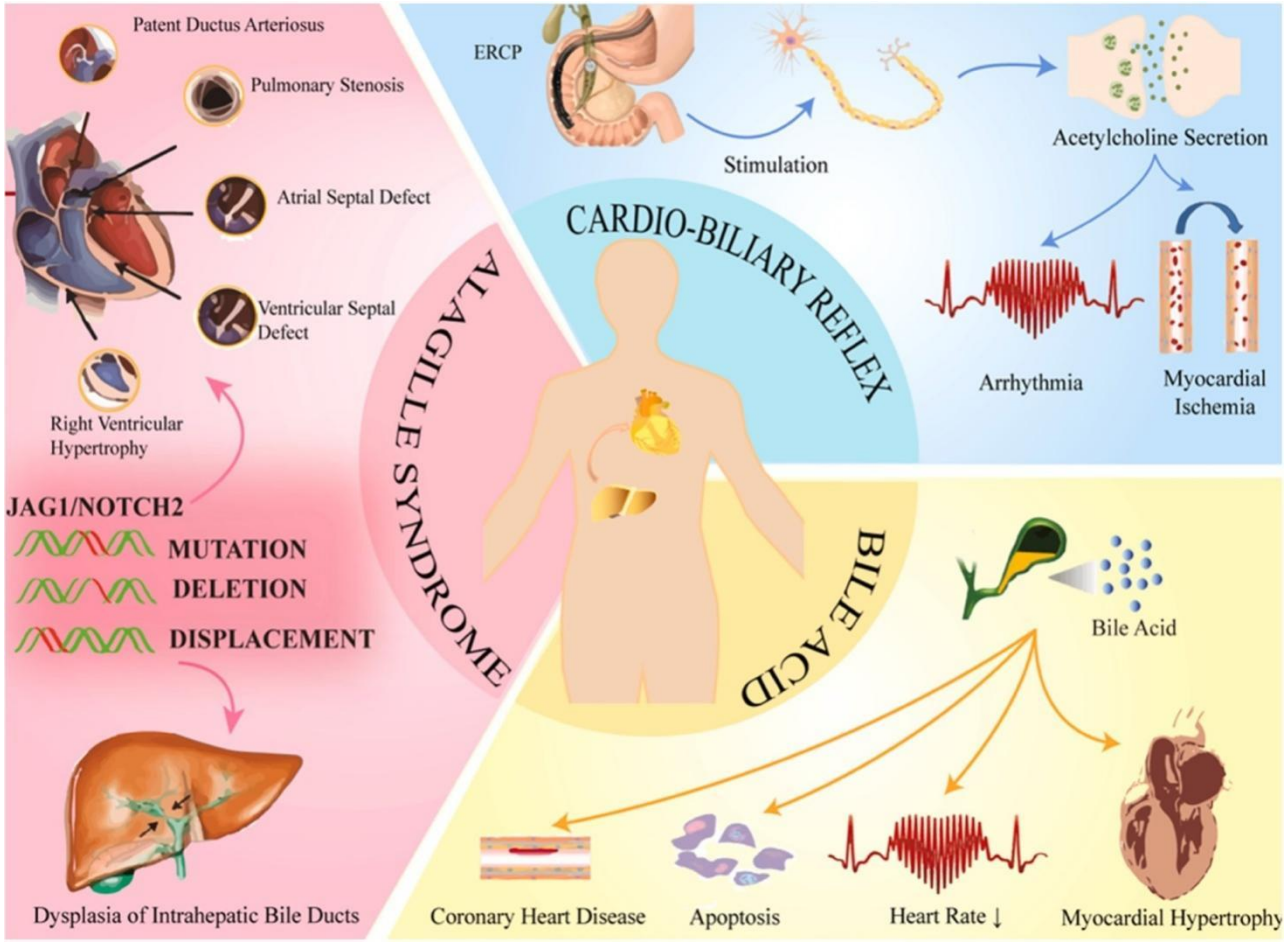

Fig.1.Theetiologyandpathogenesisofcholecardiasyndromedescribedfromperspectivesofbileacid(A),gene(B) andnerve(C).

A. By controlling cholesterol homeostasis, the combination of bile acid and FXR will impact coronary heart disease. B.

Congenital Alagille syndrome, which mostly manifests as intrahepatic bile duct dysplasia or deletion and heart development abnormalities, may be caused by gene mutation, displacement, and deletion. C. Gallbladder stimulation from surgical procedures like ERCP may travel via nerves to the heart, resulting in arrhythmia and/or myocardial ischemia symptoms. shown that a number of GBDs, including intrahepatic cholestasis, are brought on by aberrant bile acid. We discovered via a study of the literature that aberrant bile acid secretion may also have a direct or indirect impact on the pathophysiology of cholecardia syndrome, as shown in Fig. 2 and discussed separately. Overly high bile acids impede fatty acid oxidation, produce calcium overload, and increase the expression of Fas, caspase-8, and caspase-9 in myocardial cells, all of which lead to heart damage. In addition, the binding of excess bile acids to FXR may control the expression of apo-A1, CYP7A1, and I-BABP, ultimately disrupting cholesterol homeostasis and raising the risk of coronary heart disease. Bileacidon cardiomyocyte direct effect Bile acid is an amphiphilic steroid that may lower the surface tension between water and oil, encourage lipid emulsification, and have a significant impact on fat metabolism. On the other hand, too much bile acid may decrease fatty acid oxidation in cardiomyocytes and suppress the production of pGc1α, a crucial regulator of fatty acid metabolism, which might result in cardiac dysfunction [5]. Bile acids increase the concentration of calcium ions in cardiac myocytes [66] and decrease the activity of the sinoatrial node [66,67], respectively, to provide a positive inotropic and negative timetropic impact within a certain concentration range. Furthermore, atrial trabecular arrhythmias may be induced by taurocholic acid (TCA), a crucial component of bile acids, in a concentration-dependent manner [68]. This implies that the elevated bile acid may have a direct correlation with the cholecarida syndrome. Bile acid nuclear receptor regulation on cholesterol homeostasis A member of the nuclear receptor (NR) superfamily, farnesolX receptor (FXR) is mostly expressed in the liver and small intestine. It has been identified as a bile acid transcriptional sensor. In order to preserve cholesterol homeostasis, bile acid binding to FXR may, on the one hand, promote the expression of the cytosolic intestinal bile acid-binding protein (I-BABP) gene and suppress the expression of the CYP7A gene, the rate-limiting enzyme of bile acid production [69]. However, FXR may decrease the activity of the apolipoprotein A1 promoter (apoA-I, the primary constituent of high-density lipoprotein), hence downregulating apoA-I production and raising the risk of coronary heart disease [70]. Consequently, the function of bile acids in maintaining cholesterol homeostasis dictates their status in coronary heart disease syndrome. Bileacide elevation's effects on the fetal heart One of the high-risk pregnancies for the fetus's pregnancy outcome is intrahepatic cholestasis of pregnancy (ICP), as is well recognized. According to animal research, a large dosage of cholic acid will immediately arise in the fetal plasma after being dispersed in the maternal plasma, but the mother or fetus won't be negatively impacted by short-term, acute elevations in the concentration of plasmabile acid [71]. Thus, the impact of bile acid on the fetus is a chronic and long-term process that may be investigated from a number of angles. First, studies on mechanical PR intervals revealed that ICP patients had altered embryonic cardiac conduction systems [53]. Furthermore, similar to the general population, high bile acid may produce calcium overload of cardiac myocytes, which can result in fetal arrhythmia and the death of the ICP fetus [72–74]. Partial activation of the M2 receptor mediates the taurocholate-induced arrhythmia in newborn rat cardiomyocytes [75]. Furthermore, recent experimental findings have demonstrated that elevated levels of Fas, Caspase-8, and Caspase-9 expression in fetal myocardial cells are linked to elevated fetal cholesterol, indicating that apoptosis may be a major factor in fetal myocardial injury [76]. mutation, displacement, and deletion of genes The genetic component of Alagilles syndrome
Congenital cardiac disease and cholestasis are the primary characteristics of Alagille syndrome (AGS), an autosomal dominant condition [65]. AGS is caused by mutations in the conservative genes Jagged1 (JAG1) or NOTCH2 in the Notch intercellular signaling system [58,60].

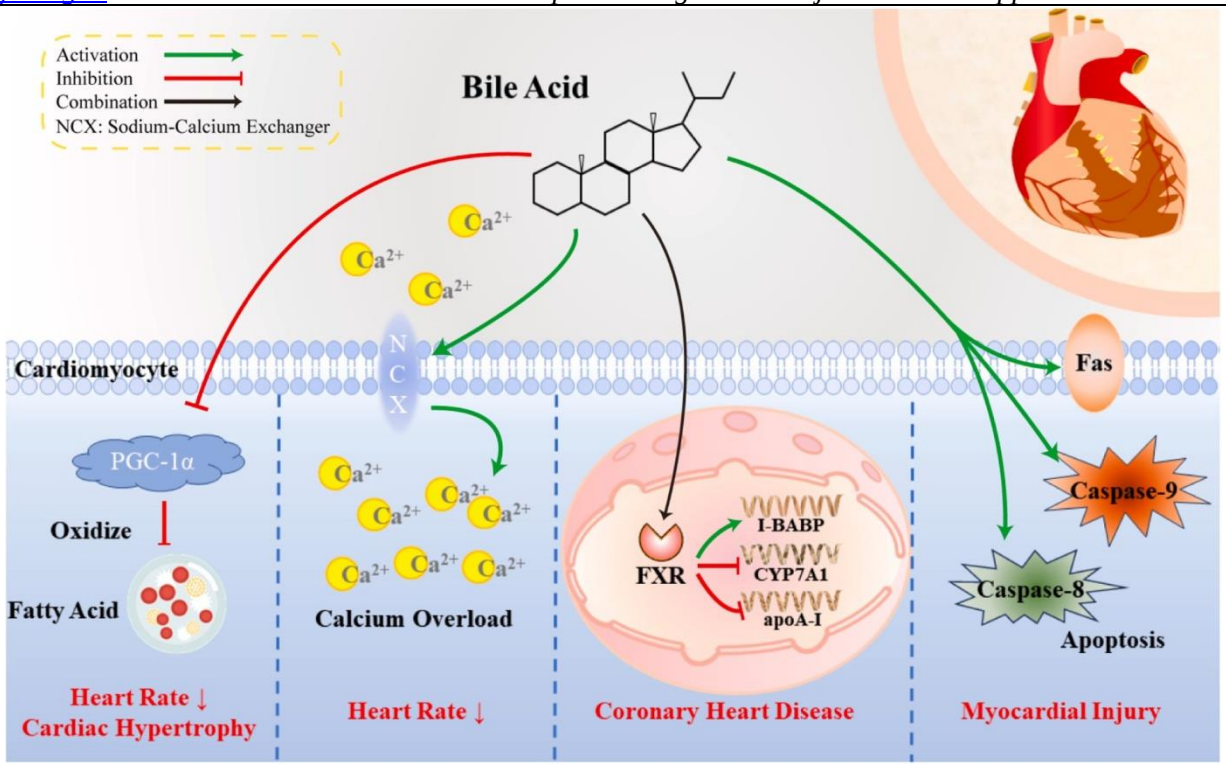

Fig.2. Molecularmechanismoftheeffectofbileacidsonmyocardial cells.

NOTE. FACS: Sorted by Fluorescence-Activated Cell. Total Bilirubin, or Tbil. Bil: Bilirubin. Direct Bilirubin (Dbil). Bilirubin Indirect (Ibil). Total Bile Acid (TBA). Alanine Aminotransferase (ALT). Aspartate Aminotransferase is known as AST. GGT: Transpeptidase of glutamyl. Alkaline phosphatase, or ALP. CHE:Cholinesterase. Intrahepatic cystestasis of pregnancy, or ICP. Ursodeoxycholic (UDCA). Total serum cholesterol, or TC. TG stands for triglycerides. CA stands for citric acid. Cardiac myocytes (CMS). Isovolumetric Relaxation Time, or IRT for short. Contraction time isovolumetric (ICT). LMPI: Modified Myocardial Performance Index of the Left Ventricular. Left Ventricular Ejection Time, or LVET. The Left Ventricular Modified Myocardial Performance Index is known as Mod-MPI. Torsional Shortening Ratio, abbreviated TSR. Primary Biliary Cholangitis, or PBC. Heart Rate Variability, or HRV. Pulmonary Artery Pressure, or PAP. Pulmonary Vascular Resistance, or PVR.

Specifically, the JAG1 gene encodes the JAGGED1 protein, a cell surface receptor of the NOTCH signal pathway that binds to NOTCH and starts the transcription of downstream signals, influencing cell proliferation and differentiation [77]. Furthermore, a variety of forms, including as mutation, duplication, and deletion of distinct gene segments, may contribute to the alterations in JAG1 and NOTCH2 [58,59]. These modifications will impact how the JAG1 protein binds to the NOTCH2 receptor. or. Loomes et al. investigated the expression pattern of JAG1 in the vascular and cardiac systems of human and mouse embryos as early as 1999. They discovered a correlation between atrial septal defect and JAG1 expression in the endocardium, myocardium, and epicardium of the atrium. Nevertheless, the expression is more restricted to the epicardium and endocardium than the ventricle's myocardium. The aforementioned findings clearly suggest that JAG1 plays a significant role in both the early and late stages of mammalian cardiovascular development [65]. In the meanwhile, cardiovascular abnormalities in embryos and adult mice may arise from endothelium specific deletion of Jag1. In the second trimester, the shift from endothelial cells

to mesenchymal cells during the formation of endocardial buffer might be destroyed by a Jag1 deletion, as opposed to a comparable Notch1 loss. Jag1 is a crucial extracellular matrix regulator that affects valve compliance, at least inside the valves [57]. ABCG5/8 and CYP7A1: how gallstones and myocardial infarction interact Gallstones (GSDs) and myocardial infarction (MI), two conditions that seem to be unrelated, are intrinsically connected by the metabolism of cholesterol. Acute myocardial infarction may result from the development of atherosclerotic plaques brought on by persistently high plasma cholesterol. Gallstones and the proliferation of cholesterol crystals will result from the supersaturation of the cholesterol generated by the liver cells as well as the bile acid's promotion of cholesterol nucleation and crystallization in the bile. In the traditional route, the first and rate-limiting step that catalyzes the conversion of cholesterol to bile acids is cholesterol 7 alpha-hydroxylase (CYP7A1). Low CYP7A1 activity may thereby raise cholesterol levels by decreasing their conversion to bile acids. Additionally, the downregulation of low-density lipoprotein (LDL) receptor expression in the artery will result in secondary hypercholesterolemia. According to Qayyum et al., CYP7A1 gene variants linked to lifelong elevated plasma LDL levels are linked to a higher risk of MI and GSDs in the general population. Bile acid sequestrants and other bile-acid pool modulators were thought to lower the risk via raising CYP7A1 activity [45]. In contrast to CYP7A1, theadenosinetriphosphatebindingboxtransporter G5/8 (ABCG5/8) was able to exhale sterols, including cholesterol, from intestinal cells and hepatocytes into the intestine and bile, respectively. This ultimately led to a simultaneous decrease and increase in cholesterol levels in plasma and biliary excretion. According to Stender et al., a variant in the ABCG5/8 gene is linked to reduced plasma LDL levels, which protects against myocardial infarction. However, compared to MI in the general population, the incidence of gallstone disease was higher for ABCG5/8 gene variant [78]. Nerve The heart-biliary reflex The term "biliary reflex" (sometimes known as "vagus reflex") describes the slowed heart rate and decreased blood pressure brought on by gallbladder involvement or biliary tract explosion during biliary tract surgery. Reflex coronary spasm may induce heart ischemia, arrhythmia, and even cardiac arrest in extreme situations. The T4–9 and T2–8 spinal nerves, which meet at the T4–5 spinal nerve segments, innervate the gallbladder and heart independently. Acetylcholine release and vagus nerve tension rise throughout the procedure due to the gallbladder's activation. The heart's coronary artery receives acetylcholine via the reflex arc, which causes an arrhythmia.
contraction and spasm that cause irregular heartbeats. Since cardiac myocytes will never contract as they once did, ischemia, a drop in heart rate, and even cardiac arrest may occur when the heart's ability to pump oxygen diminishes. The autonomic nervous system
The peripheral efferent nerves, which may be further classified as sympathetic and parasympathetic nerves, include the autonomic nerve, which primarily controls smooth muscle activity in the viscera and arteries. Cardiovascular autonomic dysfunction affects 63% of PBC patients, with para-sympathetic nervous system dysfunction accounting for the majority of these cases [79]. Additionally, PBC patients often have systemic neuropathy with sensory or autonomic nerve dysfunction, whose etiology may be linked to blood bilirubin and albumin levels. Pruritus is also associated with autonomic neuropathy, one of the primary clinical manifestations of PBC [18,79]. Jones et al. noted the overall pattern of alterations in cardiac function in PBC patients. Increased cardiac regurgitation may be a compensatory strategy used by patients with varying degrees of autonomic nerve dysfunction to lessen the effects of myocardial function abnormalities [80]. 3. Therapy As of right now, no particular medications or treatment plans for cholecardia syndrome have been

reported. Only a small number of clinical instances and experimental investigations have produced some medications and techniques to halt, avoid, or lessen symptoms. Therefore, in order to serve as a reference for next relevant research, we evaluated a few medications and measurements and spoke about particular dosages, administration schedules, and their limits. One typical therapeutic medication that may be given orally to replace the harmful and natural hydrophobic bile acid is ursodeoxycholicacid (UDCA). According to the mechanism of action, UDCA may raise bile acid production, alter the composition of bile, lower plasma and bile cholesterol levels, and aid in the slow dissolution of cholesterol-containing gallstones. For PBC and ICP patients, UDCA medication will diminish the fetal cardiac abnormalities brought on by high blood bile acid concentration and lower the diastolic volume, respectively [82]. Additionally, an increase in NT-proBNP concentration, PR interval duration, and HRV is indicative of abnormalities in ICP patients [90]. However, research on cells and animals has also produced some unexpected findings. By inhibiting the expression of Fas, Caspase-8, and Caspase-9 in cardiac myocytes, UDCA can effectively improve fetal liver function and serum total bile acid concentration. It can also reverse the impairment of fetal cardiac myocytes [76]. Through its effect on the development of myofi-broblasts in the embryonic heart, UDCA may indirectly prevent ICP-induced arrhythmias in vitro [83]. Inhibitor of Nitric Oxide Synthesis Neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and inducible nitric oxide synthase (iNOS) are the three subtypes of nitric oxide synthase, an enzyme that is part of the nervous system. Normal circumstances result in the expression of nNOS and eNOS, while damage induces iNOS. While nitric oxide formed from eNOS has a neuroprotective impact, that derived from iNOS and NOS has a neurotoxic effect. In biliary cirrhotic hearts, suppression of nitric oxide synthase was shown to enhance myocardial contractility and coronary artery pressure as early as 1996 [84]. Additionally, a study on the sensitivity of cholestatic liver illness to ischemia/reperfusion arrhythmias revealed that the non-selective nitric oxide syn-thaseinhibitor L-NAME (N (U)-nitro-L-arginine methyl ester) may correct the lengthening of QTincholestasisrats.

Table3
Treatmentthatcanimprovecholecardiasyndromeinbothexperimentalandclinicalsettings.

Treatment	Subject	Gallbladderandbiliarydiseases	Model	CardiovascularDisease	Administration	DrugDose	Duration	Reference
UDCA	Human	ICP		Fetalcardiac Dysfunction		500–2,500mg/d		[81]
	Human	PBC PNC		Hemodynamic Changes		3mg/kg/d	1month	[82]
	Rats	ICP	EE2 Injection	FetalMyocardial Apoptosis	Intragastric Administration	50 mg/kg	5d	[76]
	Cell	ICP		FetalArrhythmia		0.1~100 μmol/L		[83]
LNMMA	Rats	PBC	BDL	DecreasedCoronary Pressure	ExtracorporealCardiac Perfusion	6 ml/h	30min	[84]
L-NAME	Rats	BiliaryCirrhosis	BDL	Bradycardia	DailySubcutaneous	3mg/kg	6d	[15]
L-NAME	Rats	BiliaryCirrhosis	BDL	Cirrhotic Cardiomyopathy	SubcutaneousTwicea Day	0.5 mg/kg	7d	[20]
Thrombolytic	Human	Gallstone		AcuteInferior		1 500000 U	1h	[46]

Therapy (Streptokinase)				WallMyocardial Infarction				
SteroidTherapy (Prednisolone)	Human	PBC		HeartFailure dueto Myocarditis		45 mg/d	3m	[85]
Teprenone	Rats		BDL	Cirrhotic Cardiomyopathy Chronotropic Incompetence	Gavage	100 mg/kg	21d	[86]
1-Methy Tryptophan	Rats	Cholestasis Impaired	BDL	Bradycardia Chronotropic	Injected IntraperitoneallyOnce a Day (ip)	1,3, 9mg/kg	21d	[87]
Terbutaline	Rats	Secondary Biliary Cirrhosis	BDL	ReflexTachycardia	Infusionthrough a VenousCatheter	2, 4, 8,16,32, 64 µg/min/kg	Each Dilutionof Terbutalineis Perfusedfor10min	[88]
ChronicLosartan Treatment	Rats	BiliaryCirrhosis	BDL	Cirrhotic Cardiomyopathy	Oral	6mg/kg/d	25d	[89]

NOTE. UDCA: Ursodeoxycholic Acid. PNC: Postnecrotic Liver Cirrhosis. ICP: Intrahepatic Cholestasis of Pregnancy. EE2: 17α-ethynyl Estradiol. PNC: Postnecrotic LiverCirrhosis. Primary Biliary Cholangitis, or PBC. BDL: Bile Duct Ligation. while having no effect on blood pressure, heart rate, or arrhythmia. Nonetheless, bradycardia, hypotension, QT prolongation, and arrhythmia resistance in cholestasis patients may be corrected by the combination use of L-NAME and altrexone [15]. Furthermore, rats with bile duct ligation may have increased NO production, which might impair cardiac pacemaker cells' sensitivity to adrenergic stimulation and ultimately result in bradycardia. The aberrant cardiac chro-notropic incompetence is linked to the rise in protein-bound nitrotyrosine in the heart tissue of rats with biliary cirrhosis. In rats with biliary cirrhosis, administration of L-NAME or N-acetylcysteine restored the heart rate and cardiac response to adrenergic stimulation while lowering the amount of nitrotyrosine in the tissue [20]. Others Thrombolytic treatment One popular therapeutic procedure that may rapidly dissolve new thrombus, recanalize blood arteries, and restore the function of injured organs as soon as possible is thrombolytic treatment. It should be utilized in the early stages of acute arterial thrombotic disorders and is often appropriate for emergency therapy. On the other hand, ST segment elevation on the ECG may infrequently accompany severe pancreatitis and be mistaken for an abrupt myocardial infarction. Furthermore, because of the potential hazards, thrombolytic therapy is not advised in cases with acute pancreatitis without a confirmed diagnosis [46, 47]. The use of steroids Steroids are a broad class of cyclopentanoperhydro-phenanthrene derivatives that are extensively found in the biological world. Because of their structural similarities to hormones, synthetic derivatives of steroids have been developed into anti-inflammatory drugs, steroid medications that stimulate protein synthesis, and oral contraceptives. Prednisolone is a representative synthetic steroid medication that has been used primarily to treat inflammatory conditions related to allergies and autoimmune diseases, collagen diseases, etc. An older lady with primary biliary cirrhosis who had a high titer of M2 anti-mitochondrial antibody and chronic heart failure was described by Matsumoto et al. They declared that heart failure is caused by mitochondrial damage linked to autoimmunity. and the patients responded well to high-dose corticosteroids. This is the first example of heart failure caused by primary biliary cirrhotic myocarditis that was effectively treated with steroids [85]. Teprenone Teprenone is a terpenoid compound that has the ability to repair tissue. In addition to treating acute and chronic gastritis, it is a frequently used protective medication for the stomach mucosa. Under typical conditions, cells typically express heat shock protein 70 (HSP70) at a low level. Under extreme heat and other detrimental stressors, it has cytoprotective and anti-apoptotic effects on the heart and liver. According to reports, teprenone may prevent cell damage by altering HPS70 gene expression. The preventive benefits of teproli-done on cirrhotic cardiomyopathy via the regulation of

myocardial cell dysfunction, congestion, and pyknosis are also shown in an animal experiment. Atthedoseof100mg/kg,theQT abnormalities and level of stress biomarkers (TNF- α, IL-6, ALT, AST and MCP-1)inCCMwerereduced,whilechronotropiccardiacdysfunction and BNP alterations could not be treated eventually [86].
1. Methytryptophan 1-Methyltryptophan (1-MT), an indoleamine 2, 3-dioxygenasein- hibitor, could reduce the cardiac dysfunction in rats withbiliary cirrhosis and improve the levels of serum CRP and IL-6 in a dose- dependent manner. Long-term use of 1-MT may also enhance the histological abnormalities in the liver, including lowering bile duct hyperplasia, fibrosis, and inflammation [87]. Terbutaline A β2-receptoragonist with bronchiectasis effects is terbutaline. Itisusuallyusedtotreatconditionslikeemphysema,bronchialasthma, and asthmatic bronchitis. Also, terbutaline is highly selective for bron- chial smoothmuscle,while haslow excitatory impact and no centralef- fectontheheart. The impact of milder butaline on hemodynamics in rats with biliary cirrhosis was investigated by POEtal in 1991. The findings demonstrated that in rats with secondary biliary cirrhosis, terbutaline may increase blood flow in portal tributaries and lower portal pressure [88]. Treatment of chronic losartan
As the primary active ingredient in the renin-angiotensin-aldosterone pathway, angiotensin II has evolved into a potent vasoconstrictor. Losartan is the first particular non-peptide angiotensin II receptor antagonist to be sold commercially. It has a low incidence of side effects in addition to efficiently blocking angiotensin II receptors and lowering blood pressure. Chronic losartan medication may decrease atrial TGF-βexpression and increase heart adrenergic reactivity, according to research by Jazerietal. Furthermore, there was no discernible impact on atrial fibrosis, which may have been caused by the brief course of therapy; nonetheless, long-term losartan treatment may reduce atrial fibrosis [89]. A multilateral investigation is required to investigate the therapy choices for cirrhotic cardiomyopathy since medications like teprenone, losartan, and do not alter all of the symptoms of the condition.

3. Conclusion and viewpoint The pathophysiology, clinical manifestations, and therapeutic approaches of cholecardia syndrome were succinctly outlined in this review. Cholecardia syndrome is still diagnosed and treated based on professional experience at this time, with no specific diagnostic standards or treatment strategy in place. As modern medicine advances, the death rate from cancer is declining annually, but the non-cancer cause of death for cancer patients is rising. This is also re- flected in biliary disorders. Gallbladder cancer patients have a much greater risk of cardiovascular mortality than the overall population [91]. To accurately and meaningfully forecast, diagnose, and treat cholecardia syndrome, we must therefore continue to devote more effort to the investigation of pathophysiology and medicines.
Bile acid metabolism, cholesterol metabolism, NO production, and nerve reflex are the primary pathophysiological factors of cholecardia syndrome. Among them, bile acid cycle metabolism is the primary focus of cellular and molecular pathway research. By binding to FXR receptors, bile acid controls the metabolism of cholesterol, which impacts cardiovascular health. Additionally, it alters cardiomyocyte electrical signal transmission and raises intracellular calcium concentration. Cholelithiasis, one of the most prevalent gallbladder conditions, may have a similar route with coronary atherosclerosis. Through the metabolism of low-density LDL, the two might be connected. There is no direct link between raised plasma LDL cholesterol levels and a higher chance of developing symptoms of cholelithiasis, according to a meta-analysis research [92]. Moreover, cholecystectomy cannot counteract the elevated cardiovascular risk in cholelithiasis patients [93]. The general cholecardia syndrome does not apply in this case. Furthermore, one of the most significant pathologies that merits consideration is the NO cycle. NO may operate on smooth muscle cells via the cell membrane, relaxing them and dilating blood vessels, hence reducing blood pressure. Additionally, it may penetrate the bloodstream via the cell membrane, lower platelet activity, stop it from adhering to the vascular endothelium and clumping together, and stop fatherosclerosis from happening. Therefore,theroleofNO in cholecardia syndrome is deserving of further investigation.
Currently, the primary methods used outside of clinical care are surgery or conservative treatment to lessen or eradicate biliary disorders. or provide symptomatic assistance to the clinical

expression of the heart. While there are medications and treatments that may help with cholecardia syndrome, this is

not a fundamental solution. Therefore, the creation of particular medications to treat cholecardia syndrome is a pressing issue that has to be resolved. Artemisinin and silymarin are two examples of the tiny molecular compounds and their structural modifiers from traditional Chinese medicines that have been introduced recently and shown promising healing benefits. Therefore, in order to produce a successful therapy for the clinical treatment of cholecardia syndrome in the future, we aim to identify appropriate natural components from Chinese traditional herbal medicine. Based on the facts now available, its prospects for the future may be reflected in the following three areas.

(a) First of all, it is important to remember that no direct gene has yet been approved for the diagnosis and management of cholecardia syndrome. Although not influenced by GBDs, the geness discussed in this article also has some effect on heart disease. For instance, two types of genes (ABCG5/8 and CYP7A1) that dysregulate cholesterol homeostasis may be able to modify the risk of myocardial infarction and gallstones, according to some research based on population cohort analysis. However, these genes are not specific for cholecardia syndrome. In order to advance the next stage of clinical diagnosis and medication development, it is necessary to filter out the particular regulatory genes based on a large number of clinical samples.
(b) Secondly, autoimmunity is a possible etiology in cholecardia syndrome that merits consideration. Some inflammatory and autoimmune abnormalities have been documented to be associated with early atherosclerosis [94]. Furthermore, a large number of PBC clinical cases provide us useful data. PBC is a chronic progressive cholestatic liver disease that is weakly linked to antibodies against M2 in the mitochondria. Skeletal muscle is affected by mitochondrial damage during autoimmunity, which may result in cardiac muscle issues [85,95]. For instance, a female PBC patient with chronic heart failure and a high level of M2 anti-mitochondrial antibody was reported by Matsumoto et al. [85]. Additionally, it implies that autoimmunity may be one of the routes ogenesis of cholecardia, although the particular mechanism of involvement requires a further investigation.
(c) From the standpoint of Traditional Chinese Medicine (TCM), the "strange" phenomena of heart damage brought on by GBDs is not accidental. The heart and gallbladder were regarded as "cousins" in traditional Chinese medicine. First, the two are linked in the meridians according to TCM theory. Meridians connect the heart and gallbladder, and the heart's blood and qi can be transferred to the gallbladder to support it. In the meantime, the heart can also carry the qi from the gallbladder upward. Second, according to TCM, the gallbladder is the phasefire and the heart is the king fire, both of which are organs that symbolize "fire." The phasefires assist the kingfire so that it may carry out its regular duties. Additionally, under the direction of the mind and spirit, the gallbladder can withstand and eliminate the impact of negative emotional impulses, allowing the body's visceral processes, qi, blood, essence, and fluids to continue operating normally. The heart's role of controlling the divine cannot be carried out correctly if the gallbladder is indecisive and the heart and gallbladder are out of order, which leads to aberrant fluctuations in emotions and moods. According to ancient Chinese medical texts (Sanyin Ji Yi Bingzheng Fang Lun), the Wendan decoction for hyperlipidemia (angina pectoris with hyperlipidemia in coronary heart disease) has good clinical efficacy when used as a Chinese medicine treatment. This further demonstrates that treating cardiovascular disorders from GBD's perspective is a realistic therapy option.

In conclusion, myocardial damage is one of the frequent and dangerous side effects of GBDs, exhibiting a variety of clinical symptoms. Given the variety of its pathophysiology, further prospective and retrospective research is required in order to provide more useful data for the clinical diagnosis and management of cholecardia syndrome.

References

[1] J.Li,X.Jin,J.Ren,R.Li,L.Du,Y.Gao,J.Zhang,X.Liu,X.Wang,G.Wang,Globalburden of gallbladder and biliary diseases: a systematic analysis for the GlobalBurdenofDiseaseStudy2019,J.Gastroenterol.Hepatol.37(7)(2022)1389–1399,https://doi.org/10.1111/jgh.15859.
[2] R. Tennant,H.M.Zimmerman, Associationbetween disease in thegall-

bladderandintheheart,asevidencedatautopsy,YaleJ.Biol.Med.3(6)(1931)495–503.

[3] A.G.Hampton,J.R.Beckwith,J.E.WoodJr.,Therelationshipbetweenheartdiseaseandgall-bladderdisease,Ann.Intern.Med.50(5)(1959)1135–1148,https://doi.org/10.7326/0003-4819-50-5-1135.

[4] J.K. Trinkle, Electrocardiographic changes with icterus and a common bile ductstone, Am. J. Surg. 103 (1962) 469–471, https://doi.org/10.1016/0002-9610(62)90154-x.

[5] M.S.Desai,B.Mathur,Z. Eblimit,H. Vasquez,H. Taegtmeyer,S.J.Karpen,D. J.Penny,D.D.Moore,S.Anakk,Bileacidexcessinducescardiomyopathyandmetabolic dysfunctions in the heart, Hepatology 65 (1) (2017) 189–201, https://doi.org/10.1002/hep.28890.

[6] G.Targher, C.D.Byrne,Gallstonediseaseandincreasedriskof ischemicheartdisease: causal association or epiphenomenon? Arterioscler., Thromb., Vasc. Biol.35 (10) (2015) 2073–2075, https://doi.org/10.1161/atvbaha.115.306339.

[7] J.Lv,L.Qi,C.Yu,Y.Guo,Z.Bian,Y.Chen,L.Yang,J.Shen,S.Wang,M.Li,Y.Liu, L. Zhang, J. Chen, Z. Chen, L. Li, Gallstone disease and the risk of ischemic heartdisease, Arterioscler., Thromb., Vasc. Biol. 35 (10) (2015) 2232–2237, https://doi.org/10.1161/atvbaha.115.306043.

[8] M.Christensen,H.W.Hendel,V.Rasmussen,L.Højgaard,S.Schulze,J.Rosenberg,Endoscopicretrogradecholangiopancreatographycausesreducedmyocardialbloodflow,Endoscopy34(10)(2002)797–800,https://doi.org/10.1055/s-2002-34270.

[9] S.D. Johnston, A. McKenna, T.C. Tham, Silent myocardial ischaemia duringendoscopic retrograde cholangiopancreatography, Endoscopy 35 (12) (2003) 1039–1042,https://doi.org/10.1055/s-2003-44597.

[10] J. García-Cano, Severe cardiogenic pulmonary edema precipitated by a therapeuticERCP,authorreply568,Endoscopy36(6)(2004)567,https://doi.org/10.1055/s-2004-814429.

[11] Z.Khan,Acasereportofendoscopicretrogradecholangiopancreatography(ERCP)and acute pancreatitis induced takotsubo cardiomyopathy (TCM) in a patient withgallstonesinduced acutepancreatitis and cholangitis, Cureus 14 (5) (2022),e24708,https://doi.org/10.7759/cureus.24708.

[12] A.Singh,Familialhyperlipoproteinemiaandgallstones,Can.Med.Assoc.J.113 (8)(1975)733–735.

[13] V.M. Daliparty, B. Amoozgar, A. Razzeto, S.U.M. Ehsanullah, F. Rehman,Cholecystitis masquerading as cardiac chest pain: a case report, Am. J. Case Rep.22(2021),e932078,https://doi.org/10.12659/ajcr.932078.

[14] M.V.O'Reilly,M.J.Krauthamer,"Cope'ssign"andreflexbradycardiaintwopatients with cholecystitis, Br. Med. J. 2 (5754) (1971) 146, https://doi.org/10.1136/bmj.2.5754.146.

[15] A.R.Hajrasouliha,S.Tavakoli,P.Jabehdar-Maralani,F.Ebrahimi,H.Shafaroodi, S.H.Mirkhani,S.Amanpour,A.R.Dehpour,Cholestaticliverdiseasemodulatessusceptibility toischemia/reperfusion-induced arrhythmia,butnotnecrosisandhemodynamicinstability:theroleofendogenousopioidpeptides,J.Hepatol.43 (3)(2005)491–498,https://doi.org/10.1016/j.jhep.2005.02.043.

[16] S.Grautoff,M.Balog,G.Winde,Pseudo-Wellens'syndromeandintermittentleftbundle branchblockinacutecholecystitis,Am.J.Emerg.Med. 36(7)(2018)1323.e1–1323.e6, https://doi.org/10.1016/j.ajem.2018.03.081.

[17] S.Fang,L.Gao,F.Yang,Y.J.Gong,Delayedreversibilityofcompleteatrioventricular block: cardio-biliary reflex after alcohol septal ablation in a patient with hypertrophic obstructive cardiomyopathy, BMC Cardiovasc. Disord. 21 (1)(2021), 372,

[18] K.Keresztes,I.Istenes,A.Folhoffer,P.L.Lakatos,A.Horvath,T.Csak,P.Varga, P.Kempler,F.Szalay,Autonomicandsensorynervedysfunctioninprimarybiliarycirrhosis, World J. Gastroenterol. 10 (20) (2004) 3039–3043,

[19] J.L. Newton, J. Allen, S. Kerr, D.E. Jones, Reduced heart rate variability andbaroreflexsensitivityinprimarybiliarycirrhosis,LiverInt.:Off.J.Int.Assoc.StudyLiver26(2)(2006)197–202,

[20] A.R.Mani,S.Ippolito,R.Ollosson,K.P.Moore,Nitrationofcardiacproteinsis associated with abnormal cardiac chronotropic responses in rats with biliarycirrhosis,Hepatology43(4)(2006)847–856,

[21] P.Jiang,Z.Feng,L.Sheng,C.Hu,X.Ma,S.Zhang,L.Wu,X.Xiao,Q.Wang, C. Guo,D.Qiu,J. Fang,J. Xu,M.E. Gershwin,M. Jiang,X.Ma,J. Pu,Morphological, functional, and tissue characterization of silent myocardialinvolvement in patients with primary biliary cholangitis, Clin. Gastroenterol.Hepatol.:Off.Clin.Pract.J.Am.Gastroenterol.Assoc.20(5)(2022)1112–1121.e4,

[22] M.S.Desai,Z.Eblimit,S.Thevananther,A.Kosters,D.D.Moore,D.J.Penny,S. J.Karpen,Cardiomyopathyreverseswithrecoveryofliverinjury,cholestasisandcholanemiainmousemodelof biliaryfibrosis,LiverInt.:Off.J.Int.Assoc.StudyLiver 35 (4) (2015) 1464–1477,

[23] S.Y.Kim,K.H.Kim,J.M.Schilling,J.Leem,M.Dhanani,B.P.Head,D.M.Roth,A. E. Zemljic-Harpf, H.H. Patel, Protective role of cardiac-specific overexpression ofcaveolin-3incirrhoticcardiomyopathy,Am.J.Physiol.Gastrointest.LiverPhysiol.318(3)(2020)G531–G541,

[24] Z.Ma,J.B.Meddings,S.S.Lee,Membranephysicalpropertiesdeterminecardiac beta-adrenergicreceptorfunctionincirrhoticrats,Am.J.Physiol.267(1Pt1)(1994) G87–G93,

[25] Z.Haddadian,G.Eftekhari,R.Mazloom,F.Jazaeri,A.R.Dehpour,A.R.Mani,Effect of endotoxin on heart rate dynamics in rats with cirrhosis,Auton. Neurosci.:Basic Clin. 177 (2) (2013) 104–113,

[26] M. Rodríguez-Martínez, L.L. Sawin, G.F. DiBona, Arterial and cardiopulmonarybaroreflex control of renal nerve activity in cirrhosis, Am. J. Physiol. 268 (1 Pt 2)(1995)R117–R129,

[27] S.James,D.Waterhouse, K. McDonald,R.O'Hanlon, Dilatedcardiomyopathy and progressivefamilialintrahepaticcholestasis,BMJcaseRep.2014(2014),

[28] F.Alfonso,A.L.Caforio,J.DelToro,E.Torrecilla,M.Rey,P.DeRabago,Rightventriculardilatedcardiomyopathyassociatedwithprimarybiliarycirrhosis,Eur.Heart J. 12 (11) (1991) 1240–1243,

[29] J.Inserte, A. Perello´, L. Agullo´, M.Ruiz-Meana,K.D.Schlüter,N. Escalona, M. Graupera, J. Bosch, D. Garcia-Dorado, Left ventricular hypertrophy in rats withbiliarycirrhosis,Hepatol.(Baltim.,Md.)38(3)(2003)589–598,C. de Zwaan, F.W. B¨ar, H.J. Wellens, Characteristic electrocardiographic patternindicating a critical stenosis high in left anterior descending coronary artery inpatients admitted because of impending myocardial infarction, Am. Heart J. 103 (4Pt 2) (1982) 730–736,

[30] M.T.La Rovere, J.T. Bigger Jr., F.I. Marcus, A. Mortara, P.J. Schwartz, Baroreflexsensitivity and heart-rate variability in predictionof totalcardiac mortality aftermyocardial infarction. ATRAMI (Autonomic Tone and Reflexes After MyocardialInfarction) Investigators, Lancet (Lond., Engl.) 351 (9101) (1998) 478–484,

[31] M.Nakamura,J.Sadoshima,Mechanismsofphysiologicalandpathologicalcardiachypertrophy, Nat. Rev. Cardiol. 15 (7) (2018) 387–407,

[32] E.A.Bortnichak,D.H.FreemanJr.,A.M.Ostfeld,W.P.Castelli,W.B. Kannel, M. Feinleib, P.M. McNamara, The association between cholesterol

[33] , KubaRamos,M.Uribe,Strongassociationbetween gallstones and cardiovascular disease, Am. J. Gastroenterol. 100 (4)(2005)827–830,N.M´endez-S´anchez,D.Zamora-Vald´es,J.A.Flores-Rangel,J.A.P´erez-Sosa, F. V´asquez-Ferna´ndez, J.I. Lezama-Mora, G. Va´zquez-Elizondo, G. Ponciano-Rodríguez, M.H. Ramos, M. Uribe, Gallstones are associated with carotidatherosclerosis, Liver Int.: Off. J. Int. Assoc. Study Liver 28 (3) (2008) 402–406,Y.Zheng,M.Xu,Y.Li,A.Hruby,E.B.Rimm,F.B.Hu,J.Wirth,C.M.Albert,K. M. Rexrode, J.E. Manson, L. Qi, Gallstones and risk of coronary heart disease:prospective analysis of 270 000 men and women from 3 US cohorts and meta-analysis, Arterioscler., Thromb., Vasc. Biol. 36 (9) (2016) 1997–2003,

[34] W.Su,J.G.Zhu,W.P.Li,H.Chen,H.W.Li,Gallstonediseaseandtheriskofcardiacmortality in patients with acute coronary syndrome, Front. Cardiovasc. Med. 9(2022), 1033959,

[35] C.H.Chen,C.L.Lin,C.H.Kao,Theriskofcoronaryheartdiseaseafterdiagnosisofgallbladder polyp: a retrospective nationwide population-based cohort study, Ann.Transl.Med.7(23)(2019)753, H.Nagasaka,T.Yorifuji,K.Kosugiyama,H.Egawa,M.Kawai,K. Murayama, M.Hasegawa,R.Sumazaki,J. Tsubaki,H.Kikuta,A.Matsui,K.Tanaka, N. Matsuura, K. Kobayashi, Resistance to parathyroid hormone in two patientswith familial intrahepatic cholestasis: possible involvement of the ATP8B1 gene incalcium regulation via parathyroid hormone, J. Pediatr. Gastroenterol. Nutr. 39 (4)(2004) 404–409, https://doi.org/10.1097/00005176-200410000-00018.

[36] W.L.Gregory,W.Mehal,A.N.Dunn,G.Cavanagh,R.Chapman,K.A.Fleming,A.

K. Daly, J.R. Idle, O.F. James, M.F. Bassendine, Primary biliary cirrhosis:contribution of HLA class II allele DR8, Q. J. Med. 86 (6) (1993) 393–399.

[37] O.Roth,Coronaryocclusionwithmyocardialinfarctionfollowingcholecystectomyfor reliefof anginalpain inapatient withcholelithiasis, Am.Heart J.36 (6)(1948)939–942, https://doi.org/10.1016/0002-8703(48)90288-9.

[38] M. Solaymani-Dodaran, G.P. Aithal, T. Card, J. West, Risk of cardiovascular andcerebrovascular events in primary biliary cirrhosis: a population-based cohortstudy, Am. J. Gastroenterol. 103 (11) (2008) 2784–2788, https://doi.org/10.1111/j.1572-0241.2008.02092.x.

[39] F. Bergman, W. van der Linden, H. Mo¨ell, The connexion between calciumcontaining gallstones, cholecystitis and stasis, Acta hepato-Splenol. 15 (5) (1968)326–330.

[40] F.Qayyum,B.K.Lauridsen,R.Frikke-Schmidt,K.F.Kofoed,B.G.Nordestgaard, A. Tybjærg-Hansen, Genetic variants in CYP7A1 and risk of myocardial infarctionand symptomatic gallstone disease, Eur. Heart J. 39 (22) (2018) 2106–2116,https://doi.org/10.1093/eurheartj/ehy068.

[41] C. Cafri, A. Basok, A. Katz, A. Abuful, H. Gilutz, A. Battler, Thrombolytic therapy inacutepancreatitispresentingasacutemyocardialinfarction,Int.J.Cardiol.49(3)(1995) 279–281, https://doi.org/10.1016/0167-5273(95)02312-k.

[42] T.S.Burge,E.R.Chilvers,Acutepancreatitismimickingmyocardialinfarction: potentialforinadvertentuseofthrombolytictherapy,J.R.ArmyMed.Corps139 (3)(1993)130–131,https://doi.org/10.1136/jramc-139-03-14.

[43] J.K. Leubner, Z. Ortiz, J. Wolfrey,L. Drake, Can gallstones break the heart?Pancreatitis-induced Takotsubo cardiomyopathy mimicking acute myocardialinfarction,J.Am.Geriatr.Soc.62(9)(2014)1814–1815,https://doi.org/10.1111/jgs.12999.

[44] G. Cucchiaro,C.R.Watters,J.C.Rossitch,W.C.Meyers,Deathsfromgallstones.Incidence and associated clinical factors, Ann. Surg. 209 (2) (1989) 149–151,https://doi.org/10.1097/00000658-198902000-00002.

[45] M.T. Olaiya, H.Y. Chiou, J.S. Jeng, L.M. Lien, F.I. Hsieh, Significantly increased riskof cardiovascular disease among patients with gallstone disease: a population-basedcohortstudy,PloSOne8(10)(2013),e76448,https://doi.org/10.1371/journal.pone.0076448.

[46] O.Kirbas,E.H.Biberoglu,A.Kirbas,K.Daglar,O.Kurmus,N. Danisman, K.Biberoglu,Evaluationofventricularrepolarizationinpregnantwomenwithintrahepatic cholestasis, Int. J. Cardiol. 189 (2015) 25–29, https://doi.org/10.1016/j.ijcard.2015.04.001.

[47] T.Joutsiniemi,U.Ekblad,K.G.Ros´en,S.Timonen,WaveformanalysisofthefetalECG in labor in patients with intrahepatic cholestasis of pregnancy, J. Obstet.Gynaecol.Res.45(2)(2019)306–312,https://doi.org/10.1111/jog.13812.

[48] S.L.Strehlow,B.Pathak,T.M.Goodwin,B.M.Perez,M.Ebrahimi,R.H.Lee,Themechanical PR interval in fetuses of women with intrahepatic cholestasis ofpregnancy,Am.J.Obstet.Gynecol.203(5)(2010)455.e1-5,https://doi.org/10.1016/j.ajog.2010.05.035.

[49] A.Ozel,E.AliciDavutoglu,M.EricOzdemir,F.Oztunc,R.Madazli,Assessmentoffetal left ventricular modified myocardial performance index and its prognosticsignificance for adverse perinatal outcome in intrahepatic cholestasis of pregnancy, J.Matern.-FetalNeonatalMed.:Off.J.Eur.Assoc.Perinat.Med.,Fed.AsiaOcean.Perinat.Soc.,Int.Soc.Perinat.Obstet.33(12)(2020)2000–2005,https://doi.org/10.1080/14767058.2018.1535588.

[50] C.Y. Sanhal, O. Kara, A. Yucel, Can fetal left ventricular modified myocardialperformanceindexpredictadverse perinataloutcomesinintrahepaticcholestasisof pregnancy? J. Matern. -Fetal Neonatal Med.: Off. J. Eur. Assoc. Perinat. Med.,Fed. Asia Ocean. Perinat. Soc., Int. Soc. Perinat. Obstet. 30 (8) (2017) 911–916,https://doi.org/10.1080/14767058.2016.1190824.

[51] X.Fan,Q.Zhou,S.Zeng,J.Zhou,Q.Peng,M.Zhang,Y.Ding,Impairedfetalmyocardial deformation in intrahepatic cholestasis of pregnancy, J. UltrasoundMed.:Off.J.Am.Inst.UltrasoundMed.33(7)(2014)1171–1177,https://doi.org/10.7863/ultra.33.7.1171.

[52] J.J.Hofmann,A. Briot,J. Enciso,A.C.Zovein,S.Ren,Z.W.Zhang,F.Radtke, M.Simons,Y.Wang,M.L.Iruela-Arispe,EndothelialdeletionofmurineJag1leadsto valve calcification and

congenital heart defects associated with Alagillesyndrome,Dev. (Camb., Engl.) 139 (23) (2012) 4449–4460, https://doi.org/10.1242/dev.084871.

[53] Y.Liu,H.Wang,C.Dong,J.X.Feng,Z.H.Huang,Clinicalfeaturesandgeneticanalysisofpediatricpatientswithal agillesyndromepresentinginitiallywithliverfunction abnormalities, Curr. Med. Sci. 38 (2) (2018) 304–309, https://doi.org/10.1007/s11596-018-1879-0.

[54] L.Guo,S.T.Zhao,Y.Cheng,M.Deng,H.Li,Y.Z.Song,X.R.Cai,Q.Zhou,Clinicaland genetic analysis of eleven pediatric patients with Alagille syndrome, Zhonghuaerkezazhi= Chin.J.Pediatr.56(5)(2018)353–358,https://doi.org/10.3760/cma.j.issn.0578-1310.2018.05.009.

[55] J.M.Cho,S.H.Oh,H.J.Kim,J.S.Kim,K.M.Kim,G.H.Kim,E.Yu,B.H.Lee,H. W.Yoo,Clinicalfeatures,outcomes,andgeneticanalysisinKoreanchildrenwithAlagillesyndrome,Pediatr.Int. :Off.J.Jpn.Pediatr.Soc.57(4)(2015)552–557,https://doi.org/10.1111/ped.12602.

[56] F.B.Li,J.Chen,J.D.Yu,H.Gao,M.Qi,AChinesegirlmolecularlydiagnosedwithAlagille syndrome, World J. Pediatr.: WJP 6 (3) (2010) 278–280, https://doi.org/10.1007/s12519-010-0226-8. H.Li,J.J.Liu,M.Deng,L.Guo,Y.Cheng,Y.Z.Song,Clinicalandgeneticstudyofan infant with Alagille syndrome: identification of a novel chromosomal interstitialdeletionincludingJAG1gene,Zhongguodangdaierkezazhi=Chin.J.Contemp. Pediatr.19(10)(2017)1098–1103,https://doi.org/10.7499/j.issn.1008-8830.2017.10.013.

[57] Y.Cheng,S.T.Zhao,L.Guo,M.Deng,Q.Zhou,Y.Z.Song,IdentificationofanovelJAG1mutationinafamilyaffected byAlagillesyndrome,Zhongguodangdaierkezazhi= Chin.J.Contemp.Pediatr.18(11)(2016)1130–1135,https://doi.org/10.7499/j.issn.1008-8830.2016.11.015.

[58] D.B.McElhinney,I.D.Krantz,L.Bason,D.A.Piccoli,K.M.Emerick,N.B.Spinner, E. Goldmuntz, Analysis of cardiovascular phenotype and genotype-phenotypecorrelation in individuals with a JAG1 mutation and/or Alagille syndrome,Circulation 106 (20) (2002) 2567–2574, https://doi.org/10.1161/01.cir.0000037221.45902.69.

[59] K.M.Loomes,L.A.Underkoffler,J.Morabito, S.Gottlieb,D.A. Piccoli,N.B.Spinner, H.S.Baldwin,R.J.Oakey,TheexpressionofJagged1inthedevelopingmammalianheart correlates with cardiovascular disease in Alagille syndrome, Hum. Mol.Genet. 8 (13) (1999) 2443–2449, https://doi.org/10.1093/hmg/8.13.2443.

[60] J.Gao,G.Yuan,Z.Xu,L.Lan,W.Xin,Chenodeoxycholicanddeoxycholicacidsinducedpositiveinotropicandn egativechronotropiceffectsonratheart,Naunyn-Schmiede'S.Arch.Pharmacol.394(4)(2021)765–773,https://doi.org/10.1007/s00210-020-01962-7.

[61] P.Joubert,Cholicacidandtheheart:invitrostudiesoftheeffectonheartrateandmyocardial contractility in the rat, Clin. Exp. Pharmacol. Physiol. 5 (1) (1978)9–16, https://doi.org/10.1111/j.1440-1681.1978.tb00646.x.

[62] P.P.Rainer,U.Primessnig,S.Harenkamp,B.Doleschal,M.Wallner,G.Fauler, T.Stojakovic,R.Wachter,A.Yates,K.Groschner,M.Trauner,B.M.Pieske,D.vonLewinski, Bile acids induce arrhythmias in human atrial myocardium–implicationsforalteredserumbileacidcompositioninpatientswithatrialfibrillation,Heart(Br.Card.Soc.)99(22)(2013)1685–1692,https://doi.org/10.1136/heartjnl-2013-304163.

[63] M.Makishima,A.Y.Okamoto,J.J.Repa,H.Tu,R.M.Learned,A.Luk,M.V.Hull,K. D. Lustig, D.J. Mangelsdorf, B. Shan, Identification of a nuclear receptor for bileacids, Sci. (N. Y., N. Y.) 284 (5418) (1999) 1362–1365, https://doi.org/10.1126/science.284.5418.1362.

[64] T.Claudel,E.Sturm,H.Duez,I.P.Torra,A.Sirvent,V.Kosykh,J.C.Fruchart, J. Dallongeville, D.W. Hum, F. Kuipers, B. Staels, Bile acid-activated nuclearreceptor FXR suppresses apolipoprotein A-I transcription via a negative FXRresponseelement,J. Clin.Investig. 109(7)(2002)961–971,https://doi.org/10.1172/jci14505.

[65] R. Perez, M. Garcia, N. Ulloa, C. Jara, L. Bardisa, M.I. Rudolph, A singleintravenous high dose of cholic acid to a pregnant ewe does not affect fetal well-being, Res. Exp. Med. Z. die Gesamt Exp. Med. Einschl. Exp. Chir. 194 (1) (1994)63–67,https://doi.org/10.1007/bf02576367.

[66] J.Gao,Z.Guo,J.Cheng,B.Sun,J.Yang,H.Li,S.Wu,F.Dong,X.Yan,Differentialmetabolic responses in breast cancer cell lines to acidosis and lactic acidosisrevealed by stable isotope assisted metabolomics, Sci. Rep. 10 (1) (2020), 21967,https://doi.org/10.1038/s41598-020-78955-2.

[67] H.Gao,L.J.Chen,Q.Q.Luo,X.X.Liu,Y.Hu,L.L.Yu,L.Zou,Effectofcholicacidonfetal cardiac myocytes in intrahepatic choliestasis of pregnancy, J. Huazhong Univ.Sci. Technol. Med. Sci. =Hua zhong ke ji da xue xue bao. Yi xue Ying De. wen Ban.
=HuazhongkejidaxuexuebaoYixueYingdewenBan.34(5)(2014)736–739,
https://doi.org/10.1007/s11596-014-1344-7.

[68] C. Williamson, J. Gorelik, B.M. Eaton, M. Lab, M. de Swiet, Y. Korchev, The bileacid taurocholate impairs rat cardiomyocyte function: a proposed mechanism forintra-uterine fetal death in obstetric cholestasis, in: Clinical science (London,England: 1979), 100, 2001, pp. 363–369.

[69] S.H.SheikhAbdulKadir,M.Miragoli,S.Abu-Hayyeh,A.V.Moshkov,Q.Xie,
V.Keitel,V.O.Nikolaev,C.Williamson,J.Gorelik,Bileacid-
inducedarrhythmiaismediatedbymuscarinicM2receptorsinneonatalratcardiomyocytes,PloSOne5 (3)(2010),e9689,https://doi.org/10.1371/journal.pone.0009689.

[70] Z.Song,X.Tian,Q.Shi,Fas,Caspase-8,andCaspase-9pathway-mediatedbileacid-induced fetal cardiomyocyte apoptosis in intrahepatic cholestasis pregnant ratmodels, J. Obstet. Gynaecol. Res. 47 (7) (2021) 2298–2306, https://doi.org/10.1111/jog.14765.

[71] P.D.Turnpenny,S.Ellard,Alagillesyndrome:pathogenesis,diagnosisandmanagement,Eur.J.Hum.Genet.:E JHG20(3)(2012)251–257,https://doi.org/10.1038/ejhg.2011.181.

[72] S. Stender,R. Frikke-Schmidt,B.G. Nordestgaard, A. Tybjærg-Hansen, The ABCG5/8 cholesterol transporter and myocardial infarction versus gallstone disease, J. Am.Coll. Cardiol. 63 (20) (2014) 2121–2128, https://doi.org/10.1016/j.jacc.2013.12.055.

[73] M.T. Hendrickse, D.R. Triger, Autonomic and peripheral neuropathy in primarybiliary cirrhosis, J. Hepatol. 19 (3) (1993) 401–407, https://doi.org/10.1016/s0168-8278(05)80549-5.

[74] D.E.Jones,K.Hollingsworth,G.Fattakhova,G.MacGowan,R.Taylor,A.Blamire,
J.L.Newton,Impairedcardiovascularfunctioninprimarybiliarycirrhosis,Am.J.Physiol.Gastrointest.LiverP hysiol.298(5)(2010)G764–G773,https://doi.org/10.1152/ajpgi.00501.2009.

[75] T.Vasavan,S.Deepak,I.A.Jayawardane,M.Lucchini,C.Martin,V.Geenes,
J.Yang,A.Lo¨vgren-Sandblom,P.T.Seed,J.Chambers,S.Stone,L.Kurlak,P.
H.Dixon,H.U.Marschall,J.Gorelik,L.Chappell,P.Loughna,J.Thornton,F.
B. Pipkin, B. Hayes-Gill, W.P. Fifer, C. Williamson, Fetal cardiac dysfunction inintrahepatic cholestasis of pregnancy is associated with elevated serum bile acidconcentrations,J.Hepatol.74(5)(2021)1087–1096,https://doi.org/10.1016/j.jhep.2020.11.038.

[76] Y.Baruch,N.Assy,F.Weisbruch,S.A.Reisner,D.Rinkevich,R.Enat,L.M.Blendis,
A.Bomzon,Apilotstudyonthehemodynamiceffectofshort-termursodeoxycholicacid therapy in patients with stable liver cirrhosis, Am. J. Gastroenterol. 94 (10)(1999) 3000–3004, https://doi.org/10.1111/j.1572-0241.1999.01450.x.

[77] M.Miragoli,S.H.Kadir,M.N.Sheppard,N.Salvarani,M.Virta,S.Wells,M.J.Lab,
V.O.Nikolaev,A.Moshkov,W.M.Hague,S.Rohr,C.Williamson,J. Gorelik,
A protective antiarrhythmic role of ursodeoxycholic acid in an in vitro rat model ofthe cholestatic fetal heart, Hepatol. (Baltim., Md.) 54 (4) (2011) 1282–1292,https://doi.org/10.1002/hep.24492.

[78] L.vanObbergh,Y.Vallieres,G.Blaise,Cardiacmodificationsoccurringintheasciticratwithbiliarycirrhosisare nitricoxiderelated,J.Hepatol.24(6)(1996)747–752, https://doi.org/10.1016/s0168-8278(96)80272-8.

[79] K.Matsumoto,H. Tanaka,S. Yamana,A.Kaneko,T.Tsuji,K.Ryo,K. Sekiguchi,
F. Kawakami, H. Kawai, K. Hirata, Successful steroid therapy for heart failure dueto myocarditis associated with primary biliary cirrhosis, Can. J. Cardiol. 28 (4)(2012)515.e3-6,https://doi.org/10.1016/j.cjca.2011.12.010.

[80] Z.Esmaeili,Q.Niaz,P.M.Saffari,A.R.Dehpour,S.M.Rezayat,F.Jazaeri,Evaluation of the effect of heat shock protein 70 targeted drugs on cirrhoticcardiomyopathyinbiliarycirrhoticrats,LifeSci.273(2021),119261,https://doi.org/10.1016/j.lfs.2021.119261.

[81] S.Shayesteh,G.J.Guillemin,A.Rashidian,H.Faghir-Ghanesefat,A.R.Mani,S.
M.Tavangar,A.R.Dehpour,1-Methyltryptophan,anindoleamine2,3-

dioxygenaseinhibitor,attenuatescardiacandhepaticdysfunctioninratswithbiliarycirrhosis,Eur. J. Pharmacol. 908 (2021), 174309, https://doi.org/10.1016/j.ejphar.2021.174309.

[82] J.L.Poo,A.Braillon,A.Hadengue,C.Gaudin,D.Lebrec,Hemodynamiceffectsofterbutaline, a beta 2-adrenoceptor agonist, in conscious rats with secondary biliary

cirrhosis, Hepatol.(Baltim., Md.)15 (3) (1992) 459–463, https://doi.org/10.1002/hep.1840150318.

[83] F. Jazaeri, R. Afsharmoghaddam, A. Abdollahi, G. Ghamami, A.R. Dehpour,Evaluation of chronic losartan treatment effect on cardiac chronotropicdysfunctioninbiliarycirrhoticrats,ActaMed.Iran.56(1)(2018)4–13.

[84] T. Vasavan, E. Ferraro, E. Ibrahim, P. Dixon, J. Gorelik, C. Williamson, Heart andbile acids - Clinical consequences of altered bile acid metabolism, Biochim. Et.Biophys. Acta Mol. basis Dis. 1864 (4 Pt B) (2018) 1345–1355, https://doi.org/10.1016/j.bbadis.2017.12.039.

[85] C.Chen,F.Xu,S.Yuan,X.Zhao,M.Qiao,D.Han,J.Lyu,Competingriskanalysisof cardiovascular death in patients with primary gallbladder cancer, Cancer Med.12(3)(2023)2179–2186,https://doi.org/10.1002/cam4.5104.

[86] S.Stender,R.Frikke-Schmidt,M.Benn,B.G.Nordestgaard,A.Tybjærg-Hansen,Low-densitylipoproteincholesterolandriskofgallstonedisease:aMendelianrandomization study and meta-analyses, J. Hepatol. 58 (1) (2013) 126–133,https://doi.org/10.1016/j.jhep.2012.08.013.

[87] J.Wirth,R.diGiuseppe,A.Wientzek,V.A.Katzke,M.Kloss,R.Kaaks,H.Boeing, C.Weikert,Presenceofgallstonesandtheriskofcardiovasculardiseases:theEPIC-Germany cohort study, Eur. J. Prev. Cardiol. 22 (3) (2015) 326–334, https://doi.org/10.1177/2047487313512218.

[88] M. Sanjadi, Z. Rezvanie Sichanie, H. Totonchi, J. Karami, R. Rezaei, S. Aslani,Atherosclerosisand autoimmunity: a growingrelationship, Int. J. Rheum.Dis. 21 (5)(2018)908–921,https://doi.org/10.1111/1756-185x.13309.

[89] T. Uenaka, H. Kowa, K. Sekiguchi, K. Nagata, Y. Ohtsuka, F. Kanda, T. Toda,Myositis with antimitochondrial antibodies diagnosed by rectus abdominis musclebiopsy,MuscleNerve47(5)(2013)766–768,https://doi.org/10.1002/mus.23730.