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Cardiac Arrhythmias in Surgical Jaundice Patients: A Review

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ABSTRACT

Objectives: Impairment of cardiac function and arrhythmias often coexist in patients with liver diseases. Many studies have proved this coexistence and put forward various theories toward its pathophysiology. This narrative review tries to find the answers with supporting evidence on five main questions:

Do high serum bilirubin levels have a strong association with cardiac arrhythmias?

Can corrected QT interval (QTc) be relied upon for predicting a risk factor toward imminent arrhythmias?

Is there an association between QTc prolongation and mortality?

Are high serum bilirubin and cardiac dysfunction, closely associated?

What is the probable pathophysiology behind this association? Materials and methods: Clinical evidence was obtained by using search engines, namely, Cochrane Library, PubMed, and Google Scholar. Studies published in journals in the English language, between January 1969 and December 2019, which mentioned the relationship between cardiac arrhythmia and liver disease, were included. We used the keywords: jaundice, bilirubin, arrhythmia, ECG, QTc interval, QT dispersion, liver, and cirrhosis. Relevant animal or human studies answering the five main questions were extracted and reviewed. Conclusion: The evidence included in our review sheds light on the fact that approximately 50% of liver cirrhosis cases develop cirrhotic cardiomyopathy (CC) and there has been an association between liver abnormalities and cardiac pathology. The present review also supports that there exists a strong association between high levels of serum bilirubin levels and cardiac arrhythmias, QTc value can be relied upon as a risk factor for predicting imminent arrhythmias, and that it is associated with mortality. Its basic pathophysiology can be explained by the potential action of bile acids in prolonging the QT interval. It also causes cardiac hypertrophy and apoptosis of cardiomyocytes leading to cardiac dysfunction. Keywords: Arrhythmia, Bilirubin, Bradycardia, Cirrhosis, Corrected QT interval, Dysrhythmias, ECG, Jaundice, Levels, Liver, QT dispersion, QT interval, Serum. Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23695

I. INTRODUCTION

Liver disease rates are steadily increasing over the years. According to National statistics in the UK, liver diseases have been ranked as the fifth most common cause of death. Liver diseases are recognized as the second leading cause of mortality among all digestive diseases in the US.1,2 The global prevalence of cirrhosis falls in the range between 4.5 and 9.5% of the general population. It was estimated that more than 50 million people in the world suffer from chronic liver disease.3,4 Deaths from cirrhosis are constantly increasing and it would make it the 12th leading cause of death in 2020.

Cardiac arrhythmias are frequently seen in patients with jaundice, especially in cases with "acute decompensation of chronic liver disease", frequently admitted to intensive care units. Mostly these are new-onset arrhythmias, and they pose a real challenge to the intensivists in understanding their pathophysiology and hence managing them.

They are often resistant to treatment and tend to recur. It has been estimated that these arrhythmias are associated with 200% higher mortality, longer hospital stay, and therefore higher expenditure on medical management. It is also associated with higher rates of shock, respiratory, and kidney failures. Due to this reason, it is suggested that a robust system needs to be evolved toward screening and follow-ups of end-stage liver disease (ESLD) patients for dysrhythmias.6,7

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What Every Intensivist Should Know about Impairment of Cardiac Function and Arrhythmias in Liver Disease Patients

which if found can be acted upon promptly and hence would prevent a significant amount of morbidity and mortality. We have summarized evidence that supports the relationship between high serum bilirubin levels and cardiac arrhythmias. A detailed literature search was also done to explain the pathophysiology behind this phenomenon. Therefore, the objective is set to find answers with supporting evidence on five main questions:

Do high serum bilirubin levels have a strong association with cardiac arrhythmias?

Can corrected QT interval (QTc) be relied upon for predicting a risk factor toward imminent arrhythmias?

Is there an association between QTc prolongation and mortality?

Are high serum bilirubin and cardiac dysfunction, closely associated?

What is the probable pathophysiology behind this association? MAterIAls And Methods Data Sources and Search Strategy We used the Cochrane Library, Google Scholar, and PubMed to search for the eligible studies. English language studies which were published in journals during the years 1969–2019, addressing the relationship between cardiac arrhythmia and liver dysfunction. We used the keywords: jaundice, bilirubin, arrhythmia, ECG, QTc interval, QT dispersion, liver, and cirrhosis. Letters to editor, conference papers, book reviews, book chapters, newspaper, expert opinions, and theses or dissertations were not used. We excluded the articles that were not published in the English language. Relevant studies answering the five main questions were extracted. Titles were screened first, then abstracts, based on inclusion and exclusion criteria. Questionable eligibility based on title and abstract was read in full and judged for eligibility. Duplicates were eliminated and irrelevant articles were excluded from the review. The references of all articles, selected for full-text evaluation, were reviewed for the potentially eligible studies. dIscussIon The functioning of the liver and the heart interact mutually. Often liver induced cardiac disease goes underdiagnosed due to its complex pathophysiology. The present review was conducted to find evidence regarding this interaction with the help of five questions. The very first question raised in our review is whether cardiac arrhythmias have a strong association with serum bilirubin levels or not. We found that there is a significant coexistence between the functioning of the liver and heart, a liver disease affecting the heart, and vice versa. 8 The heart is the most affected organ in the patient with liver cirrhosis and the frequent cardiac symptoms experienced with liver failure are palpitations, dyspnea, angina chest discomfort, electrocardiographic changes, tachycardia, and bradycardia.9 The risk of arrhythmia is influenced by factors, such as, cirrhotic cardiomyopathy (CC), cardiac-ion-channel remodeling, impaired autonomic functions, impaired electrolyte balance, hepatorenal syndrome, and impaired drug metabolism, which advocates closed monitoring of cirrhotic patients.10 In the mid-70s, a study demonstrated a high incidence of cardiac arrhythmias in patients with fulminant hepatic failure. A high number of these patients suffered from heart block and developed bradycardia. A quarter of these patients had sudden cardiac death. More than a quarter of the total number of patients enrolled showed T wave and ST-segment changes, out of which, only 10% of patients who had arrhythmias survived. Almost 50% of the patients who died of arrhythmias did not show any macroscopic changes in the heart on autopsy. Therefore, this study strongly advocated close cardiac monitoring in acute hepatic failure cases.

Nakasone et al. and Yamamoto and Friedman in their case report found that Torsade de Pointes, a rare, life-threatening arrhythmia, is associated with alcoholic liver cirrhosis and CC, respectively. Even peripheral autonomic neuropathy which is often seen in cirrhotic patients can cause arrhythmias.

Yet, another study done in the late 70s found that 35% of patients with alcoholic liver disease showed PR prolongation and intraventricular conduction defect was seen in 50%.A study done in recent years showed a high incidence and prevalence of atrial fibrillation in patients with liver disease. It also showed that the magnitude of liver disease, as estimated by model end-stage liver disease (MELD), is a good predictor for new-onset atrial fibrillation.

The second question was to find out whether QTc can be relied upon as a risk factor or for predicting imminent arrhythmias. A few studies have demonstrated that there exists a strong association between high bilirubin levels and QTc. Corrected QT interval refers to the length of ventricular electric inactivity during cardiac repolarization, its prolongation increases chances of impairment of the cardiac function and ventricular arrhythmias.Reddy and Boddu showed that QTc was significantly higher in patients with liver cirrhosis who were admitted to special care units. Earlier a study done by Kempler

demonstrated that patients with primary biliary cirrhosis had remarkable prolongation of the QTc.

Prolongation of QT interval is multifactorial caused by acquired conditions like electrolyte imbalance, alcohol toxicity, coronary disease, an autonomic imbalance with sympathetic factor hyperactivity, and vagal neuropathy. QT, QTc, and their dispersions were significantly longer ($p < 0.01$) in patients with cirrhosis than in controls. QT prolongation was common in liver cirrhosis and ESLD. Corrected QT interval prolongation is correlated not only with the severity of the cirrhosis but also with some of the most severe complications of liver disease, such as, hepatorenal syndrome and hepatic encephalopathy. Additionally, the Child-Pugh score which depicts the severity of cirrhosis is statistically related to QTc duration.Yet, another study found that sudden cardiac deaths due to QTc prolongation in patients prepared for liver transplant result in significant loss of resources.

Since we have got sufficient evidence that QTc can be used as a reliable risk factor for eminent arrhythmias, we now need to find that "is there a strong association between QTc prolongation and mortality?". Few previous studies by Mahmud et al., Liang et al.,and Bernal and Wendon demonstrated that acute or acute-on-chronic liver disease is associated with high short- and long-term mortalities. The commonest cause of death among patients admitted to the hospitals was liver failure (24%). Most of the patients with "well-compensated cirrhosis" do not require hospital admission and they stay at home. This group of patients, in particular, is at high risk of having sudden cardiac death. This could be prevented if QTc values are recorded and managed promptly by starting empirical anti-arrhythmic medications and by keeping such patients under close monitoring.

A prolonged QT interval is associated with an increased risk of sudden death due to arrhythmias.According to various studies, after in-hospital cardiopulmonary resuscitation (CPR), the outcomes are usually poor in patients with ESLD and even worse than patients with metastatic cancer, sudden death is also considered an important feature of CC. Corrected QT interval prolongation is commonly found in patients with ESLD and it is a significant independent predictor of mortality (OR = 1.69, $p = 0.039$). Prolonged QTc (>440 ms) is associated with increased mortality ($p < 0.05$) in liver cirrhosis and therefore, QT-prolonging drugs must be prescribed cautiously in such patients.But a study done by Bal and Thuluvath found conflicting results with the studies mentioned above. They showed that prolonged QTc interval was common in patients with cirrhosis, but its presence had no independent effect on mortality.

Many studies explored the probable pathophysiology behind dysrhythmias in jaundiced patients. In this review article, we have also tried to find the answer to this question. Experiments conducted in humans and animals with cirrhotic liver disease have shown marked hemodynamic changes. In the heart, basal contractility, responsiveness to βadrenoceptor activation, and excitation-contraction coupling (ECC) are negatively affected in models of cirrhosis and portal hypertension with portosystemic shunting (PVS) and these events comprise the CC. It was realized that the reason behind these events may be the increased levels of circulating levels of bile acids.

Zavecz and Battarbee investigated the action of bile acids in rats which were anesthetized, and then cirrhosis was induced. They found that the bile acids act as a toxicant to myocardial cells, as demonstrated by exposing cardiac muscle in vitro to bile acids impair the cardiac, in addition to that, there was a depressed β-adrenoceptormediated inotropism and decreased calcium entry during the depolarization phase. These findings suggest that lipophilic bile acids have a potential role in the myocardial consequences of chronic portal vein stenosis and carbon-tetra chloride (CCl4) induced cirrhosis.

Binah et al. studied the effects of bile acids on ventricular muscle and electrophysiological properties, they found that all types of bile acids (primary, conjugated, and secondary) in the plasma of patients with cholestatic jaundice showed a negative inotropic effect. Bile acids caused a reduction in the duration of the ventricular action potential, but resting potential, action potential amplitude, and maximum upstroke velocity of phase 0 depolarization remain unaffected.44 Gazawi et al. in a study on in rat cardiac membrane demonstrated the effects of deoxycholic acid (DCA), chenodeoxycholic acid (C-DCA), and their taurine conjugates, namely T-DCA and T-CDCA, on the binding features of β-adrenoceptors, membrane fluidity, and the extent of lipid peroxidation. They proposed that bile acid is a causative factor for the cardiomyopathy of cholestatic liver disease as they cause negative inotropism and chronotropism and attenuate cardiac responsiveness to sympathetic stimulation. They also modify membrane fluidity and generate reactive oxygen species (ROS).

The role of β-adrenoceptor signal transduction in the pathophysiology of CC was

studied by Ma et al. in a rat model of cirrhosis. They found that it is the contractile element of the heart that is impaired in cirrhosis, associated with altered β-adrenergic receptor signaling function and guanine nucleotide-binding protein expression.The relationship between bile acid metabolism and cardiac dysfunction has been determined with both in vitro systems and experimental models in intact animals.

Direct effects of bile acid exposure can be observed in vitro using isolated cardiomyocytes and muscle strips. The indirect effect of bile metabolism can also be determined through animal models of cirrhosis which are known to result in CC. Ferreira et al. conducted a study to test a hypothesis that bile acids are toxic to heart mitochondria for concentrations that are relevant for cholestasis. The mitochondria of heart cells were isolated from the rat and subjected to incubation with selected bile acids. The authors concluded that the bile acids alter mitochondrial bioenergetics and cause impairment of mitochondrial function. This may be an important cause for the observed cardiac dysfunction during cholestasis.

Torregrosa et al. found that patients with cirrhosis had higher left ventricular wall thickness ($p < 0.05$) and ejection fraction ($p < 0.001$) than controls. Bogin et al., in their experiment, studied the effect of jaundiced serum and bile salts on the beating heart cells. The jaundiced serum which was collected from the common bile duct ligated rats were added to cultured heart cells. It was seen that the beating rate of the cultured heart cells decreased, with early cessation of beating occurred, associated with the production of higher levels of lactate in the media. These findings suggest that patients with liver failure produce deoxycholate which is the main toxic substance responsible for altering heart function. Vasavana et al. in their study demonstrated that an elevation of serum bile acid concentration is associated with impaired cardiac function, the formation of CC.

The last question raised in our review article was whether high serum bilirubin is associated with cardiac dysfunction. It has been estimated that almost half of all cases of liver cirrhosis result in the development of CC, which shows systolic and diastolic dysfunction, changes in the electrophysiology of the heart.Chronic liver disease is frequently associated with cardiovascular complications, such as, tachycardia, myocardial infarction, and congestive heart failure as shown in retrospective studies conducted by Matsumori et al. and Baratta et al.

Ward et al. conducted a study in a rat model, with induced cirrhosis, to explore the underlying mechanisms for the electrophysiological abnormalities that develop as a consequence of cirrhosis of the liver. Various review articles also proved that liver disorders have an association with heart abnormalities.A study designed to assess the cardiac involvement in jaundiced patients found a significantly reduced response to intravenous dobutamine, as compared to, that seen in the normal controls. It suggests that such myocardial refractoriness to β-1 stimulation makes jaundiced patients more susceptible to postoperative shock and multiorgan failure.

Ward et al. in their study concluded that cardiac contractility is depressed in cirrhotic patients due to malfunction of the Ca2+ -regulatory system.

On the contrary, Demir et al.60 conducted a study among 102 patients with non-valvular chronic atrial fibrillation without any other cardiovascular disease (mean age 62.51 ± 5.88) and found that total, direct, and indirect serum bilirubin levels were significantly lower among persons with atrial fibrillation when compared with controls ($p < 0.001$), respectively. They concluded that an inverse relationship exists between serum bilirubin and non-valvular atrial fibrillation. Similarly, Cüre et al.61 in their observational study found that Gilbert syndrome patients are associated with increased bilirubin levels which consequently might decrease the incidence of cardiac arrhythmias, suggesting myocardial protection provided by serum bilirubin levels.

II. CONCLUSION

The evidence included in our review suggested that cardiac arrhythmias are associated with high levels of serum bilirubin levels, QTc is a reliable risk factor for imminent arrhythmias, and it is associated with mortality. Approximately 50% of liver cirrhosis cases develop CC. The basic pathophysiology behind this is the bile acids that cause prolonging the QT interval. They cause cardiac hypertrophy and apoptosis of cardiomyocytes. Also, a high level of serum bilirubin is associated with cardiac dysfunction. These observations directly suggest that there has been an association between liver abnormalities and cardiac pathology.

Future PersPectIve

We have tried our best to depict the relationship between the pathologies of liver and heart and the probable mechanism behind this association through the evidence present in the literature but further randomized controlled studies

are needed to establish the causality between these two.

Author's contribution

Conceptualization is done by—Sanjeev Arya, Haider Abbas, Sanjay Saxena, and Shantanu Belwal. Data curation—Sanjeev Arya and Shantanu Belwal. Formal analysis —Sanjeev Arya, Sanjay Saxena, and Prashant Kumar. Methodology—Sanjeev Arya, Prashant Kumar, Haider Abbas and Bhuwan Tiwari. Resources—Sanjeev Arya, Sanjay Saxena, and Bhuwan Tiwari. Supervision—Sanjeev Arya, Prashant Kumar, and Shantanu Belwal. Writing (original draft)—Sanjeev Arya. Writing (review and editing)— Sanjeev Arya, Prashant Kumar, and Bhuwan Tiwari, Haider Abbas.

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