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Probing the Liver-Heart Axis: Cardiac MRI in Early Assessment of Myocardial Injury in Cirrhosis and Pre-Cirrhosis

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Abstract

Cirrhotic cardiomyopathy (CCM), a critical clinical entity in cirrhotic patients, adversely affects post-liver transplantation prognosis and all-cause mortality. However, CCM and its early stages often remain unrecognized when using traditional cardiovascular imaging modalities. In this context, cardiac magnetic resonance (CMR) may play an essential role in the early detection of cardiac insults, by characterization of cardiac impairments with higher resolution (i.e., functional, morphological, and tissue compositional features) and higher sensitivity (e.g., detection of silent myocardial injury). In this mini-review article, we summarized the role of CMR in the assessment of cardiac dysfunction in liver diseases at pre-cirrhotic and cirrhotic stages, and their potential clinical relevance. Here, we emphasize the CMR tissue features in CCM, the capability of CMR in the early detection of silent cardiac impairment at early-stage liver diseases, and the prognostic impacts of CMR findings in cirrhosis.

Keywords: Cirrhotic cardiomyopathy; Cirrhosis; Primary biliary cholangitis; Nonalcoholic fatty liver disease

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Introduction

Cardiac insults caused by end-stage liver disease are clinically recognized as cirrhotic cardiomyopathy (CCM) [1, 2]. High output state, systolic and diastolic dysfunction, and electromechanical abnormalities such as prolonged Q-T intervals are the common manifestations [2]. The lower peripheral resistances decrease left ventricular afterload which frequently silenced the cardiac symptoms. CCM are often recognized only when acute heart failure ensues. Liver transplantation (LT) is the last resort for CCM in patients with end-stage liver disease. However, the remarkable effects of LT may be overshadowed by the emergence of comorbid cardiovascular diseases. It was reported that up to 21% of deaths following LT can be attributed to heart failure and up to 40% to cardiovascular disease in general [3, 4]. Although the liver-heart interaction is generally accepted, the clinical parameters for early detection of asymptomatic myocardial disease are still scarce.

Using noninvasive techniques to detect myocardial impairment is of great importance due to clinical feasibility. Biomarkers of myocardial ischemia (troponins T and I), myocardial wall stress (B-type natriuretic peptide), and systolic function (LVEF) are the most commonly used for the evaluation of cardiac diseases however, changes in these parameters typically reflect an advanced stage of heart disease [5]. CCM usually remains unrecognized when using traditional cardiovascular imaging modalities [6]. The ability to identify patients at a much earlier stage or to predict the development of cardiac impairment would allow earlier intervention and thus reduce the incidence of overt left ventricular dysfunction. The emerging use of cardiac magnetic resonance (CMR) enabled characterization of cardiac impairments with higher resolution and higher sensitivity [7, 8]. These unique advantages provide valuable opportunities for early and more comprehensive detection of cardiac insults in liver diseases [8]. Therefore, we summarized the existing data of CMR findings on cardiac impairments in cirrhosis and pre-cirrhosis status in this mini-review.

Literature Review

A Pubmed (1970 to December 2021) search was performed using the key words including “cirrhotic cardiomyopathy”, “cirrhosis”, “primary biliary cholangitis”, “alcohol”, “hepatitis”, “nonalcoholic

fatty liver disease", "cardiovascular magnetic resonance", and their abbreviations or variations. All retrieved citations were screened hierarchically assessing the title, abstract, and article. References of all selected publications were screened for further identification of related studies. No language or subject (e.g., human only) restrictions were set. Corresponding authors were contacted when necessary for better clarification of study content.

A Brief Introduction of CMR Advantages

CMR imaging is a multiparametric imaging modality that is changing clinical practice, and has a growing impact on diagnosis, clinical management, and decision making in cardiac disorders [9, 10]. CMR not only serves as a reference standard for volumetric and functional assessment in both atriums and ventricles, but also provides a noninvasive "biopsy" of the underlying histopathological myocardial changes by its unique abilities of reflecting myocardial characterization, which have been validated against histological findings in biopsy tissues or explanted hearts [11, 12]. In particular, the specific delay enhancement pattern in the myocardium after gadolinium contrast injection provides valuable insights to determine the underlying etiology of cardiomyopathy [7, 13].

CMR employs different imaging sequences to provide specific anatomical, functional, tissue characteristics, or perfusion information based on the imposed clinical question. The commonly used CMR imaging sequences and relevant uses are as follow: (i) Assessment of ventricular function, volumes, and mass by steady-state free precession (SSFP) cine sequences. Cine sequences provide high resolution, contiguous 2-dimensional images covering the whole heart, which allow satisfactory identification of the endocardial and epicardial borders and the subsequent 3-dimensional estimations of ventricular volumes, function, and mass with high levels of accuracy and reproducibility [9]. (ii) Assessment of myocardial edema. CMR enables the detection of myocardial edema. Sequences including T2 mapping, T2-STIR imaging sequences are available for this applicatoon. Edematous areas are characterized by higher signal intensity than the surrounding myocardium [8]. T2 mapping allows for the quantification of the extent of edema. Signs of myocardial edema are also strong evidence of enhanced vasodilatation and vascular permeability in early gadolinium enhancement sequence. (iii) Assessment of myocardial scarring/fibrosis. Cardiac fibrosis can be assessed by late gadolinium enhancement (LGE). Regional hyperintense signals can be appreciated since gadolinium preferentially distributes in the extracellular space since it cannot cross the intact cell membrane [14-16]. T1 maps and extracellular volume (ECV) have been proven as promising imaging techniques to track the extracellular changes that lead to an increase in extracellular matrix volume [17]. They have potential for detecting diffuse cardiac impairment and advancing our understanding of the pathophysiologic processes of the heart. These above-mentioned CMR parameters are commonly used in the clinical settings, and more detailed introduction for CMR parameters and application were reviewed elsewhere [9, 10].

CMR Findings of Cardiac Injury in End-stage Liver Disease

The available studies regarding CMR findings in end-stage liver disease/cirrhosis included patients with various etiologies [18-25]. As the reference standard for ventricular function measurement, CMR-derived functional parameters (e.g., left ventricular ejection fraction, global circumferential strain, global longitudinal strain) were regularly measured in almost every study. Consistent with the conventional understanding, CMR findings demonstrated hyper-contractile or normal function at rest in cirrhosis patients while contractile reserve was impaired in response to pharmacological stimuli (i.e., dobutamine) [25].

Regarding myocardial tissue characterization, T1 mapping based ECV estimation (reflecting diffuse fibrosis) was used widely. Reports consistently suggested significantly increased ECV in cirrhosis patients compared to healthy participants [22, 23]. Further subgroup analysis demonstrated that ECV showed a positive correlation with Child-Pugh score, supporting an association between severity of liver cirrhosis and extent of diffuse myocardial fibrosis. Moreover, ECV was identified as an independent predictor for the combined endpoint of liver transplantation and mortality [20, 23]. It is interesting that a study observed significant decrease in cardiac ECV during a 2-year follow-up in patients with stable cirrhosis but not in progressive cirrhosis, suggesting a partial reversibility of diffuse cardiac fibrosis in cirrhosis. This was further supported by another study showing a decrease in cardiac diffuse fibrosis after liver transplantation, underscoring the value of CMR in assessing response to treatment. However, the decrease in cardiac ECV was accompanied by a further increase in QTc interval (a prototypical electrophysiological feature in cirrhotic cardiomyopathy) in these stable cirrhosis patients, suggesting that mechanisms underlying prolonged QTC interval may be independent of diffuse cardiac fibrosis (**Figure 1**).

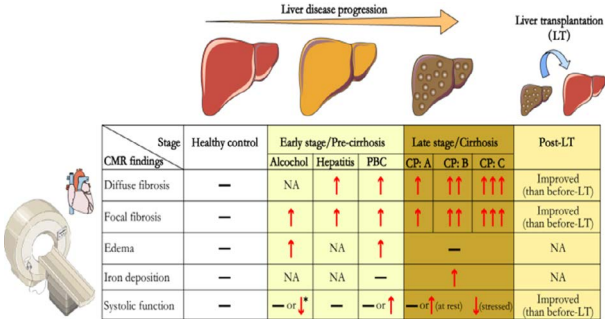

Figure 1 A summary of CMR findings in specific liver diseases at different stages of severity

Others tissue characterization parameters including regional scarring/fibrosis (LGE lesions) and cardiac iron deposition (T2* mapping). Some studies reported that the presence of positive LGE ranged from 5% to more than 50% patients [19, 21, 22]. The explanations for the highly variable findings remain unclear, one of the potential reasons was the different etiologies for

cirrhosis, with alcohol assumption for some of studies 10 and viral hepatitis for the other [19]. One of the advantages of CMR is to suggest the etiology of cardiomyopathy based on the pattern and location of LGE [7, 13]. CMR imaging in myocardial infarction, cardiac amyloidosis, and hypertrophic cardiomyopathy are characterized by specific LGE patterns. A recent study reported that patchy or striatal LGE was preferably located at the inferolateral and inferoseptal wall in patient with cirrhosis [22]. Despite the widely accepted significance of LGE presence in predicting adverse outcomes in a variety of cardiomyopathies [14-16]. Studies evaluating the prognostic values of LGE lesions in cirrhosis patients are still lacking. As for T2* mapping, Lewin et al. investigated the prognostic roles of T2* mapping, and the results suggested that lower T2* mapping (reflecting cardiac iron overload) was associated with higher risk of all-cause mortality in cirrhosis [24].

CMR Findings of Cardiac Injury in the Pre-cirrhotic Stages of Liver Diseases

As a late-stage liver condition, cirrhosis is caused by diverse forms of chronic hepatic disorders. The commonly studied etiologies for cirrhosis include alcoholism, hepatitis, autoimmune liver diseases, and nonalcoholic fatty liver disease (NAFLD). Cardiac injuries occur but are less well appreciated at early stages of these liver diseases in the absence of prior heart disease. CMR assessment has been used in patients with alcoholism, hepatitis, and autoimmune liver diseases, but not in NAFLD.

CMR Findings in Patient with Primary Biliary Cholangitis (PBC)

PBC, formerly known as primary biliary cirrhosis, is an autoimmune liver disease characterized by progressive damage of the small intra-hepatic bile ducts. Incomplete response to medical treatment will eventually lead to cirrhosis. Earlier study reported ejection fraction impairment and whole heart enlargement. However, the inclusion of both cirrhotic and non-cirrhotic PBC patients in this study make it less clear whether the functional and structural changes were associated with PBC per se or cirrhosis. Indeed, an CMR imaging study by Newton, et al. included biopsy-based early stage PBC patients and demonstrated that cardiac function and left ventricular morphology were similar between PBC and control subjects. However, early stage PBC patients exhibited reduced cardiac muscle bioenergetic integrity and had an abnormal left ventricular ejection time in response to tilting from a supine to upright position. Recent CMR study from Jiang, et al. provided further insights into the unique tissue characteristics of silent myocardial impairment in early stage PBC without previous heart disease. The median PBC duration in this study was 51 months and patients with cirrhosis were excluded. No significant difference in systolic and diastolic function were observed between PBC and control patients, while the study surprisingly observed that LGE lesions were detected in 36% patients with early-stage PBC. Interestingly, PBC-related LGE lesions presented a specific and unique pattern. A typical myocardial LGE characteristic in PBC was a mid-wall “stripe” located at the left ventricular septum (100% of the LGE located at the mid-wall layer, and 95% of the LGE lesions was a “stripe” pattern). In addition to LGE-defined focal fibrosis, diffuse fibrosis was also significantly increased in early stage PBC patients. Moreover, Jiang, et al. observed myocardial edema in PBC patients, which was absent in patients with cirrhosis by another study, suggesting a potential involvement of acute inflammation in cardiac injury in early-stage of PBC.

The mechanisms underlying these silent cardiac injuries in early stage PBC remain largely unknown. Antimitochondrial antibodies (AMA) is present in about 90% PBC cases. It was reported that infusion of AMA collected from PBC patients led to AMA accumulation in myocardium in a canine model. More evidence are emerging indicating an association of AMA with cardiomyopathy. Thus, an immune mechanism may account for PBC related cardiac injury. Moreover, PBC is known to be correlated with increased total serum bile acid concentrations. The cardiotoxicity of bile acids was observed as early as 100 years ago, and the negative inotropic effects of bile acids was demonstrated in isolated myocytes 38. Moreover, our previous findings indicated the activation of farnesoid X receptor (FXR), a nuclear receptor activated by bile acids, promoted cardiomyocyte apoptosis in both in vivo and in vitro models. These data imply that bile acid dysregulation may represent another potential mechanism mediating the early cardiac impairment in PBC.

CMR Findings in Patient with Viral Hepatitis or Chronic Alcohol Consumption

Earlier studies reported dilated left ventricle, increased LV mass, and the subsequent diastolic dysfunction and contractile reduction in patients with viral hepatitis or alcoholism. These cardiac changes are manifestations of advanced myocardial injury. Recent CMR studies provided novel understanding that focal and diffuse cardiac fibrosis were present in these patients. Positive LGE was found significantly increased in patient with chronic hepatitis C than the control participants without impairment in LVEF, and the LGE showed an epicardial pattern in all the hepatitis C patients. In patients with chronic alcoholism, focal cardiac fibrosis was observed in a high proportion of patients. Moreover, acute alcohol consumption was reported to induce myocardial edema. The early silent myocardial involvement is conceivable, because causal roles and mechanisms of viral hepatitis and alcohol in cardiac dysfunction have been well validated by clinical and animal studies. Thus, detection of early cardiac impairment in these conditions is of clinical significance for decision making of early intervention.

Conclusion

CCM remains a critical condition with no effective pharmacological therapies. CCM not only contributes to various complications in cirrhosis such as hepatorenal syndrome, but also leads to increased hepato-cardiac syndrome and mortality. There is an imperative need for early detection of CCM and improved methods for prognostication. This review of the CMR findings in cirrhosis and specific hepatic conditions suggests that CMR imaging is a valuable tool to achieve these goals. CMR sequences including Cine, T1, and T2 mapping, and LGE are currently among the most useful techniques in the assessment of cardiac injury in liver diseases. In addition to reproducible morphological and functional

evaluation, CMR was highly sensitive to detect and quantify both focal and diffuse cardiac fibrosis, as well as myocardial edema and iron deposition in cirrhosis (Figure 1). Though more efforts are required to explore the clinical significance of these CMR features, emerging evidence suggested important prognostic values of CMR parameters such as ECV in predicting liver transplantation free survival and all-cause mortality. Importantly, CMR imaging enables early detection of silent cardiac impairments in liver diseases (e.g., PBC, hepatitis, alcoholism) at pre-cirrhotic stages even when cardiac structural and functional parameters remain unchanged (Figure 1). This early detection capability makes early intervention possible and is especially relevant for patients with modifiable risk factors (e.g, alcohol consumption). Despite these insightful findings, further studies are warranted to explore the clinical significance of CMR findings in patients with liver diseases.

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Conflict of Interest

None

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