Morphological, Functional and Tissue Characterization of Silent Myocardial Involvement in Patients with Primary Biliary Cholangitis

Early Identification of Myocardial Impairment in PBC (EARLY-MYO-PBC)

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STUDY PROTOCOL SYNOPSIS

Title	Morphological, Functional and Tissue Characterization of Silent Myocardial Involvement in Patients with Primary Biliary Cholangitis
Sponsor	Investigator-Initiated Trial (IIT)
Primary Objectives	1. The incidence of cardiac involvement (LGE and T2-STIR positive) Late gadolinium enhancement (LGE) indicates myocardium viability in patients which can be recognized by regional high signal area in cardiac image. Meanwhile, T2-STIR positive indicate the myocardium edema. The outcome assessments base on the presence of myocardium late gadolinium enhancement and T2-stir positive in all participants 2. Quantitative assessment in cardiac injury T1 mapping–derived extracellular volumes (ECV) were used to detect changes in the myocardium interstitial matrix. ECV was calculated according to the ECV formula including T1 mapping value.
Study Design	EARLY-MYO-PBC study was a prospective, three-center, multi-modality cardiac imaging study (Trial Registration: NCT03545672) designed to early identify silent myocardial impairment in PBC patients. We hypothesized that myocardial injuries could occur at the early-stage of PBC without presenting any reported cardiac clinical manifestation. Participants undergoing cardiovascular magnetic resonance (CMR) were enrolled. Demographic, serological, and cardiac imaging data were prospectively collected. All participants were free of cardiac discomfort or a prior history of heart disease and had normal electrocardiographic results. (1) CMR Protocol All images were acquired and then processed in a core lab 1. The LV volumetric and systolic assessment was performed with cine imaging by whole-heart coverage using a balanced, steady-state, free precession sequence in combination with parallel imaging and retrospective gating during a gentle, expiratory breath hold. T2 maps were acquired in several contiguous short axis slices, using a multi-echo GraSE black-blood sequence. An electrocardiogram-triggered, STIR T2-weighted multi-slice spin-echo sequence also was performed to determine edema and the T2 ratio. T2*-mapping is used for detecting iron deposition. Native and post-contrast myocardial T1 mapping were used to determine the ECV. A MOLLI R5.1 sequence was used for T1 mapping, and a “5-3-3” scheme (in seconds) was chosen. The scheme was performed on a 3 mid-diastolic LV short-axis slice (basal, mid-ventricle, and apex) before and 15 min after a bolus intravenous injection of 0.15 mmol/kg gadobutrol (Bayer Healthcare, Berlin, Germany). Segmented LGE images with at least three matching slices and native T1 images were also acquired. Visual assessment of LGE positive (LGE+) was recorded. The detailed methods and acquisition parameters can be found in publication 2: Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40671.

	(2) Image Analysis All contours were manually examined, adjusted if necessary and assessed. Myocardial deformation was voxel-tracked to acquire LV global circumferential strain (GCS), global longitudinal strain (GLS) and global radial strain (GRS). The LGE was examined for the presence of regional fibrosis. T1, ECV images were examined for extent of extracellular volume. Reported T1 values were derived with the operator blinded to the LGE images. Hematocrit was acquired on the same day in all subjects.
Number of Subjects	Enrollment:120[anticipate] PBC group: 60[anticipate] Healthy group:60[anticipate]
Enrollment Criteria	Inclusion criteria were: (1) All patients were PBC older than 18 without any cardiac symptoms. (2) The diagnosis of PBC was established when patients met at least two of three criteria: 1) elevated alkaline phosphatase or γ-glutamine transpeptidase; 2) positive anti-mitochondrial antibodies (AMA) or specific antinuclear antibody (ANA) (sp100, gp210) positive; 3) histological findings of chronic and non-suppurative inflammation, which surrounds and destroys interlobular and septal bile ducts. Exclusion criteria were : (1) having cardiac discomfort or a prior history of heart disease, abnormal electrocardiographic results; stress echocardiography proved wall motion abnormality, coronary CT or angiography proved coronary artery stenosis >50% when Framingham risk score was over 10. (2) having cirrhosis or other known liver diseases such as viral hepatitis, alcohol-induced liver injury, drug-induced liver injury, and inherited metabolic liver disease. (3) life expectancy of less than 6 months due to any condition. (4) for magnetic resonance safety reasons: standard metallic contraindications to CMR, or severe infection and renal failure (i.e., an estimated glomerular filtration rate < 30 ml/min/1.73 m2); (5) patient with any medical conditions that in the opinion of the investigators will not be appropriate to participate in the study.
Safety Assessments	Participants will be assessed for AEs at scanning while on the study. Adverse events will be graded according to the CTCAE v4.03. Type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities will be reported.
Endpoints	1.LGE and T2-STIR 2.ECV mapping
Statistical Analysis	Continuous variables are expressed as median (quartile) and categorical variables as numbers and percentages. Ventricular volume was acquired by both echocardiography and CMR; the latter was used for analysis. For continuous variables, the Mann-Whitney U test was used to compare between two groups.

	Categorical variables were compared using the Pearson's chi-squared test or Fisher's exact test. Logistic regression was used to identify the predictors of elevated ECV. Variables with P value <0.1 in univariable analyse were included into multivariable anaylse. Comparisons of variables between controls and PBC groups were adjusted for age and body surface area with covariance analysis. The interobserver reproducibility of CMR measurements was assessed using the interclass correlation coefficient (ICC), as well as intraclass coefficient analysis. The methods of sample size calculation could be found in supplementary materials. Statistical analysis was performed primarily using the SPSS 20.0 (SPSS Inc, Chicago, IL) system. P<.05 was statistically significant. ***Sample Size Calculation.*** This study aimed to explore clinically silent myocardial impairments in PBC patients without presenting any reported cardiac clinical manifestation. According to previous CMR studies 3,4, ECV is one of the most valuable and sensitive indices reflecting myocardial change. In our pre-test including 10 PBC and 10 controls, the mean of ECV was 30% and 24%, respectively. The standard deviation of ECV in the entire group was 0.3. A margin of 4% was expected to differentiate between PBC and controls group. On the basis of margin and sample ratio (nPBC/nControl=1) and a type I error (two-side) of 5% and a power of 0.8, the final sample size required at least 42 subjects in each group.