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ORIGINAL ARTICLE
Metabolic Disorder

Impaired Myocardial Perfusion Reserve in Patients With Fatty Liver Disease Assessed by Quantitative Myocardial Perfusion Magnetic Resonance Imaging

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Background: The purpose of this study was to determine whether the presence of fatty liver is associated with an alteration in myocardial perfusion reserve (MPR).

Methods and Results: A retrospective analysis of 65 asymptomatic subjects who underwent both plain abdominal computed tomography and cardiac magnetic resonance imaging (MRI), and who had normal left ventricular wall motion, no regional myocardial ischemia and no myocardial scar on MRI was performed. Stress and rest myocardial perfusion MRI were analyzed by Patlak plot method to quantify myocardial blood flow (MBF) and MPR in 16 myocardial segments. Fatty liver was detected in 18 (28%) of the 65 subjects. No significant difference was found in rest-MBF between subjects with and without fatty liver (1.2±0.75 vs. 1.1±0.67 $ml \cdot min^{-1} \cdot g^{-1}$, P=0.59). However, MPR was significantly lower in subjects with fatty liver than the non-fatty liver subjects (2.3±0.74 vs. 3.3±1.4, P<0.001). Subjects with fatty liver had a higher prevalence of MPR <2.5 (78% vs. 38%, P<0.005) and higher triglyceride levels (206±61 vs. 92±37 mg/dl, P<0.001). Multivariate analysis revealed the presence of fatty liver as a significant predictor of reduced MPR with an odds ratio of 8.2 (P<0.01).

Conclusions: Nonalcoholic fatty liver disease is related to reduced MPR, suggesting impaired coronary microcirculation. (*Circ J* 2012; **76:** 2234–2240)

Key Words: Abdominal computed tomography; Cardiac magnetic resonance; Fatty liver; Myocardial perfusion reserve

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition characterized by fatty infiltration of liver cells resembling that of alcohol-induced liver injury but occurring in patients who do not abuse alcohol.[1–3] For a long time, the presence of NAFLD was considered a benign condition with little or no clinical significance.[4] However, recent results indicate that individuals with NAFLD, even without metabolic syndrome (MetS), are at high risk for coronary artery disease (CAD)[5] and the severity of the liver histology in NAFLD patients is closely associated with intima-media thickness.[2,3,6,7] Furthermore, Villanova et al showed that NAFLD is a risk factor for endothelial dysfunction, by evaluating the flow-mediated vasodilatation of the brachial artery.[8] This result has stimulated interest in a possible common pathway of disease progression between fatty liver and atherosclerosis. In a recent study evaluating NAFLD patients in Europe, abnormal coronary flow reserve was found in 42% of patients without clinical signs of CAD, by using transthoracic Doppler harmonic echocardiography.[9] However, no data are currently available regarding the relationship between fatty liver and altered myocardial perfusion reserve (MPR) in the Japanese population. First-pass contrast-enhanced myocardial perfusion magnetic resonance imaging (MRI) has emerged as a method of detecting the presence and measuring the extent of hypoperfusion caused by flow-limiting CAD.[10–16] Stress-rest perfusion MRI may also provide a more objective evaluation of altered MPR in subjects with flow-limiting CAD and of microcirculation dysfunction in patients without flow-limiting epicardial coronary artery stenosis, through quantitative evaluation of myocardial blood flow (MBF), and by analysis of the myocardial and blood signal intensity time curves.[17,18] Accordingly, the purpose of our study was to determine whether the presence of a fatty liver on abdominal computed tomography (CT) is associated with alteration of MPR in subjects without flow-limiting CAD

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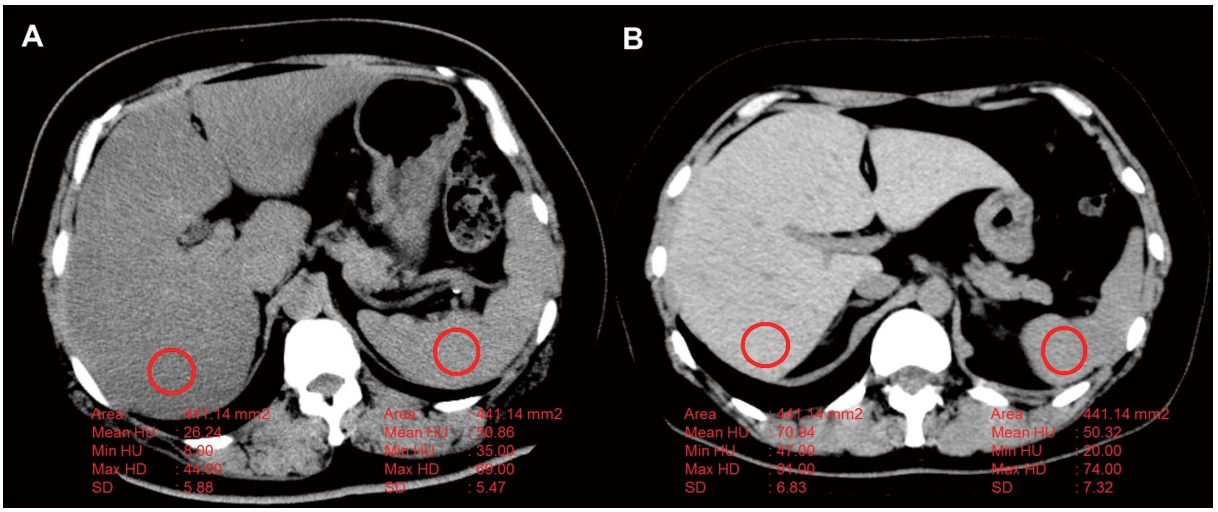

Figure 1. Definition of fatty liver. Non-contrast computed tomography (CT) images in patients with (**A**) and without (**B**) fatty liver. Unenhanced CT in patients with fatty liver shows diffuse fat accumulation in the liver. Liver attenuation (26 HU) minus spleen attenuation (51 HU) equals –25 HU. Fatty liver was considered to be present when the liver HU is less than the spleen HU minus 10. HU, Hounsfield units.

or myocardial infarction. Quantitative analyses were performed to determine the stress-rest MBF and MPR in patients with fatty liver as compared to patients without fatty liver.

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Methods

Study Subjects

All examinations were approved by the institutional review board on medical ethics and clinical investigation. We studied 65 adult patients (24 women; 67±10 years) without a clinical history of CAD who had normal global and regional left ventricular (LV) function, normal stress perfusion MRI and no myocardial scar on late gadolinium-enhanced MRI and who underwent abdominal CT within 6 months of cardiac MRI testing. These subjects were selected from 1,132 patients who had completed cardiac MR studies in our hospital between 2003 and 2008. In this study, individuals with cardiomyopathies, myocarditis, sarcoidosis, amyloidosis, valvular heart disease, congenital heart disease, typical chest pain, percutaneous intervention and coronary bypass grafting and general contraindications to MRI such as claustrophobia, pacemakers or implantable defibrillator devices were not included. Individuals with viral hepatitis and hepatobiliary disorders were also excluded. None of the subjects consumed more than 20 g/day of alcohol or were taking medications that would induce hepatic steatosis (eg, estrogens, amiodarone, steroids, or methotrexate).

Clinical and Biochemical Measurements

All subjects underwent a physical examination, anthropometric measurements, risk factor evaluation, and biochemical screening. Body mass index (BMI) was calculated from measurements of height and weight. Obesity was considered present if the calculated BMI exceeded 25 kg/m^2. Diabetes mellitus was diagnosed as fasting glucose >126 mg/dl, hemoglobin A_{1c} >6.5, self-reported history of diabetes, or taking diabetic medications. Blood pressure (BP) was measured using a mercury sphygmomanometer in a quiet room after more than 10 min of rest. Hypertension was defined as systolic BP >140 mmHg, diastolic BP >90 mmHg, self-reported history of hypertension, or current use of antihypertensive medications. Hypercholesterolemia was defined as total cholesterol >240 mg/dl, self-reported history of hypercholesterolemia, or taking lipid-lowering medications. Smoking status was assessed by a self-administered questionnaire. Routine blood samples were obtained after an 8-h fast, and blood counts and chemical analyses were performed.

CT Scan Protocol

CT images were acquired with 16- or 64-slice CT scanner (Aquilion, Toshiba Medical Systems, Otawara, Japan). Fatty liver was considered to be present when the liver Hounsfield units (HU) were less than the spleen HU minus 10 on plain CT (Figure 1).[5,19] The reviewers who measured liver and spleen attenuation were blinded to individual clinical information. The hepatic attenuation was measured by means of a random selection of 3 circular regions of interest (ROI) on 3 transverse sections at different levels of the liver. For each ROI, we selected the largest possible region and avoided areas of visible hepatic vascular and biliary structures to accurately represent liver parenchymal attenuation. The ROI values were averaged as the mean hepatic attenuation. To provide an internal control, the mean splenic attenuation was also calculated by averaging 3 random ROI values of splenic attenuation on 3 transverse sections at different levels of the spleen.

MRI Acquisitions

Initial scout images were obtained in 3 orthogonal directions to determine the position of the heart and diaphragm. Next, transaxial cine MR images and vertical long-axis cine MR images of the LV were acquired. First-pass contrast-enhanced myocardial perfusion MR images were obtained during ATP stress and in the resting state using a 1.5-T MR imager (Achieva,

Table 1. Characteristics of Patients With and Without Fatty Liver

Parameter	Fatty liver (–) (n=47)	Fatty liver (+) (n=18)	P value
Age (years)	67±10	67±11	0.9
Male (%)	31 (66)	10 (56)	0.4
Hypertension (%)	30 (64)	14 (78)	0.3
Systolic BP (mmHg)	125±18	133±20	0.1
Diastolic BP (mmHg)	71±10	76±12	0.1
Diabetes mellitus (%)	5 (11)	5 (28)	0.2
Hypercholesterolemia (%)	13 (28)	5 (28)	0.9
BMI (kg/m^2)	23±4	25±3	0.1
Current smoking (%)	11 (23)	2 (12)	0.3
Aspartate aminotransferase (IU/L)	25±10	26±14	0.8
Alanine aminotransferase (IU/L)	20±11	27±23	0.2
Alkaline phosphatase (IU/L)	231±60	242±54	0.5
γ-glutamyltransferase (IU/L)	44±33	54±53	0.4
Fasting glucose (mg/dl)	99±19	107±18	0.1
Total cholesterol (mg/dl)	193±40	201±30	0.3
LDL-cholesterol (mg/dl)	111±32	110±28	0.9
HDL-cholesterol (mg/dl)	61±14	51±10	0.01
Triglycerides (mg/dl)	92±37	206±61	<0.001
CRP (mg/dl)	0.15±0.17	0.46±0.39	0.01
eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)	59±16	64±15	0.3
Hematocrit (%)	40±4	42±4	0.1
Liver attenuation minus spleen attenuation (HU)	4.5±5.5	–12.7±1.9	<0.001

BP, blood pressure; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HU, Hounsfield units.

Table 2. Cardiac MRI Findings of of Patients With and Without Fatty Liver

Parameter	Fatty liver (–) (n=47)	Fatty liver (+) (n=18)	P value
End-diastolic volume (ml)	116±25	107±20	0.2
End-diastolic volume index (ml/m^2)	73±16	65±10	0.01
End-systolic volume (ml)	45±16	38±13	0.1
End-systolic volume index (ml/m^2)	28±10	23±7	0.05
Ejection fraction (%)	62±8	65±7	0.3
LV mass (g)	99±30	91±18	0.2
LV mass index (g/m^2)	62±19	55±12	0.07
Myocardial vascular resistance ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot g^{-1}$)	123±69	127±86	0.8
Rest-myocardial blood flow ($ml \cdot min^{-1} \cdot g^{-1}$)	1.1±0.67	1.2±0.75	0.6
MPR	3.3±1.4	2.3±0.74	<0.001

MRI, magnetic resonance imaging; LV, left ventricular; MPR, myocardial perfusion reserve.

Philips Medical Systems, Best, The Netherlands) with 5-channel cardiac coils around the chest. Perfusion MR images were acquired with a steady-state perfusion MR sequence with non-slice-selective preparation (4 short-axis imaging slices, 2 images per heart beat, repetition time of 3.0 ms, echo time of 1.2 ms, flip angle of 45 degrees, time between saturation preparation pulse and centre of k-space acquisition of 150 ms, field of view 36×32 cm, acquisition matrices of 128×128, section thickness of 8 mm). For both stress and rest perfusion MRI, gadolinium contrast medium (Gadopentetate dimeglumine, Magnevist, Schering, Berlin, Germany) was injected into the right antecubital vein at a dose of 0.05 mmol/kg and a flow rate of 4 ml/s, followed by a 20-ml saline flush. Dynamic MR images were acquired for 1 min. The subjects were instructed to begin holding their breath at the start of image acquisition and to maintain the breath hold as long as possible. In order to correct for the nonlinear relationship between the blood concentration of MR contrast medium and MR signal intensity during the first-pass, the dual bolus method was used by injecting a bolus of contrast medium diluted to 10% with saline (0.005 mmol/kg) prior to perfusion MRI, which does not cause saturation of the blood signal.[20] Pharmacological stress was achieved by injecting ATP ($160\,\mu g \cdot kg^{-1} \cdot min^{-1}$) in the left antecubital vein for 4 min. Symptoms, BP, heart rate, and ECG were monitored while the subjects were in the magnet, and any serious adverse reaction caused by the pharmacological stress was recorded throughout the MRI examination. At 3 min after starting ATP administration, the acquisition of stress myocardial perfusion MR images was initiated and ATP was continuously injected during stress perfusion MRI. Rest myocardial perfusion MRI was performed at least 10 min after finishing stress myocardial perfusion MRI.

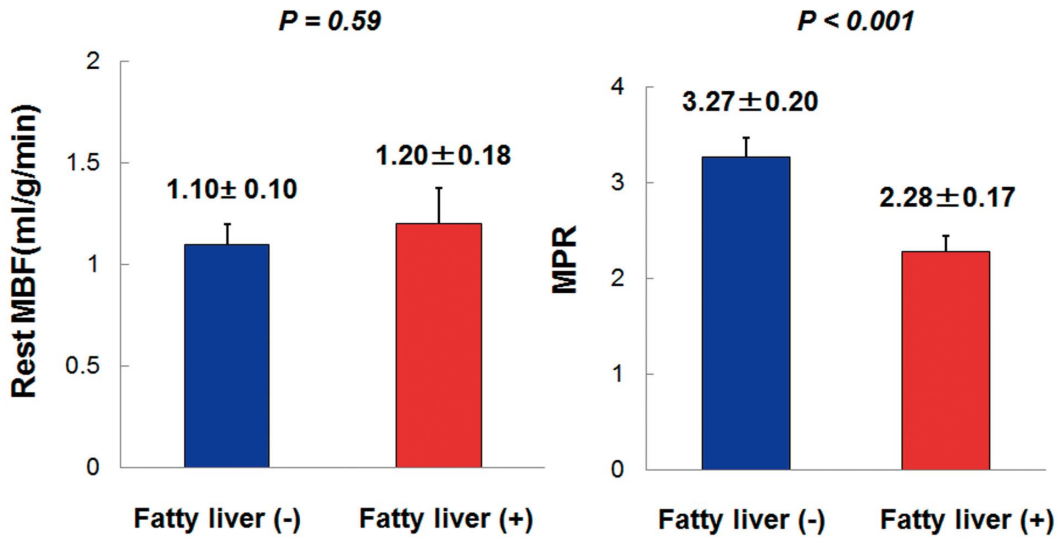

Figure 2. Comparisons of the rest myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) in patients with and without fatty liver. MPR was 3.3 in patients without fatty liver (empty columns) and 2.3 in patients with fatty liver (filled columns), indicating that MPR was significantly reduced in patients with fatty liver (P<0.001). Mean±standard error. MRI, magnetic resonance imaging.

Table 3. Multivariate Stepwise Analysis of All Subjects Using MPR as the Dependent Variable

	β	SE	P value
Age (/10 years)	–0.214	0.108	0.048
Hematocrit (%)	0.270	0.030	0.013
LV mass index (g/m²)	–0.237	0.007	0.02
Liver-spleen attenuation (HU)	0.549	0.013	<0.001

Other independent variables included in the model were sex, systolic BP, fasting glucose, total cholesterol, triglycerides, BMI, eGFR and log CRP.
Abbreviations as in Tables 1,2.

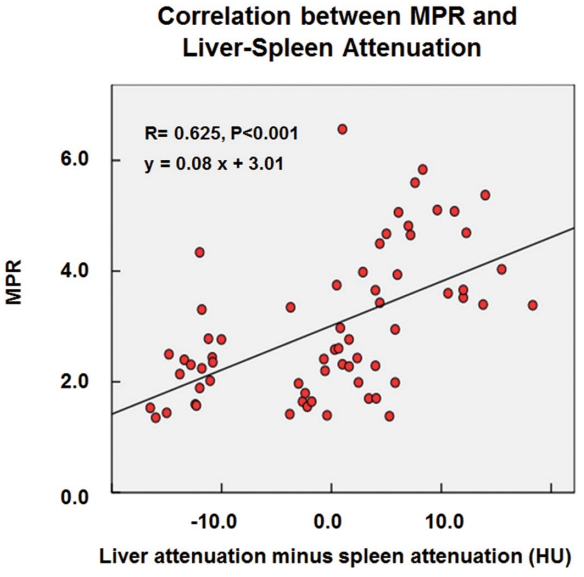

Figure 3. Correlation between myocardial perfusion reserve (MPR) and liver minus spleen attenuation. There is a significant correlation between the MPR and the difference in liver minus spleen attenuation with an R value of 0.6. HU, Hounsfield units.

MRI Analysis

Stress-rest first-pass myocardial perfusion MR images were analyzed using an image analysis workstation (Virtual Place, Aze, Tokyo, Japan). Epicardial and endocardial contours of the LV myocardium were manually determined to obtain myocardial time-intensity curves, and the ROI was placed in the LV chamber to generate the blood time-intensity curve. The LV myocardium was divided into 16 segments, comprising 6 basal segments, 6 mid-ventricular segments, and 4 apical segments based on the AHA 17-segment model and excluding the apical segment. Signal saturation of the LV blood signal was corrected using the dual bolus method. Patlak plot analysis was performed using a blood time-intensity curve as an input function and a regional myocardial time-intensity curve as an output function. The range of the least square fitting for Patlak plot analysis was automatically optimized using an algorithm that maximizes the correlation coefficient of the smallest square fitting. After calculating the perfusion parameter K1 in the 16 myocardial segments, MBF was calculated as K1 divided by the extraction fraction of Gd-DTPA, using extraction fraction values from a previous study.[21] MPR was determined as stress MBF divided by rest MBF.

Statistical Analysis

Values are presented as mean±standard deviation. Statistical analysis was performed using commercially available software (SPSS 11.0, Chicago, IL, USA). Comparisons were made be-

Table 4. Univariate and Multivariate Logistic Regression Analyses of MPR (<2.5)

Parameter	Univariate		Multivariate	
	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (/10 years)	1.89 (1.10–3.23)	0.02		
Sex	0.73 (0.27–2.01)	0.54		
Hypertension	2.63 (0.89–7.80)	0.08		
Diabetes mellitus	1.67 (0.43–6.59)	0.5		
Obesity	0.56 (0.19–1.70)	0.3		
Smoking	0.60 (0.17–2.09)	0.4		
Hypercholesterolemia	0.77 (0.26–2.28)	0.6		
Hypertriglyceridemia	4.36 (1.34–14.2)	0.02		
Hematocrit (%)	0.97 (0.87–1.09)	0.6	0.85 (0.72–1.00)	0.046
CRP (mg/dl)	7.98 (0.73–87.1)	0.09		
GFR <60 ml/min	1.54 (0.58–4.10)	0.4		
LV mass index (g/m^2)	1.02 (0.99–1.06)	0.1	1.05 (1.00–1.09)	0.03
Fatty liver	5.64 (1.6–19.8)	0.007	8.16 (1.69–39.4)	0.009

OR, odds ratio. Other abbreviations as in Tables 1,2.

tween each group using unpaired t tests for continuous variables and chi-square analysis for categorical data. Univariate analysis between MPR and liver attenuation minus spleen attenuation was performed using Spearman's correlation. To obtain an independent predictor for MPR and the presence of reduced MPR (<2.5), multivariate stepwise regression analysis and multivariate logistic regression were performed for each parameter as a dependent variable. A P-value <0.05 was considered to be significant.

Results

On CT studies, fatty liver was detected in 18 (27.7%) of the 65 subjects. Liver attenuation minus spleen attenuation was lower in patients with fatty liver when compared to subjects without fatty liver (–12.7±1.9 vs. 4.5±5.5 HU; P<0.001). Baseline clinical and biochemical characteristics of the groups are summarized in Table 1. The 2 groups did not differ with regard to age, sex, BMI, hypertension, diabetes mellitus, hypercholesterolemia, and current smoking. Subjects with fatty liver had higher concentrations of triglycerides and C-reactive protein (CRP) and lower concentrations of high-density lipoprotein (HDL) compared to those without fatty liver. Cardiac MRI parameters are presented in Table 2. There were no significant differences in ejection fraction, end-diastolic and end-systolic volumes or LV mass index (LVMI) between subjects with and without fatty liver. No major adverse reactions were observed during hyperemia. No significant differences were found between the groups for rest MBF or myocardial vascular resistance, calculated by dividing the mean arterial pressure by rest MBF, (1.2±0.75 vs. 1.1±0.67 ml·min^{-1}·g^{-1} P=0.59). However, MPR was significantly lower in subjects with fatty liver than in non-fatty liver subjects (2.3±0.74 vs. 3.3±1.4, P<0.005) (Figure 2). Subjects with fatty liver had a higher prevalence of MPR <2.5 (78% vs. 38%, P<0.005).

Table 3 shows the results of a multiple stepwise regression analysis investigating the relationships between MPR and age, BMI, systolic BP, hematocrit, fasting glucose, total cholesterol, triglycerides, estimated glomerular filtration rate (eGFR), log$_{10}$ CRP, LVMI and liver minus spleen attenuation in all subjects. Liver attenuation minus spleen attenuation was the strongest independent predictor of MPR after adjusting for all the other variables (P<0.001). Older age (P=0.048), hematocrit (P=0.013) and LVMI (P=0.020) were also independently associated with MPR. The correlation between MPR and liver minus spleen attenuation is illustrated in Figure 3. There was a significant correlation between the MPR and the difference in liver minus spleen attenuation with an R value of 0.6 (P<0.001). We also found a correlative relationship between log$_{10}$ CRP and MPR (Pearson's correlation coefficient: r=–0.31, P=0.03), and it should be noted that the CRP concentration was not significantly but only moderately associated with liver minus spleen attenuation (Pearson's correlation coefficient: r=–0.38; P=0.007). We also evaluated the univariate association of clinical variables with reduced MPR <2.5. Age, hypertriglyceridemia and the presence of fatty liver were significant predictors of reduced MPR. When all the clinical variables were considered in the multivariate logistic regression analysis, LVMI, hematocrit and fatty liver were independent predictors of reduced MPR. Presence of fatty liver (P=0.009) was strongly associated with reduced MPR (Table 4).

Discussion

Previous studies have demonstrated impaired flow-mediated dilatation in the peripheral circulation of patients with fatty liver.[8,22] However, data from flow-mediated dilatation in the brachial artery cannot be automatically extrapolated to the coronary circulation.[23] In the present study, reduced MPR was found in patients with fatty liver who had no inducible regional ischemia. LV function and rest MBF of patients with fatty liver, however, were similar to those of patients without fatty liver. Moreover, liver minus spleen attenuation was positively associated with MPR. To the best of our knowledge, this study is the first to show a direct positive relationship between liver minus spleen attenuation and MPR in subjects with a normal MRI study. Interestingly, we demonstrated that the presence of fatty liver independently reveals an 8-fold higher risk for reduced MPR, even after taking classical coronary risk factors and other potential confounders into consideration.

Ultrasonography (US) is widely available and is a low-cost technique for the diagnosis of fatty liver. However, the main disadvantages of US are the inherent subjectivity of the technique, the lack of specificity, and the inability to quantify the degree of steatosis. In a recent systematic review investigating the diagnostic performance imaging techniques for the evalu-

ation of fatty liver compared to liver biopsy, mean specificity ranges were 69.6–85.2% (US) and 88.1–94.6% (CT).[24] CT is more specific for the diagnosis of fatty liver and accurate for a semiquantitative evaluation of macrovesicular steatosis of 30% or greater,[25] although it has comparable sensitivity and is somewhat limited due to the patient's exposure to ionizing radiation. For these reasons, non-contrast CT was used for the diagnosis of fatty liver. In the current study, we found that liver enzyme concentrations were normal or only mildly elevated in patients with fatty liver diagnosed by CT, which is in agreement with previous observations.[1] Thus, many patients with fatty liver remain undiagnosed until other significant manifestations of the disease occur.

Regarding the mechanisms of the effect of fatty liver disease on reduced MPR, we considered the following. First, systemic inflammation has been linked to both fatty liver[26] and CAD, and therefore would be a potential underlying mechanism common to fatty liver and impaired MPR. In the present study, there was a correlative relationship between $\log_{10}$ CRP and MPR, and it should be noted that the CRP concentrations differed among the patients with and without fatty liver, and was not significantly but only moderately associated with liver minus spleen attenuation. The results may be explained by the fact that coronary microvascular dysfunction partly reflects the early stage of coronary atherosclerosis. Second, oxidative stress, which may play a separate role in the progression of fatty liver, is another possible underlying mechanism linking fatty liver and atherosclerosis. We therefore cannot exclude the possibility that the progression of liver fat content may cause increased oxidative/inflammatory stress, which in turn may affect MPR.

The effects of other factors influencing MPR can be argued. Although a high triglyceride concentration showed significant univariate association with reduced MPR, this relationship was no longer significant in the multivariate analysis. This observation in our study supports previous work by Yokoyama et al who reported that myocardial vasodilatation was reduced in patients with hypertriglyceridemia without overt coronary stenosis.[27] Previous reports have shown that MBF and MPR are affected not only by classical coronary risk factors, such as hypertension, dyslipidemia, and diabetes mellitus,[28–32] but also anemia, LVMI and renal dysfunction.[33–35] Inconsistent with earlier works, the present study indicates that fatty liver rather than diabetes mellitus, hypercholesterolemia and hypertension is strongly associated with reduced MPR. It should be noted that the prevalence of diabetes mellitus was low (15%) and diabetes mellitus and hypercholesterolemia was not severe in the subjects in this study (fasting glucose: 107±18 in patients with fatty liver vs. 99±19 mg/dl in control subjects; HbA_{1c}: 5.5±0.8 vs. 5.3±0.5%;total cholesterol: 201±30 vs. 193±40 mg/dl). There are numerous mechanisms that may explain impaired MPR in patients with hypertension, including higher myocardial oxygen consumption,[36] and reduced coronary microvascular bed in the presence of LV hypertrophy.[34] However, all subjects had normal LV morphology and function, which may explain the discrepancy in the results. Although we found no association between subclinical alteration of MPR and classical coronary risk factors, diabetes mellitus, hypercholesterolemia, hypertension, smoking, and MetS are, as a matter of course, also associated with coronary microvascular dysfunction in the general population.

Study Limitations

Several limitations should be acknowledged in this study. First, the study was limited to subjects who had undergone cardiac MRI and therefore this is not an epidemiological study. Second, we cannot exclude the possibility that the duration of hepatic fatty infiltration may be a determining factor for MPR, because we observed a cross-association between the degree of fatty liver and MPR. The small number of subjects and the non-performance of confirmatory liver biopsies for ethical reasons should be pointed out.

In conclusion, patients with fatty liver showed decreased MPR compared to patients without fatty liver. Altered MPR may indicate an early alteration in myocardial tissue and vascular properties in patients with fatty liver. The presence and severity of fatty liver on CT were closely associated with reduced MPR, independent of classical risk factors. The casual detection of fatty liver on CT examination should alert the clinician to the potential coexistence of impaired microcoronary circulation. This may represent the early stages of atherosclerosis and warrant evaluation and treatment for CAD, as well as assessing the risk for advancing liver disease. Further study is recommended to assess the pathophysiological pathways and prognostic significance of the relationship between fatty liver and altered MPR.

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