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Flow in the left anterior descending coronary artery in patients with cirrhosis

Przepływ w gałęzi przedniej zstępującej lewej tętnicy wieńcowej u pacjentów z marskością wątroby

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Abstract

Introduction. Although cardiac function appears normal in patients with cirrhosis at rest, cardiac function deteriorates in these patients under stress conditions. Decreased cardiac function against stress may be due to coronary microvascular dysfunction in these patients. In this study, we aimed to evaluate coronary microvascular dysfunction in patients with cirrhosis by measuring coronary flow reserve (CFR) by transthoracic echocardiography.

Materials and methods. Thirty-eight patients with cirrhosis and 32 healthy subjects (as control group) were examined. In addition to standard two-dimesional (2D) and Doppler echocardiography, coronary flow velocity was measured by pulsed-wave Doppler from the middle to the distal part of the left anterior descending artery at the beginning and after dipyridamole infusion in the hyperemic state. CFR was measured as the ratio of hyperemic peak diastolic flow rate to basal peak diastolic flow rate.

Results. CFR was significantly lower in the cirrhosis group than in the control group (2.01 ± 0.31 and 2.84 ± 0.62; $p < 0.0001$). Increasing age, increasing myocardial mass, high aspartate aminotransferase and alanine aminotransferase, low hemoglobin, high C-reactive protein, decreased cholesterol and platelet levels were found to be associated with the reduction in CFR. Among all these factors only, the hemoglobin level and age were independent determinants of impaired CFR.

Conclusions. Impaired CFR in patients with cirrhosis promotes coronary microvascular dysfunction. The coronary microvascular dysfunction can potentially contribute to the development of cirrhotic cardiomyopathy.

Key words: echocardiography, coronary flow reserve, cirrhosis

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Introduction

There are several structural and functional cardiovascular changes in end-stage liver disease and these cardiovascular changes are known as cirrhotic cardiomyopathy [1]. Cardiac function in cirrhotic cardiomyopathy appears normal at rest, but heart cannot give the expected response to stress. For example, ventricular inotropic and chronotropic response in patients with cirrhosis is impaired in physical exercise and ejection fraction (EF) of left ventricular (LV) is depressed during stress even if it is normal at rest [2, 3].

Coronary flow reserve (CFR) measured by transthoracic Doppler echocardiography (TTDE) evaluates microvascular myocardial function in the absence of epicardial coronary artery stenosis [4]. TTDE is a highly practical (easily applicable at the bedside), non-invasive, easily reproducible and inexpensive method of assessing CFR without radiation exposure. CFR measurement by TTDE was confirmed by positron emission tomography and Doppler wire measurement methods used to evaluate CFR [5, 6]. In this study, we aimed to evaluate coronary microvascular dysfunction by measuring TTDE in patients with cirrhosis without coronary artery disease.

Materials and methods

Study population

Thirty-eight cirrhotic patients (mean age 46 ± 10 years, 26 male) diagnosed by either liver biopsy and/or laboratory, clinical and ultrasonography findings were included in the study. The control group of 32 healthy individuals of similar age and sex were included in the study group. The study protocol was in conformity with the Declaration of Helsinki and has been approved by the institutional ethics committee.

Criteria of the exclusion from the study were determined as coronary artery disease (CAD), diabetes mellitus, hypertension, severe heart valve disease, chronic heart failure, hypertrophic cardiomyopathy, rhythms other than sinus rhythm, renal dysfunction, thyroid disease, chronic obstructive pulmonary disease, pulmonary hypertension, cor pulmonale, and poor echocardiographic image quality.

Systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg in at least two measurements or the use of any antihypertensive drug therapy was defined as hypertension in patients. Diabetes mellitus was defined as the use of active antidiabetic drugs or fasting plasma glucose levels higher than 126 mg/dL or glucose levels higher than 200 mg/dL in any measurement.

The severity of cirrhosis was calculated based on the five clinical features of the patient: 1) total bilirubin level, 2) prothrombin time, 3) serum albumin, 4) acid grade and 5) hepatic encephalopathy grade. The total score of the patient was used to determine the Child-Pugh class [7].

Echocardiographic examination and evaluation of coronary flow reserve

Each patient underwent TTDE. Acuson Sequoia C256 ultrasound machine (Mountain View, CA, USA) was used. All patients included in the study underwent standard 2D and Doppler echocardiography in accordance with standard echocardiography guidelines [8]. EF was calculated using the modified Simpson's method. Myocardial performance index (MPI) of LV were calculated using TDI of the mitral annulus. LV mass was measured using Devereux's formula [9].

The distal part of the LAD coronary artery in the epicardial part of the anterior wall of the heart was examined by modifying the apical 2-chamber image. Coronary flow velocities were recorded from the middle distal part of LAD coronary artery by pulse Doppler wave. Coronary flow rate was measured in a typical biphasic flow pattern consisting of diastolic and systolic components. Hyperemia was induced by infusion of 0.56 mg/kg dipyridamole for 4 minutes. Coronary diastolic peak velocities (DPV) were measured at baseline and hyperemia (Figure 1). The highest 3 Doppler recordings were averaged for each measurement. CFR was calculated as the ratio of hyperemic to baseline DPV [10]. In many studies, CFR value ≥ 2 has been considered normal [11–13]. Normal cut-off value for CFR ≥ 2 accepted and patients were divided into two groups as group 1 (49 patients) with preserved CFR ≥ 2 and group 2 (21 patients) with impaired CFR < 2.

Statistical analyses

Normal distribution of continuous variables was controlled by the Shapiro-Wilk test. Student's *t* test was used to compare the two groups with respect to the variables with normal distribution and homogeneous group variances. Mann Whitney U test was used for non-homogeneous variables. The results were expressed as mean ± standard deviation and median value. Categorical variables were analyzed using Fisher Exact test. Stepwise multivariate logistic regression analysis was performed to investigate the effect of other variables on CFR. A $p < 0.05$ was considered statistically significant. The data set was evaluated using the SPSS program (Statistical Package for the Social Sciences, version 16; SSPS Inc., Chicago, Illinois).

Results

The clinical and laboratory variables of the two groups were compared in Table 1. There were no differences in age and sex between patients and controls. Serum total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, hemoglobin and platelet levels were significantly lower and C-reactive protein (CRP), aspartate aminotransferase (AST), alanine

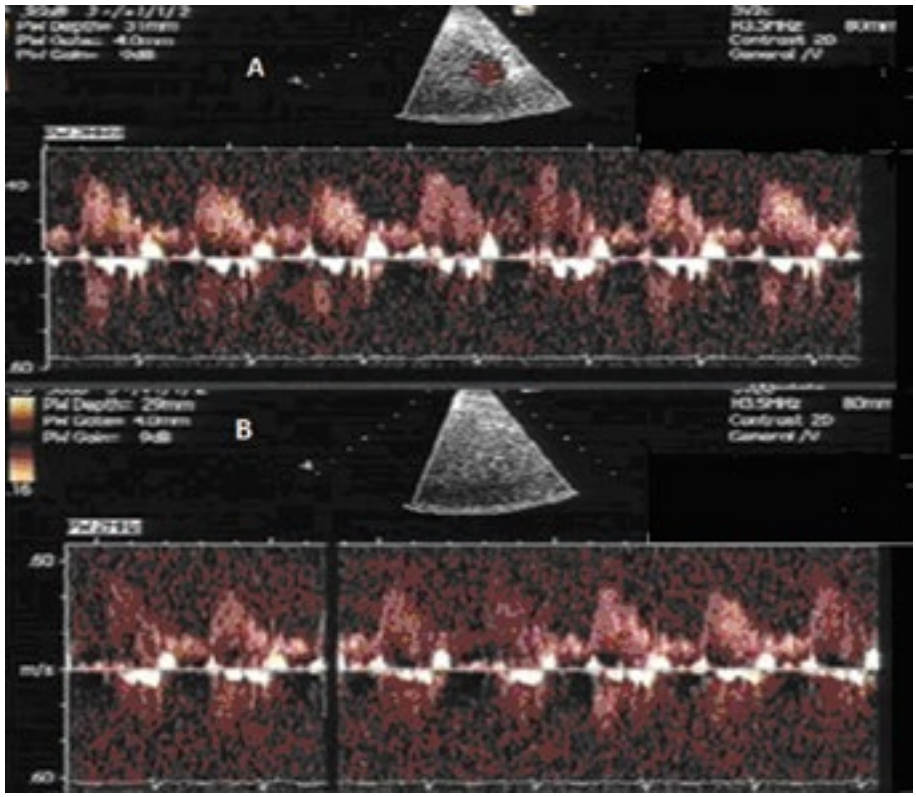

Figure 1. Upper illustrates the distal left anterior descending artery coronary flow by color Doppler and illustrates the corresponding pulsed wave Doppler of the coronary flow with diastolic dominance at hyperemia (**A**); display as (**B**) at rest. Note the increase in coronary flow velocities

Table 1. Baseline clinical characteristics and laboratory findings of the groups

Parameter	Cirrhosis (N = 38)	Control (N = 32)	p value
Age	46 ± 10	41 ± 12	0.07
Men/woman	26/12	18/14	0.4
Body surface area [m^2]	1.8 ± 0.1	1.8 ± 0.1	0.5
Systolic blood pressure [mm Hg]	109 ± 11	117 ± 9	**0.003**
Diastolic blood pressure [mm Hg]	68 ± 7	75 ± 6	**< 0.0001**
Heart rate [beats/min]	73 ± 11	74 ± 13	0.6
Laboratory findings			
Creatinine [mg/dL]	0.7 ± 0.2	0.8 ± 0.2	0.2
LDL cholesterol [mg/dL]	62.9 ± 20.8	98.1 ± 32.4	**< 0.0001**
Triglycerides [mg/dL]	82.0 ± 50.6	109.9 ± 47.0	**0.002**
CRP [mg/L]	13.9 ± 13.5	1.9 ± 2.4	**< 0.0001**
AST [U/L]	69.9 ± 50.8	22.1 ± 8.5	**< 0.0001**
ALT [U/L]	43.2 ± 27.2	20.5 ± 18.2	**< 0.0001**
Hemoglobin [g/dL]	11.3 ± 2.1	14.4 ± 1.7	**< 0.0001**
Platelets [× $10^3/\mu L$]	101.8 ± 62.4	253.7 ± 65.0	**< 0.0001**

LDL — low-density lipoproteins; CRP — C-reactive protein; AST — aspartate aminotransferase; ALT — alanine aminotransferase

Table 2. Transthoracic two-dimensional and Doppler echocardiography findings

Parameter	Cirrhosis (N = 38)	Control (N = 32)	p value
IVS [cm]	1.07 ± 0.11	1.00 ± 0.09	**0.006**
PW [cm]	1.06 ± 0.11	1.00 ± 0.09	**0.002**
LAD [cm]	3.84 ± 0.43	3.42 ± 0.32	**< 0.0001**
Mitral E [cm/s]	86.7 ± 18.0	86.5 ± 14.9	0.9
E/A ratio	1.2 ± 0.3	1.2 ± 0.2	0.5
Mitral E-wave DT [ms]	216.6 ± 30.0	210.7 ± 26.3	0.6
IVRT [ms]	107.1 ± 15.7	90.4 ± 15.0	**0.03**
End-diastolic volume [mL]	105.5 ± 20.8	93.0 ± 15.3	**0.006**
End-systolic volume [mL]	43.5 ± 9.9	36.6 ± 7.3	**0.001**
Ejection fraction [%]	59.0 ± 2.3	60.1 ± 3.0	0.07
LV mass index [g/m^2]	106.7 ± 16.8	88.5 ± 11.3	**< 0.0001**

IVS — interventricular septum; PW — posterior wall; LAD — left atrium diameter; E/A — early diastolic annular velocity; DT — deceleration time; IVRT — isovolumetric relaxation time; LV — left ventricular

Table 3. Corresponding pulsed wave Doppler of coronary flow

Parameter	Cirrhosis (N = 38)	Control (N = 32)	p value
Baseline PSV [cm/s]	19.9 ± 2.8	20.3 ± 3.3	0.6
Baseline PDV [cm/s]	30.1 ± 4.1	28.1 ± 4.7	**0.006**
Hyperemic PSV [cm/s]	32.1 ± 5.5	41.3 ± 9.1	**< 0.0001**
Hyperemic PDV [cm/s]	60.7 ± 10.6	78.9 ± 16.5	**< 0.0001**
Coronary flow reserve	2.01 ± 0.31	2.84 ± 0.62	**< 0.0001**

PSV — peak systolic velocity; PDV — peak diastolic velocity

aminotransferase (ALT) levels were higher in patients with cirrhosis compared with the control group.

There were no significant differences with regard to ejection fraction; however, left ventricular wall thickness, left atrial diameter, left ventricular volumes and left ventricular mass were higher in patients with cirrhosis compared with the control group (Table 2). Additionally, MPI of LV were higher in patients with cirrhosis than in controls (0.28 ± 0.04 and 0.23 ± 0.05, p = 0.001).

The mean baseline peak systolic coronary flow velocity was also similar in both groups. However, baseline peak diastolic coronary flow velocity, hyperemic peak systolic coronary flow velocity, hyperemic peak diastolic coronary flow velocity was significantly lower in patients with cirrhosis compared with the control group (Table 3). CFR was significantly less in liver transplant candidates than in the control group (2.01 ± 0.31 and 2.84 ± 0.62; p < 0.0001). The groups included in the study were compared in Table 4 for preserved and impaired CFR. Age and left ventricular mass were higher and hyperemic heart rate was lower in the group 2. Among laboratory parameters, AST, ALT, CRP, total cholesterol, hemoglobin and platelet values were found to be statistically different between group 1 and group 2. Beta-blocker and diuretic use were more frequent in group 2. Univariate logistic regression analysis was performed in terms of parameters affecting microvascular dysfunction and age, myocardial mass index, AST, ALT, hemoglobin, CRP, total cholesterol and platelet values were found to affect CFR (Table 5A). However, stepwise multivariate logistic regression analysis revealed that only hemoglobin and age were determinant for CFR. It was observed that the probability of CFR to be below 2 was increased 1.5 times for each unit of hemoglobin decrease and 1.1 times for each age increase (Table 5B).

Among patients with cirrhosis, the most frequent underlying disease was hepatitis B infection (42.1%), cryptogenic cirrhosis (18.4%), hepatitis C infection (15.7%), alcohol (10.5%) primary sclerosing cholangitis (2.6%), ulcerative colitis (2.6%) and other causes (7.8%). Regarding the Child-Pugh Scoring for cirrhosis, 47.3% of the cirrhotic patients were stratified in the Child score B, 44.7% of the

Table 4. The comparison of patients with impaired and preserved coronary flow reserve (CFR)

Parameter	CFR ≥ 2	CFR < 2	p value
Age [y]	**42.06 ± 11.73**	**48.71 ± 8.6**	**0.01**
Gender [E]	29 (59%)	15 (71%)	NS
Body surface area [m^2]	1.84 ± 0.15	1.83 ± 0.21	NS
Basal heart rate [beats/min]	74 ± 12	73 ± 10	NS
Basal SBP [mm Hg]	114 ± 11	109 ± 10	NS
Hyperemic heart rate [beats/min]	**92 ± 16**	**81 ± 11**	**0.01**
Hyperemic SBP [mm Hg]	107 ± 10	105 ± 16	NS
LV mass index [g/m^2]	**93.85 ± 14.81**	**108.09 ± 18.29**	**0.003**
Ejection fraction [%]	**59.73 ±2.82**	**59.05 ± 2.50**	**NS**
Glucose [mg/dL]	92.0 ± 12.1	97 ± 15.1	NS
Creatinine [mg/dL]	0.8 ± 0.2	0.7 ± 0.2	NS
AST [U/L]	**38.1 ± 29.0**	**75.1 ± 62.3**	**0.004**
ALT [U/L]	**28.4 ± 21.8**	**43.1 ± 32.0**	**0.009**
GGT [U/L]	44.40 ± 41.50	38.05 ± 24.36	NS
Hemoglobin [g/dL]	**13.3 ± 2.4**	**11.4 ± 2.1**	**0.006**
Platelets [× $10^3/\mu L$]	**192.4 ± 102.6**	**123.0 ±70.1**	**0.01**
Total cholesterol [mg/dL]	**142.7 ± 42.6**	**115.4 ± 41.9**	**0.04**
HDL cholesterol [mg/dL]	44.6 ± 6.6	34.7 ±16.1	NS
LDL cholesterol [mg/dL]	83.6 ± 34.4	66.1 ± 20.8	NS
Triglycerides [mg/dL]	96.6 ± 43.9	90.6 ± 65.5	NS
C-reactive protein [mg/L]	**6.9 ± 10.8**	**15.0 ± 13.7**	**0.001**

NS — non significant; SBP — systolic blood pressure; LV — left ventricle; AST — aspartate aminotransferase; ALT — alanine aminotransferase; GGT — gamma-glutamyl transferase; HDL — high-density lipoprotein; LDL — low-density lipoprotein

Table 5A. The determinants of impaired coronary flow reserve (CFR) according to the univariate logistic regression analysis

Parameter	Risk ratio	Confidence interval	Beta	p value
Age [y]	1.04	0.99–1.09	0.05	0.06
Myocardial mass index [g/m^2]	1.05	1.01–1.09	0.05	**0.01**
AST [U/L]	1.02	1.01–1.04	0.02	**0.01**
ALT [U/L])	1.02	0.90–1.04	0.02	0.07
Hemoglobin [g/dL]	1.40	1.09–1.79	–0.33	**0.01**
CRP [mg/L]	1.05	1.01–1.11	0.05	**0.03**
Total cholesterol [mg/dL]	1.01	1.01–1.03	–0.014	0.05
Platelets [× $10^3/\mu L$]	1.01	1.00–1.01	–0.007	**0.01**

AST — aspartate aminotransferase; ALT — alanine aminotransferase; CRP — C-reactive protein

Table 5B. Independent determinants for impaired coronary flow reserve (CFR) according to stepwise multivariate logistic regression analysis

Parameter	Risk ratio	Confidence interval	Beta	p value
Hemoglobin [g/dL]	1.5	1.07–2.11	–0.40	**0.01**
Age [year]	1.1	1.01–1.18	0.08	**0.04**

patients were classified as Child score C and 7.8% of them were categorized in the child score A.

Discussion

This study shows that CFR is impaired in patients with cirrhosis. This result supports coronary microvascular dysfunction in these patients. The inflammatory environment is likely to cause coronary microvascular dysfunction in patients with cirrhosis. Coronary microvascular dysfunction may play an important role in the pathogenesis of cirrhotic cardiomyopathy.

Cirrhotic cardiomyopathy is a clinical syndrome with abnormalities in the beta-adrenergic signaling pathway and cardiomyocyte plasma membrane and pathogenetic mechanisms in which vasodilator cytokine levels such as nitric oxide are increased [14]. However, the role of coronary microvascular dysfunction in the development of cirrhosis cardiomyopathy is unknown. CFR demonstrates the ability of the microvascular system to react to a stimulus [15]. CFR is used to evaluate microvascular function [16, 17]. In our study, CFR was lower in patients with cirrhosis than in the control group. Decreased CFR is an important prognostic finding [17, 18]. It has been reported that impaired coronary microvascular function is reversible in the absence of significant epicardial coronary stenosis [19].

We found that increasing age, increasing myocardial mass, high aspartate aminotransferase and alanine aminotransferase, low hemoglobin, high C-reactive protein, decreased cholesterol and platelet levels were found to be associated with the reduction in CFR. Among all these factors, only the hemoglobin level and age were independent determinants of impaired CFR. Increasing age is a well-known cause of decreased CFR [20], but in our study there was no age difference between the groups. In a previous study no alterations of CFR in anemia were found [21]. Our study found a relationship between low hemoglobin and impaired CFR. This highlights the role of anemia in the deterioration of cardiovascular function in patients with cirrhosis and may be a guide in the planning of treatment. Our study showed that LV mass was increased in patients with cirrhosis and associated with decreased CFR. Previous studies have reported conflicting data on the effect of LV hypertrophy on CFR. In some publications, it has been reported that LV hypertrophy is a factor that decreased CFR [19], but not in others [22]. Our findings suggest that myocardial hypertrophy, which is involved in the mechanisms of cirrhotic cardiomyopathy, could be another factor playing a role in coronary microvascular function impairment. Studies have shown that there is a consistent association between the progression of cirrhosis and systolic and diastolic myocardial dysfunction [23, 24]. In our study, there was also a relation between decreased CFR and deterioration in liver function. That is, we found lower total cholesterol, lower thrombocyte, elevated AST and ALT associated with the decrease in CFR. Previous studies have shown an increase in CRP production in patients with cirrhosis [25]. In our study, we found that CRP levels were higher in patients with cirrhosis and CRP was associated with decreased CFR. This result suggests that increased inflammatory status in cirrhotic patients may contribute to the development of coronary microvascular dysfunction.

Earlier studies have shown that early stage atherosclerosis reduces CFR [26]. In our study decreased CFR in patients with cirrhosis may be indicative of early stage atherosclerosis. This conclusion suggests that further risk adjustment and more preventive treatment may be necessary to prevent CAD in cirrhotic patients.

Previous studies have shown that LVEF is normal at rest in the majority of patients with cirrhosis [24, 27]. In our study, we also found a similar EF in cirrhosis and control groups but the end-diastolic and end-systolic volumes were found to be higher in patients with cirrhosis, probably due to increased volume loading. Moreover, MPI of LV was higher in patients with cirrhosis than in controls. High MPI supports subclinical LV systolic dysfunction in these patients.

The study has some limitations. Our study had limited number of patients. We evaluated CFR noninvasively by TTE instead of using invasive measurements. CFR calculated by TTE has an excellent correlation with CFR calculated by positron emission tomography [5] and Doppler wires [28]. In our institutional experience also, noninvasive measurement of CFR by TTE yielded very reproducible results as previously reported [29]. Another important restriction was not all patients underwent coronary angiography. Myocardial perfusion scintigraphy was performed in 28 patients in the evaluation of cirrhosis patients before liver transplantation. Coronary angiography was performed in 14 patients with abnormal myocardial perfusion scintigraphy (due to perfusion abnormality) and coronary angiographies of these patients were normal.

Conclusion

In conclusion, decreased CFR values in patients with cirrhosis show the presence of coronary microvascular dysfunction. The coronary microvascular dysfunction can potentially contribute to the development of cirrhotic cardiomyopathy. Clinical management of cirrhotic cardiomyopathy remains uncertain because of lack of the clinical evidence and challenging diagnosis of the disease. Therefore, we believe that CFR may be useful in early diagnosis of cirrhotic cardiomyopathy and may lead to a change in cirrhosis treatment.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Wstęp. Chociaż czynność serca u pacjentów z marskością wątroby oceniana w spoczynku wydaje się prawidłowa, to w warunkach wysiłku fizycznego lub obciążenia farmakologicznego ulega ona pogorszeniu. Zaburzenie czynności serca podczas obciążenia może być spowodowane dysfunkcją mikrokrążenia wieńcowego u tych chorych. Celem badania była ocena dysfunkcji mikrokrążenia wieńcowego u pacjentów z marskością wątroby przez pomiar rezerwy przepływu wieńcowego (CRF) za pomocą echokardiografii przezklatkowej.

Materiał i metody. Do badania włączono 38 chorych z marskością wątroby i 32 osoby zdrowe (grupa kontrolna). Oprócz standardowej echokardiografii dwuwymiarowej (2D) i echokardiografii doplerowskiej prędkość przepływu wieńcowego w odcinkach środkowym i dystalnym gałęzi przedniej lewej tętnicy zstępującej zmierzono za pomocą badania doplerowskiego metodą fali pulsacyjnej bezpośrednio przed wlewem dipirydamolu i po nim. Rezerwę przepływu wieńcowego mierzono jako stosunek maksymalnego przepływu rozkurczowego w obciążeniu do maksymalnego przepływu rozkurczowego w spoczynku.

Wyniki. Rezerwa przepływu wieńcowego była istotnie niższa w grupie z marskością wątroby niż w grupie kontrolnej (2,01 ± 0,31 i 2,84 ± 0,62; p < 0,0001). Stwierdzono, że ze zmniejszeniem CFR wiązały się: wiek, zwiększenie masy mięśnia sercowego, wysoka aktywność aminotransferaz asparaginianowej i alaninowej, niskie stężenie hemoglobiny, wysokie stężenie białka C-reaktywnego, obniżone stężenie cholesterolu i zmniejszona liczba płytek krwi. Jednak tylko stężenie hemoglobiny i wiek były niezależnymi determinantami zmniejszonej CFR.

Wnioski. Zmniejszenie CFR u chorych z marskością wątroby sprzyja dysfunkcji mikrokrążenia wieńcowego, która może prowadzić do rozwoju kardiomiopatii wątrobowej (marskiej).

Słowa kluczowe: echokardiografia, rezerwa przepływu wieńcowego, marskość

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