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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The relationship between circulating microRNAs and left ventricular mass in symptomatic heart failure patients with systolic dysfunction

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Abstract

Background: In recent years, many microRNAs (miRNAs) were shown to be dysregulated in specific tissues playing critical roles in the pathogenesis and progression of heart failure (HF). Left ventricular (LV) mass (LVM) has long been recognised as an important prognostic marker in systolic HF patients.

Aim: We hypothesised that circulating miRNAs may be associated with LVM in systolic HF patients. The present study aimed to evaluate the relationship between previously reported and novel dysregulated circulating miRNAs and echocardiographically determined LVM in symptomatic HF patients with LV systolic dysfunction.

Methods: Forty-two consecutive patients diagnosed with NYHA II–IV symptomatic systolic HF and a control group consisting of 15 age- and sex-matched healthy volunteers were enrolled. After labelling extracted RNA, poly-A tails were added. RNAs were later hybridised on a GeneChip miRNA 2.0 array. After hybridisation and staining, arrays were scanned to determine miRNA expression levels, and differentially expressed miRNAs were identified.

Results: Eighteen miRNAs were found to be upregulated in serum of HF patients, while 11 were demonstrated to be downregulated. When the association between dysregulated miRNAs and echocardiographic findings was investigated, miR-182 ($p = 0.04$), miR-200a* ($p = 0.019$), and miR-568 ($p = 0.023$) were found to be inversely correlated with LVM index (LVMI), while miR-155 ($p = 0.019$) and miR-595 ($p = 0.04$) were determined to be positively correlated with LVMI.

Conclusions: The results of our study revealed that dysregulated circulating miRNAs were correlated with anatomic changes in LV, in terms of LVMI, in symptomatic HF patients with systolic LV dysfunction.

Key words: miRNA, left ventricular mass, systolic heart failure

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INTRODUCTION

MicroRNAs (miRNAs) are endogenous small RNAs comprising approximately 18–23 nucleotides, which bind to the 3′-untranslated region of mRNAs of protein-coding genes to downregulate their expression [1]. miRNAs are crucial for virtually all cellular processes and have been suggested to be prerequisite for various cardiovascular (CV) conditions such us hypertrophy, heart failure (HF), and acute coronary syndromes. In this context, miRNAs have been postulated to be circulating freely in the bloodstream with marked bio-stability. They can be detected with high sensitivity and specificity in human plasma and serum [2]. In recent years, many miRNAs were shown to be dysregulated in specific tissues playing critical roles in the pathogenesis and progression of the HF [3]. Left ventricular mass (LVM) has long been recognised as an important prognostic marker in systolic HF patients [4]. The association between dysregulated miRNAs and LVM in the context of systolic HF has not been previously studied in detail.

The present study aimed to evaluate the relationship between previously reported and novel dysregulated circulating miRNAs and echocardiographically determined LVM in symptomatic HF patients with left ventricular (LV) systolic dysfunction.

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METHODS

Study subjects

Forty-two consecutive patients diagnosed with New York Heart Association (NYHA) II–IV symptomatic systolic HF in a university hospital between April 2012 and September 2012 were enrolled in this study. Subjects were classified as HF when they met the 2009 American College of Cardiology/American Heart Failure Guidelines for the Diagnosis and Treatment of Heart Failure criteria [5]. The control group consisted of 15 age- and sex-matched healthy volunteers who did not have history of any CV risk factors or illnesses. Inclusion criteria for the HF group were as follows: age > 18 years, presence of symptomatic HF, and an LV ejection fraction (LVEF) ≤ 40% as determined by echocardiography. Exclusion criteria were the presence of acute coronary syndrome, primary valvular heart disease as the cause of HF, pericardial disease, congenital heart disease, pregnancy, moderate or severe renal failure, liver failure, chronic systemic inflammatory conditions, and known or treated malignancies.

Echocardiography

All subjects underwent standard trans-thoracic echocardiographic examination on the day of serum collection, performed by a cardiologist blinded to their clinical characteristics. The examinations were carried out using a "Vingmed System Five" echocardiography machine (GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz probe. All cardiac chamber measurements were made as suggested by the American Society of Echocardiography, including LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), end-diastolic interventricular septum thickness (IVSD), end-diastolic LV posterior wall thickness (LVPWd) were measured using two-dimensional (2D), or M-mode images taken from parasternal long axis views of the LV [6]. From 2D images of the LV obtained from apical four-chamber views, LVEF (%) was calculated using the area-length method [7] by subtracting the estimated LV end-systolic volume (LVESV) from the LV end-diastolic volume (LVEDV) and dividing it by the LVEDV and multiplying by 100. LVM was calculated using the following formula: $0.80 \times (1.04\,(IVSD + LVPWd + LVEDD)^3 – LVEDD^3 + 0.6$ g. Body surface area (BSA) was calculated by the Dubois and Dubois formula: $BSA = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$. LVM index (LVMI) was calculated by dividing the LVM by the BSA. Pulmonary artery systolic pressure (PASP) was estimated by multiplying the square of the peak tricuspid regurgitant flow velocity by four (modified Bernoulli equation) and adding the right atrial pressure as estimated from the change in inferior vena caval diameter with inspiration.

RNA isolation

Blood samples were collected and serum was separated by centrifuging at 3000 rpm for 10 min (Fig. 1). RNA was extracted from serum samples using Qiagen miRNeasy Serum/Plasma Kit (Cat. No 217184, QIAGEN, gMBh, D-40724 Hilden, Germany) according to the manufacturer's specifications. Concentration and purity of RNA samples were measured with a NanoDrop 2000c spectrophotometer. All RNA samples were run on agarose gel to assess their integrity. Samples failing to meet the quality and quantity criteria were either re-isolated or completely discarded. Suitable samples were stored at -80°C until microarray analysis.

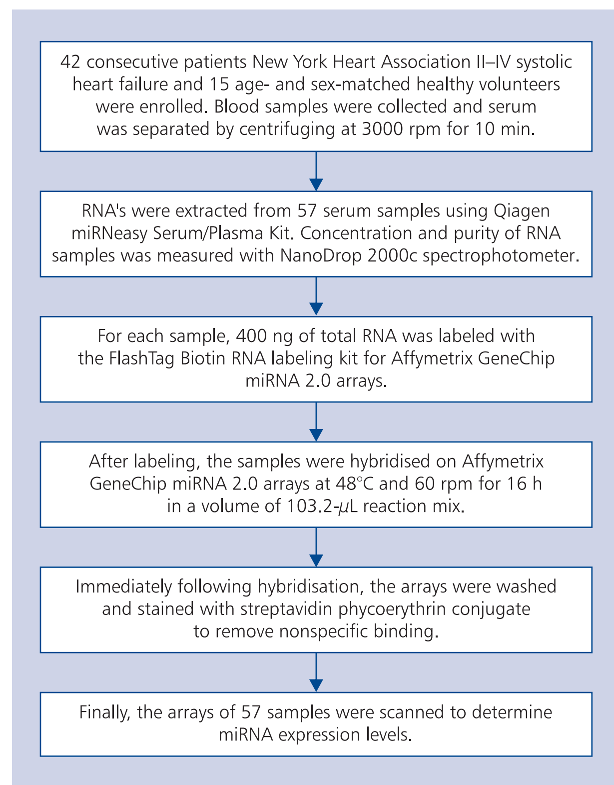

Figure 1. Methods of blood analysis

Microarray procedure

For each sample, 400 ng of total RNA was labelled with the FlashTag Biotin RNA labelling kit for Affymetrix GeneChip miRNA 2.0 arrays (Affymetrix, Santa Clara, CA, USA) according to the manufacturer's instructions. A tailing reaction was carried out at 37°C for 15 min in a volume of 15 μL reaction mix (10 μL of total RNA and spike control oligos mix, 1 × reaction buffer, 1.5 mM MnCl2, ATP, and 1 mL poly A polymerase enzyme) followed by the ligation of the biotinylated signal molecule to the target RNA sample at 25°C for 30 min (with the addition of 4 μL of 5 × FlashTag Ligation Mix Biotin and 2 μL of T4 DNA Ligase into the 23.5 mL of reaction mix). Finally, 2.5 mL of stop solution was added to stop the reaction. After labelling, the samples were hybridised on Affymetrix GeneChip miRNA 2.0 arrays (Affymetrix, Santa Clara, CA, USA) at 48°C and 60 rpm for 16 h in a volume of 103.2-μL reaction mix (which contained

21.5 μL of total biotin-labelled RNA, 50 μL hybridisation mix, 15 μL formamide, 10 μL DMSO, 5 μL eukaryotic hybridisation controls, and 1.7 μL control oligonucleotide B2). Immediately after hybridisation the arrays were washed and stained with streptavidin phycoerythrin conjugate to remove nonspecific binding. Finally, they were scanned to determine miRNA expression levels.

Statistical and bioinformatics analysis

Partek Genomics Suite (Partek Incorporated, MO, USA) was facilitated for the analysis of the raw microarray data. Visualisation of circulating miRNA expression profiles were carried out in HF patients and controls. Differentially expressed miRNAs were identified using significance analysis of microarrays (SAM), Student's T test, and one-way ANOVA. miRNAs with a fold change greater than 1.2 and a p-value less than 0.05 were chosen for further analysis in order to investigate their correlation with clinical parameters, in concordance with previous biomarker validation studies. SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA) was used for further statistical evaluation of the consequent findings and clinical parameters. Shapiro-Wilk test was used to assess the normality of the obtained data, while Pearson and Spearman tests were utilized to perform correlation analyses. The associations between continuous and categorical variables were analysed with either student's t test or Mann-Whitney U test. The associations between categorical variables were analysed using either χ^2 or Fisher's exact test. An alpha level of 0.05 was used when determining significance in all statistical analyses.

Ethics statement

The protocol of the study was carried out according to the principles of the Declaration of Helsinki and approved by local Ethics Committee (number: 03.04.2012/10058) [8]. Written informed consent was obtained from all the participants before enrolment.

RESULTS

A total of 42 HF patients and 15 healthy controls were enrolled. The patient group consisted of 12 (28.6%) females and 30 (71.4%) males, while the control group consisted of six (40%) females and nine (60%) males, with no difference between the groups in terms of gender distribution ($p > 0.05$). There was also no difference with respect to mean age between HF patients and controls (56.6 ± 10.4 vs. 51.8 ± 3.9, p = 0.09). The mean body mass index (BMI) of the HF group was found to be significantly higher than the control group (27.97 ± 4.15 kg/m^2 vs. 24.97 ± 1.83 kg/m^2, p = 0.01). Clinical characteristics of HF patients in terms of concomitant chronic diseases are given in Table 1. When the HF patients were investigated in terms of their functional status, six (14.3%) were determined to be in NYHA class II, 26 (61.9%) were in NYHA class III, and the remaining 10 (23.9%) patients were in NYHA class IV.

Table 1. Distribution of concomitant chronic diseases in heart failure patients

Stable coronary arterial disease	15 (35.7%)
Hypertension	31 (73.8%)
Hyperlipidaemia	29 (69%)
Diabetes mellitus	17 (40.4%)
Atrial fibrillation	6 (14.3%)
Chronic obstructive pulmonary disease	6 (14.3%)

Table 2. Medical treatments utilised in the heart failure group

Loop diuretic	38 (90%)
Beta-blocker	33 (78.5%)
ACE inhibitor	25 (60%)
Angiotensin receptor blocker	8 (19%)
Spironolactone	54.7 (25.6%)
Digoxin	9 (21.4%)
Amiodarone	7 (16.6%)
Calcium channel blocker	7 (16.7%)
Nitrate	9 (21.4%)
Warfarin	11 (26.1%)
Statin	25 (59.5%)
Acetylsalicylic acid	29 (69%)
CRT*	6 (14.2%)
Intravenous positive inotrope**	8 (19%)

*History of cardiac resynchronisation therapy (CRT) (prior biventricular permanent pacemaker implantation); **Dopamine and/or dobutamine; ACE — angiotensin-converting enzyme inhibitor

The details of the medical therapy given to HF patients at the time of the study are given in Table 2. Among 10 NYHA class IV patients hospitalised for decompensated HF, eight (19%) were given intravenous positive inotrope (dopamine and/or dobutamine) therapy.

The parameters of the echocardiography given to HF and control patients at the time of the study are given in Table 3.

Twenty-nine out of 1105 investigated miRNAs showed significant dysregulation. Eighteen miRNAs were found to be upregulated in the sera of HF patients, and 11 were demonstrated to be downregulated. Upregulated miRNAs showed a fold change between 1.2 and 2.1, and downregulated miRNAs showedwn a fold change between –1.20 and –2.44 (Table 4). When the association between dysregulated miRNAs and echocardiographic findings was investigated, miR-182 (r = –0.305; p = 0.04), miR-200a* (r = –0.360; p = 0.019), and miR-568 (r = –0.350; p = 0.023) were found to be inversely correlated with LVMI, while miR-155 (r = 0.361; p = 0.019) and miR-595 (r= 0.305; p = 0.04) were determined to be positively correlated with LVMI (Table 4).

Table 3. The parameters of the echocardiography in the two groups

	Heart failure	Control	P
Ejection fraction [%]	31.67 ± 7.41	58.79 ± 4.25	0.0001
PASP [mm Hg]	49.67 ± 10.94	29.86 ± 5.29	0.0001
Left ventricular mass [g]	317.67 ± 94.16	154.57 ± 22.40	0.0001
LVMI [g/m^2]	163.64 ± 42.34	82.93 ± 12.74	0.0001
Left atrial diameter [mm]	39.14 ± 3.01	36.27 ± 1.87	0.124
IVSD [mm]	12.02 ± 0.6	10.6 ± 0.51	0.39
LVPWd [mm]	11.57 ± 0.5	10.07 ± 0.59	0.106
LVEDD [mm]	65.55 ± 3.64	50.67 ± 2.06	0.035
LVESD [mm]	52.9 ± 4.72	34.13 ± 2.2	0.0001

PASP — pulmonary artery systolic pressure; LVMI — left ventricular mass index; IVSD — end-diastolic interventricular septum thickness; LVPWd — end-diastolic left ventricular posterior wall thickness; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end--systolic diameter

Table 4. Correlation analysis between circulating microRNA levels and left ventricular mass index in patients with systolic HF.

Variables	r	p
miR-182	–0.319	0.04
miR-200a*	–0.360	0.01
miR-568	–0.350	0.02
miR-155	0.361	0.01
miR-595	0.305	0.04

DISCUSSION

Specific miRNAs that have previously been shown to be involved in CV diseases are summarised in Table 5 [9]. In HF patients, dysregulated miRNAs have been suggested to play important roles in disease pathogenesis and progression [10]. The main finding of the present study is the demonstration that miRNAs, many for the first time, are dysregulated in symptomatic HF patients with systolic LV dysfunction. Moreover, we were able to show that some of these dysregulated miRNAs were significantly correlated with echocardiographically determined LVMI, which is known to be associated with prognosis in patients with systolic LV dysfunction and HF. Echocardiographic predictors of clinical outcomes in patients with LV dysfunction have been previously investigated in the SOLVD Registry and Trials, revealing an association between LV hypertrophy and CV events: LVM ≥ 298 g was associated with increased risk of death and rate of CV hospitalisations [4]. In our study, mean LVM was 317.67 ± 94.16 g in a patient population with a high frequency of history of hypertension. It must be noted that although septal and posterior LV wall dimensions tended to be higher than the control group, the difference was not statistically significant. On the other hand, marked dilatation of the LV, as evidenced from increased LVEDD and LVESD values, was thought to be responsible for increased LVM. Since BSA is proportional to weight and LVM is corrected for BSA when LVMI is calculated, the utilisation of LVMI instead of LVM while comparing the control and study groups with respect to LV hypertrophy makes it more likely that the disease processes underlying systolic LV dysfunction like hypertension and coronary arterial disease, rather than obesity, are responsible for the observed difference between the two groups. The role of circulating miRNAs in CV diseases, including cardiac hypertrophy, is still unclear. In recent years, numerous studies have addressed the association between dysregulated miRNAs and LV hypertrophy in the context of HF in animals and humans. In a study carried out on a hypertension-induced HF mouse model using polymerase chain reaction analysis for a selected panel of miRNAs it was demonstrated that circulating levels of miR-16, miR-20b, miR-93, miR-106b, miR-223, and miR-423-5p were significantly increased in response to hypertension-induced HF, while this effect was blunted in response to treatment with antimiR-208a as well as an angiotensin-converting enzyme inhibitor [11]. Endo et al. [1] demonstrated through miRNA array analysis that miRNA-15a and b, miR-20a, miR-103, miR-130a and b, miR-195, miR-210, miR-301b, miR-451, and miR-494 were dysregulated in rats with HF. Since miR-210 is well known to be upregulated by hypoxia, it was suggested as a promising candidate biomarker for HF [1]. Tijsen et al. [12] selected 16 miRNAs for validation in independent samples, including 36 healthy controls and 50 patients presenting with dyspnoea, of whom 30 were diagnosed with HF and 20 were diagnosed with dyspnoea attributable to non-HF-related causes. It was found that six miRNAs (miR-18b, miR-129-5p, miR-1254, miR-675, HS-202.1, miRNA-622) were increased in HF cases, among which the miR-423-5p level was most strongly related to the clinical diagnosis of HF [12]. Other researchers assessed the plasma concentrations of miR-126, miR-122, and miR-499 by polymerase chain reaction (PCR) in HF patients and demonstrated that miR-126 was upregulated, especially in NYHA III and IV HF cases [13]. Chen et al. [14]

Table 5. The clinical applications of circulating microRNAs in cardiovascular diseases [9]

Disorders	
Acute myocardial infarction	miR-1, miR-133a, miR-133b, miR-208a, miR-208b, miR-499-5p, miR-1291, miR-663b, miR-328, miR-21, miR-29a
Unstable angina	miR-134, miR-198, miR-370
Stable coronary artery disease	miR-126, miR-17, miR-92a, miR-155, miR-145
Heart failure	miR-423-5p, miR-18b*, miR-129-5p, miR-1254, miR-675, miR-622, miR-126, miR-210, miR-320a, miR-22, miR-92b, miR-126, miR-361-5p, miR-107, miR-139, miR-142-5p
Stroke	miR-124
Acute pulmonary embolism	miR-134
Cardiac hypertrophy and remodelling	miR-21, miR-29b, miR-129, miR-210, miR-211, miR-423, miR-30, miR-182, miR-526, miR-208b, miR-23, miR-214, miR-133, miR-195, miR-24, miR-18b, miR-1, miR-9, miR-150, miR-181, miR-199a
Arrhythmia	miR-1, miR-133, miR-208, miR-590, miR-26, miR-328, miR-21, miR-29, miR-30

demonstrated that plasma miR-361-5p concentrations were decreased significantly in all individuals with chronic HF. It was previously demonstrated that the miR-155 level was increased in the myocardium of HF patients [15]. However, miR-155 was found to be decreased and associated with sex, age, and diabetes in patients with stable coronary artery disease [9]. In contrast to these studies, Fan et al. [16] did not demonstrate any dysregulation in the plasma level of miR-155 in patients with dilated cardiomyopathy. In our study, miR-155 was found to be decreased in systolic HF patients. Furthermore, a significant positive association between miR-155 and LVMI could be demonstrated.

The association between dysregulation of circulating miRNAs and LV anatomy has been previously studied [17–19]. Goren et al. [19] measured levels of 186 miRNAs in sera of 30 stable systolic HF patients using quantitative reverse transcription PCR and came up with an miRNA score utilising four specific miRNAs with the most significant increase in the HF group (miR-423-5p, miR-320a, miR-22, miR-92b). A significant association was demonstrated between the miRNA score and LV dilatation, which was regarded as a clinical prognostic factor in systolic HF patients. In the same study, only 10 of the 186 miRNAs were reported to be dysregulated. Dysregulated miRNAs included miR-21; however, it was not included in the miRNA score, which was shown to be associated with LV dilatation [19]. MicroR-21 is one of the few miRNAs that demonstrate a consistent pattern of upregulation in heart failure. It is also highly expressed in various types of cancer tissues and cell lines and plays a pivotal role in stress response and pathological cell growth [20]. Moreover, it was found to be upregulated in peripheral artery disease by Li et al. [21].

In our study we found miR-21 to be upregulated and miR-155 to be down regulated, similar to several previous studies [19, 22]. There was no association between miR-21 level and LVMI.

On the other hand, a significant association between miR-155 and LVMI could be demonstrated.

To the best of our knowledge, the inverse relation between miR-182, miR-200a*, miR-568, and LVMI and positive correlation between miR-155, miR-595, and LVMI were demonstrated for the first time in HF patients with systolic dysfunction. Out of these, miR-155 deserves special attention because it was suggested to play a central role in the induction of cardiac inflammation and HF, since its levels were demonstrated to increase in the myocardium of HF patients [23, 24]. In a study consisting solely of dilated cardiomyopathy patients, circulating miR-155 was not shown to be dysregulated, in contrast to our study. Caution should be exercised while comparing patients with HF due to various different medical conditions and patients with dilated cardiomyopathy. Nevertheless, the presence of subjects with a history of coronary artery disease or hypertension in our study may be responsible for this discrepancy.

Limitations of the study

Several limitations of the study should be acknowledged. First, we suggest that dysregulated circulating miRNAs may be of clinical importance in HF, but larger studies are needed to confirm the diagnostic capability of the identified dysregulated miRNAs. Second, serial measurement of miRNA levels at follow up might give additional information on the clinical outcome of these patients and might also allow the assessment of the dynamic changes in serum concentration of these molecules during the course of illness. Finally, most of the patients with HF in our study had co-existing factors, like hypertension or coronary artery disease, which may result in the extrapolation of our findings to a different subset of HF patients to be difficult. The high prevalence of CV diseases other than HF in our study group may also be associated with altered miRNA serum concentrations.

CONCLUSIONS

The results of our study revealed that dysregulated circulating miRNAs were correlated with anatomic changes in LV, in

terms of LVMI, in symptomatic HF patients with systolic LV dysfunction. Our findings may be interpreted as hypothesis forming at best, since exact pathophysiological mechanisms underlying the dysregulation of these miRNAs are not clear. Further studies are needed to interpret the association of dysregulated miRNAs with LVMI, especially in terms of their therapeutic and prognostic implications.

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Conflict of interest: *none declared*

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Zależność między ekspresją krążącego mikroRNA a masą lewej komory w objawowej niewydolności serca u chorych z zaburzeniem czynności skurczowej

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Streszczenie

Wstęp: W ostatnich latach wykazano, że zaburzenia ekspresji wielu cząsteczek mikroRNA (miRNA) w określonych tkankach mają podstawowe znaczenie w patogenezie i progresji niewydolności serca (HF). Masę lewej komory (LVM) od dawna uważa się za ważny wskaźnik prognostyczny u chorych ze skurczową HF.

Cel: Autorzy niniejszej pracy stworzyli hipotezę, że ekspresja krążących miRNA może się wiązać z LVM u chorych ze skurczową HF. Celem badania była ocena zależności między opisywanymi wcześniej i nowymi miRNA oraz określoną echokardiograficznie LVM u osób z objawową HF i zaburzeniami czynności skurczowej lewej komory.

Metody: Do badania włączono 42 kolejnych pacjentów z rozpoznaniem objawowej HF w stopniu II–IV wg NYHA oraz grupę kontrolną złożoną z 15 dopasowanych pod względem wieku i płci zdrowych ochotników. Po oznakowaniu wyekstrahowanego RNA dodano odcinki poli-A. Następnie przeprowadzono hybrydyzację RNA na matrycy GeneChip miRNA 2.0. Po hybrydyzacji i barwieniu matryce poddano skanowaniu w celu określenia ekspresji miRNA oraz identyfikacji miRNA o różnym stopniu ekspresji.

Wyniki: W surowicy chorych z HF stwierdzono zwiększoną ekspresję 18 miRNA i zmniejszoną ekspresję 11 miRNA. Analiza związku między nieprawidłową ekspresją miRNA a wynikami pomiarów echokardiograficznych wykazała ujemną korelację między ekspresją miR-182 ($p = 0,04$), miR-200a* ($p = 0,019$) i miR-568 ($p = 0,023$) a wskaźnikiem LVM (LVMI) oraz dodatnią zależność między ekspresją miR-155 ($p = 0,019$) i miR-595 ($p = 0,04$) a LVMI.

Wnioski: Wykazano, że nieprawidłowe stężenia krążących miRNA korelowały ze zmianami anatomicznymi lewej komory pod względem LVMI u chorych z objawową HF i zaburzeniami czynności skurczowej lewej komory.

Słowa kluczowe: miRNA, masa lewej komory, skurczowa niewydolność serca

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