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SHORT COMMUNICATION

miR-1, miR-21, and galectin-3 in hypertensive patients with symptomatic heart failure and left ventricular hypertrophy

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INTRODUCTION

Left ventricular hypertrophy (LVH) is known as an independent risk factor for coronary heart disease, heart failure (HF), stroke, and sudden cardiac arrest. LVH implicates changes in the architecture of myocardial tissue, which consist of perivascular and myocardial fibrosis, as well as medial thickening of intramyocardial coronary arteries, in addition to cardiomyocyte hypertrophy [1–3].

The impact of miR-1 level on cardiac hypertrophy and cardiomyocyte apoptosis has been recently suggested [3, 4]. Also, the association between miR-21 and galectin-3 (gal-3) levels and maladaptive cardiac remodelling, fibrosis, and inflammation has been described [5, 6]. Nevertheless, the synergistic role of these molecules in LVH has not been explained to date. We analysed the expressions of miR-1, miR-21, and gal-3 concentration in patients with symptomatic HF (SHF) and a history of hypertension and LVH revealed in echocardiography.

METHODS

A total of 59 consecutive patients with SHF hospitalised in the 1st Chair and Department of Cardiology, Medical University of Warsaw were enrolled. SHF was defined as a decompensated acute HF, de novo, or decompensation of chronic HF. Symptomatic chronic HF was determined as a class ≥ II specified by the New York Heart Association (NYHA) criteria. Clinical or radiological signs of pulmonary congestion and left ventricular ejection fraction (LVEF) below 50% were assessed according to the Simpson's method using a Philips iE 33 ultrasound system. We measured the following M-mode parameters: interventricular septal thickness diameter (IVSD), left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular mass index (LVMI), posterior wall diastolic thickness (PWDT), and right ventricular diameter (RVD). Detailed characteristics of patients are presented in Table 1.

The concentrations of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and gal-3 were measured using a Dimension Xpand instrument (Siemens Health Care Diagnostics, Erlangen, Germany) and VIDAS family (bioMerieux SA, Marcy-I`Etoile, France), respectively. Total RNA, with the fraction of RNAs smaller than 200 nt, was extracted from 300 μL of serum using NucleoSpin miRNA Plasma kit (Macherey Nagel, Düren, Germany), and cDNA synthesis was assembled with a Universal cDNA Synthesis kit (Exiqon, Vedback, Denmark), according to the manufacturer's instructions. Quantitative real-time polymerase chain reaction (qPCR) was performed with a ViiA™ 7 Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA) using ExiLENT SYBR Green master mix (Exiqon, Vedback, Denmark) with LNA primer sets. qPCR data were normalised to miRNA-103-3p. The $^{\Delta\Delta}$Ct method was used to evaluate relative expressions of examined miRNAs in the study group compared to 17 healthy volunteers (age- and sex-matched). Finally, the results were presented as a fold change calculated using the $2^{-\Delta\Delta Ct}$ formula.

RESULTS

Of 59 analysed patients, a total of 41 had a history of hypertension and were identified with different severity of LVH (Table 1). In 27 HF patients with severe LVH (LVMI > 149 [men]/122 [women] g/m^2) there was a significant

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Table 1. miR-1, miR-21, and gal-3 in hypertensive patients with SHF and LVH

	SHF patients with LVMI > 149 g/m² (men)/ /122 g/m² (women)	SHF patients with LVMI < 149 g/m² (men)/122 g/m² (women) > 115 g/m² (men)/95 g/m² (women)	p
Demographic data			
Number of patients	27	14	NS
Age [years]	69.8 ± 12.5	72.5 ± 10.9	NS
Men	23 (85.2%)	9 (64.3%)	NS
Echocardiographic parameters			
LVEF [%]	27.6 ± 10.6	43.6 ± 17	< 0.001
LVEDD [cm]	6.53 ± 0.81	5.36 ± 0.90	< 0.001
LAD [cm]	5.35 ± 0.60	4.58 ± 0.84	0.002
RVD [cm]	3.47 ± 0.49	2.89 ± 0.31	0.001
IVSD [cm]	1.14 ± 0.20	1.14 ± 0.22	NS
Laboratory parameters			
NT-proBNP [pg/mL]	5428 (1766–15941)	1849 (642–6079)	0.024
Galectin-3 [ng/mL]	18 (13.6–23.3)	14.45 (9.9–18.4)	NS
miR-1 [change fold]	0.299 (0.163–0.72)	0.395 (0.180–1.00)	NS
miR-21 [change fold]	2.216 (1.216–4.78)	2.056 (1.101–5.31)	NS

Data are expressed as number (percentage), mean ± standard deviation or median (interquartile range). IVSD — interventricular septal thickness diameter; LAD — left atrial diameter; LVEDD — left ventricular end-diastolic diameter; LVMI — left ventricular mass index; LVEF — left ventricular ejection fraction; LVH — left ventricular hypertrophy; NS — nonsignificant; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RVD — right ventricular diameter; SHF — symptomatic heart failure

negative correlation between IVSD vs. miR-1 (Rs = –0.533, p = 0.004) and PWDT vs. miR-1 (Rs = –0.404, p = 0.037). We found also a positive correlation: IVSD vs. gal-3 (Rs = 0.383, p = 0.049), miR-1 vs. miR-21 (Rs = 0.520, p = 0.005), as well as NT-proBNP vs. gal-3 (Rs = 0.369, p = 0.019) (**Supplementary Figures 1 and 2 — see journal website**).

DISCUSSION

The main study findings could be summarised as follows: expression of miR-1 was markedly downregulated in HF patients with severe LVH, being negatively correlated with IVSD and PWDT; downregulation of miR-21 was found in all patients, independently of the LVH severity, and significantly correlated with gal-3 concentration.

In recent years, the correlation between circulating miRNA expressions and cardiac diseases has been rapidly emerging [7]. To our knowledge, this is the first study simultaneously evaluating the miR expression in association with gal-3 concentration in a population of unselected hypertensive patients with HF and LVH. Based on recent studies, miR-1 and miR-21 expressions have been hypothesised as potentially significant prognostic biomarkers in patients with SHF and LVH [8]. Karakikes et al. [9] reported that miR-1 was downregulated in hypertrophy, reversed cardiac hypertrophy, and attenuated pathological remodelling by simultaneously affecting multiple processes associated with pathological hypertrophy and HF. Further agreement with our findings is provided by recent studies revealing that hypertrophy-related microRNAs (miR-1, miR-133a, miR-26b, miR-208b, miR-499, and miR-21) show distinct expression profiles in hypertensive patients [10]. In addition, Zhang et al. [11] suggested that miR-1 could be helpful in predicting the onset of HF in patients after myocardial infarction (MI). In our survey, we found significant downregulation of miR-1 accompanied by the increase of NT-proBNP concentration. Moreover, it has been proposed that miR-1 is a potential biomarker not only for early diagnosis of acute MI, but circulating miR-1 levels can also be used to differentiate between acute MI and other cardiac events such as angina pectoris [12] and other cardiovascular diseases.

Although miR-21 is known to be the most upregulated miRNA in the cardiac remodelling process, the exact mechanisms implicated in the pathogenesis of HF remain under-explored [5]. In our study, we found significant downregulation of miR-21 associated with the increase of LVEDD.

Of note is the value of gal-3 as a prospective biomarker, also playing a key role in the fibrosis process [6, 13]. Gal-3 stimulates the synthesis of type I collagen, which causes the interruption of extracellular matrix homeostasis because loss of balance between the amount of collagen type I and III leads to impaired systolic and diastolic functions of the heart and contributes to the progression of HF [13, 14].

In our study, we found a significant positive correlation between gal-3 and NT-proBNP concentrations, as was already shown in other studies [14]. Interestingly, the concentration of gal-3 was also associated with IVSD (significantly higher in patients with IVSD > 12 mm than IVSD ≤ 12 mm).

In conclusion, in SHF patients with LVH, gal-3 concentrations and miR-1 expressions were correlated with anatomic changes of the left ventricle. Downregulation of miR-1 expression may be associated with LVH intensity. Such observations should be validated in independent and large-cohort studies. Profiling of some types of miRs might become a new tool allowing early HF and LVH diagnosis and treatment.

Conflict of interest: *none declared*

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