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SHORT COMMUNICATION

Dysregulations of miRNAs and galectin-3 may underlie left ventricular dilatation in patients with systolic heart failure

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INTRODUCTION

Left ventricular (LV) adverse remodelling represents a major feature of systolic heart failure (SHF). It has been identified as a risk factor for impaired cardiac function [1]. A potential role of miR-1 and miR-21 in adverse cardiac remodelling in HF has been recognised [2, 3]. Increased concentration of galectin-3 (gal-3) in HF patients has also been observed [4, 5].

We aimed to explore the serum expression of miR-1 and miR-21, and the concentration of gal-3 in SHF patients with different degrees of LV dilatation. The concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured and compared with new, potentially clinically useful HF biomarkers.

METHODS

Patients hospitalised in the 1st Chair and Department of Cardiology, Medical University of Warsaw due to decompensation of SHF with LV ejection fraction (LVEF) < 50% were enrolled in this study. Each patient underwent echocardiographic examination using a Philips iE 33 system, according to Simpson's method. The following parameters were measured: interventricular septal thickness diameter, left atrial diameter, left ventricular end-diastolic diameter (LVEDD), and right ventricular diameter. All patients were divided into two groups: subjects with significantly dilated LV (LVEDD > 60 mm) and without significantly dilated LV (LVEDD < 60 mm), as in the study by Abergel et al. [6].

Serum concentrations of high-sensitivity C-reactive protein (hsCRP), troponin I (TnI), and NT-proBNP were measured using a Dimension Xpand instrument (Siemens Health Care Diagnostics, Erlangen, Germany) and gal-3 level was measured using VIDAS testing system (bioMerieux SA, Marcy-I`Etoile, France). Total RNA was extracted from serum using a NucleoSpin miRNA Plasma kit (Macherey Nagel, Düren, Germany), according to the manufacturer's instruction. Reverse transcription reaction was performed with the Universal cDNA Synthesis kit (Exiqon, Vedback, Denmark), using a 2720 Thermal Cycler instrument (Thermo Fisher Scientific, Foster City, CA, USA), according to the protocol. MiRNAs were amplified using quantitative real-time polymerase chain reaction (qPCR) on a ViiA™ 7 Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA). Relative expression of investigated miRs in the study groups compared to 17 healthy volunteers was calculated using the $^{\Delta\Delta}$Ct method. Finally, qPCR results were presented as fold change using the $2^{-\Delta\Delta Ct}$ formula. MiR-103-3p was used as normalisation control.

RESULTS

A total of 59 participants were enrolled in the study, including 30 patients with LVEDD > 60 mm and 29 patients with LVEDD < 60 mm. Demographic and clinical features are presented in Table 1. The level of miR-1 was decreased, whereas the level of miR-21 was increased in patients with SHF. We observed a significant negative correlation between interventricular septum thickness (IVS) and miR-1 and a positive correlation between IVS and gal-3 in patients with LVEDD > 60 mm (Rs = –0.400, p = 0.039 and Rs = 0.418, p = 0.030, respectively). Among HF patients with LVEDD < 60 mm a positive correlation between gal-3 and NT-proBNP was observed (Rs = 0.595, p = 0.0008) (**Supplementary Figures 1 and 2 — see journal website**).

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Table 1. Baseline, clinical, and echocardiographic characteristics (n = 59)

	SHF patients with LVEDD > 60 mm (n = 30)	SHF patients with LVEDD < 60 mm (n = 29)	p
Personal factors			
Age [years]	66.3 ± 10.7	75.2 ± 10.2	< 0.001
Men	27 (90%)	20 (69%)	NS
Hospitalisation — last year	15 (50%)	13 (44.8%)	NS
Risk factors			
Current smoking	4 (13.3%)	2 (6.9%)	NS
Hyperlipidaemia	5 (16.7%)	3 (10.3%)	NS
Chronic kidney disease			
Stage 3 (eGFR < 60 mL/min/1.73 m^2)	15 (50%)	15 (51.7%)	NS
Stage 4 (eGFR < 30 mL/min/1.73 m^2)	3 (10%)	3 (10.3%)	NS
Creatinine [mg/dL]*	1.38 ± 0.45	1.41 ± 0.67	NS
Diabetes mellitus	6 (20%)	7 (24.1%)	NS
Previous cardiovascular disease			
Coronary artery disease	24 (80.0%)	19 (55.2%)	NS
CCS 1	6 (25.0%)	7 (36.8%)	NS
CCS 2 or 3	18 (75.0%)	12 (63.2%)	NS
CCS 4	0 (0.0%)	0 (0.0%)	NS
Prior STEMI	11 (36.7%)	10 (34.5%)	NS
Prior NSTEMI	13 (43.3%)	9 (31.0%)	NS
Prior PCI	18 (60.0%)	13 (44.8%)	NS
Prior CABG	8 (26.7%)	7 (24.1%)	NS
Incomplete revascularisation#	3 (10.0%)	2 (6.9%)	NS
Peripheral artery disease	1 (3.3%)	2 (6.9%)	NS
Atrial fibrillation	8 (26.7%)	7 (24.1%)	NS
Stroke	2 (6.7%)	5 (17.2%)	NS
Arterial hypertension	23 (76.7%)	22 (75.9%)	NS
Medications at presentation			
ACEI	15 (50%)	26 (89.7%)	NS
β-blocker	20 (66.7%)	23 (79.3%)	NS
Aldosterone antagonist	15 (50%)	9 (31.0%)	NS
Digoxin	7 (23.3%)	1 (3.4%)	NS
Loop diuretic	24 (80%)	24 (82.8%)	NS
Echocardiographic parameters			
LVEF [%]	26.2 ± 11.1	41.3 ± 11.5	< 0.001
LVEDD [cm]	6.8 ± 0.58	5.08 ± 0.52	< 0.001
LAD [cm]	5.40 ± 0.61	4.47 ± 0.58	< 0.001
RVD [cm]	3.58 ± 0.44	3.02 ± 0.55	< 0.001
IVS [cm]	1.10 ± 0.18	1.21 ± 0.25	NS
Laboratory			
NT-proBNP [pg/mL]	6638 (1811–14000)	3220.5 (1036–7398.5)	0.041
Galectin-3 [ng/mL]	18.1 (13.6–20.4)	18.1 (11.2–24.9)	NS
miR-1 [change fold]	0.284 (0.148–0.64)	0.588 (0.293–1.09)	0.041
miR-21 [change fold]	2.092 (1.216–3.35)	2.458 (1.101–6.34)	NS
Troponin I [ng/mL]	0.136 (0.018–1.15)[a]	0.030 (0.007–0.10)[b]	NS
hsCRP [mg/L]	13.5 (7.1–50.2)[c]	7.0 (3.4–42.85)[d]	NS

Data are expressed as number and percentage, mean ± standard deviation, or median and interquartile range. #Incomplete revascularisation as presence of a significant (> 70% by angiography; > 50% for left main artery) coronary artery stenosis in at least one epicardial artery > 2 mm in diameter. Data available for: [a]19 patients; [b]18 patients; [c]27 patients; [d]24 patients. ACEI — angiotensin receptor enzyme inhibitor; CABG — coronary artery bypass grafting; CCS — Canadian Cardiovascular Society; eGFR — estimated glomerular filtration rate; hsCRP — high-sensitivity C-reactive protein; IVS — interventricular septal thickness; LAD — left atrial diameter; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; NS — nonsignificant; NSTEMI — non-ST-segment elevation myocardial infarction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PCI — percutaneous coronary intervention; RVD — right ventricular diameter; SHF — systolic heart failure; STEMI — ST-segment elevation myocardial infarction

DISCUSSION

The main finding of our study is that miR-1 concentration is lower in SHF patients and decreases further in the group with LVEDD > 60 mm as compared to LVEDD < 60 mm. This observation may suggest that miR-1 down-regulation is associated with maladaptive cardiac remodelling in SHF.

We observed the link between miR-1 down-regulation and progression of adverse cardiac remodelling assessed by LV dilatation. Significant negative correlation between miR-1 concentration and IVS in patients with LVEDD > 60 mm was noted. It is important to underline that patients with extreme LV dilatation had also significantly larger left atrial and right ventricular dimensions and significantly lower LVEF. It may suggest that the role of miR-1 in progression of cardiac hypertrophy and contractile failure is limited to subjects at an advanced stage of heart chamber dilatation. Evidence regarding the role of miR-1 in cardiac remodelling derived from clinical trials is scarce. A significant negative correlation between miR-1 and LVEF was observed in 48 patients after acute myocardial infarction [7]. MiR-1 expression may predict the onset of HF in this subset of patients [8].

We found both decreased miR-1 and increased miR-21 levels in decompensated SHF patients. These observations are in line with previous pathophysiological reports that these miRNAs change later in the course of the disease [8]. MiR-21 level was not significantly decreased in patients with LVEDD > 60 mm as compared with LVEDD < 60 mm. MiR-21 up-regulation promoted the development of HF with preserved ejection fraction [9]; in our study decreased expression of this miR molecule favoured adverse LV dilatation and subsequent attenuation of LV function in SHF. Tatsuguchi et al. [10] confirmed that miR-21 expression may negatively regulate cardiac hypertrophy.

Another important finding of this study is that the levels of gal-3, a novel, promising biomarker of adverse cardiac remodelling, positively correlated with IVS in patients with extremely dilated LV. Increased gal-3 concentration on admission was associated with both higher NT-proBNP and echocardiographic markers of ventricular dysfunction [5]. We found a significant correlation between gal-3 and NT-proBNP, which remains consistent with a previous report [11].

In conclusion, we demonstrated that miR-1 down-regulation in the course of SHF patient subgroups was associated with more pronounced maladaptive cardiac remodelling and LV dilatation, whereas the expression of miR-21 was comparable regardless of LV size. MiR-1 expression might potentially constitute a supplementary predictor of adverse cardiac remodelling in HF patients. MiR-1 down-regulation and gal-3 overexpression might also play a role in the progression of cardiac hypertrophy.

This pilot study provides additional information on the complex effects of miRs and gal-3 on the process of cardiac remodelling. Further studies are needed for better exploration of the involvement of these molecules at different stages of cardiac remodelling.

Conflict of interest: *none declared*

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