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Investigating the Relationship Between MicroRNA Expression Profiles and Left Ventricular Remodeling in Patients with Heart Failure

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Abstract

Heart failure (HF) is a complex clinical syndrome characterized by structural and functional alterations in the heart, often leading to left ventricular (LV) remodeling. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression and have emerged as key players in cardiovascular pathophysiology. This study aimed to investigate the relationship between miRNA expression profiles and LV remodeling in patients with HF. We analyzed miRNA expression in plasma samples from 120 HF patients and 60 healthy controls using next-generation sequencing (NGS) and quantitative PCR (qPCR). LV remodeling was assessed using echocardiography, and patients were stratified based on LV ejection fraction (LVEF) and LV end-diastolic volume (LVEDV). Our results revealed distinct miRNA expression patterns associated with LV remodeling, with miR-21, miR-29, and miR-133a showing significant dysregulation. These miRNAs were correlated with markers of fibrosis, hypertrophy, and inflammation. The findings suggest that specific miRNAs may be biomarkers for LV remodeling and potential therapeutic targets in HF. This study provides new insights into the molecular mechanisms underlying LV remodeling and highlights the potential of miRNA-based diagnostics and therapeutics in HF management.

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide, affecting over 64 million people globally (1). It is a multifactorial syndrome resulting from various cardiovascular diseases, including hypertension, coronary artery disease, and cardiomyopathies. A hallmark of HF is left ventricular (LV) remodeling, characterized by LV size, shape, and function changes, ultimately leading to impaired cardiac output (2). LV remodeling is driven by complex molecular and cellular mechanisms, including cardiomyocyte hypertrophy, fibrosis, apoptosis, and inflammation (3). Despite advances in HF treatment, the underlying molecular pathways remain incompletely understood, necessitating further research to identify novel biomarkers and therapeutic targets.

MicroRNAs (miRNAs) are small, non-coding RNA molecules, approximately 22 nucleotides in length that regulate gene expression at the post-transcriptional level by binding to complementary sequences in target mRNAs (4). miRNAs play critical roles in various biological processes, including cell proliferation, differentiation, and apoptosis. In the cardiovascular system, miRNAs regulate cardiac development,

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hypertrophy, fibrosis, and remodeling (5). Dysregulation of specific miRNAs has been associated with cardiovascular diseases, including HF, making them promising candidates for diagnostic and therapeutic applications (6).

Recent studies have identified several miRNAs differentially expressed in HF patients and involved in LV remodeling. For example, miR-21 has been shown to promote cardiac fibrosis by targeting the anti-fibrotic protein Sprouty1 (7). Similarly, miR-29 regulates extracellular matrix (ECM) proteins, while miR-133a modulates cardiomyocyte hypertrophy (8, 9). Despite these findings, the relationship between miRNA expression profiles and LV remodeling in HF patients remains poorly understood. Moreover, the potential of miRNAs as biomarkers for LV remodeling and their role in the pathogenesis of HF warrant further investigation.

This study aimed to comprehensively analyze miRNA expression profiles in HF patients and investigate their association with LV remodeling. We hypothesized that specific miRNAs are differentially expressed in HF patients with LV remodeling and are associated with key pathological processes, such as fibrosis, hypertrophy, and inflammation. By identifying these miRNAs, we aimed to provide new insights into the molecular mechanisms underlying LV remodeling and explore their potential as biomarkers and therapeutic targets in HF.

Methodology

Study Design and Patient Population

This was a prospective, observational study conducted at a tertiary care center. A total of 120 HF patients and 60 age- and sex-matched healthy controls were enrolled. HF patients were diagnosed based on the European Society of Cardiology (ESC) guidelines, which include symptoms of HF, elevated natriuretic peptides, and evidence of structural or functional cardiac abnormalities (10). Patients were stratified into two groups based on LV ejection fraction (LVEF): HF with reduced EF (HFrEF, LVEF <40%) and HF with preserved EF (HFpEF, LVEF ≥50%). LV remodeling was assessed using echocardiography, and patients were further categorized based on LV end-diastolic volume (LVEDV) into those with and without significant LV remodeling.

Sample Collection and miRNA Profiling

Peripheral blood samples were collected from all participants and centrifugation isolated plasma. Total RNA, including miRNAs, was extracted using the miRNeasy Serum/Plasma Kit (Qiagen). miRNA expression profiling was performed using next-generation sequencing (NGS) on the Illumina HiSeq platform. Differentially expressed miRNAs were validated using quantitative PCR (qPCR) with TaqMan assays (Thermo Fisher Scientific).

Echocardiographic Assessment

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Transthoracic echocardiography was performed using a Philips EPIQ 7G ultrasound system. LVEF was calculated using the biplane Simpson's method, and LVEDV was measured from the apical four-chamber view. LV mass index (LVMI) and relative wall thickness (RWT) were calculated to assess LV hypertrophy. Speckle-tracking echocardiography evaluated global longitudinal strain (GLS) to measure LV systolic function.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as percentages. Differences between groups were assessed using Student's t-test or ANOVA for continuous variables and chi-square test for categorical variables. miRNA expression levels were normalized to the housekeeping gene RNU6B, and fold changes were calculated using the $2^{(-\Delta\Delta Ct)}$ method. Correlation analysis assessed the relationship between miRNA expression and echocardiographic parameters. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 summarizes the study population's baseline characteristics. Compared to healthy controls, HF patients were older and had a higher prevalence of comorbidities, including hypertension, diabetes, and coronary artery disease. LVEF and GLS were significantly lower in HF patients, while LVEDV and LVMI were higher, indicating the presence of LV remodeling.

miRNA Expression Profiles

NGS analysis identified 15 miRNAs differentially expressed in HF patients compared to controls (Table 2). Among these, miR-21, miR-29, and miR-133a showed the most significant dysregulation. qPCR validation confirmed that miR-21 and miR-29 were upregulated, while miR-133a was downregulated in HF patients.

Table 1: Baseline Characteristics of the Study Population

Characteristic	HF Patients (n=120)	Healthy Controls (n=60)	p-value
Age (years)	65.3 ± 9.8	62.1 ± 8.5	0.12
Male sex, n (%)	75 (62.5%)	36 (60.0%)	0.75
Hypertension, n (%)	90 (75.0%)	30 (50.0%)	<0.01
Diabetes, n (%)	45 (37.5%)	12 (20.0%)	0.02
Coronary artery disease, n (%)	60 (50.0%)	15 (25.0%)	<0.01
LVEF (%)	35.2 ± 10.5	58.4 ± 5.2	<0.001
LVEDV (mL)	180.5 ± 35.6	110.3 ± 20.4	<0.001
LVMI (g/m²)	125.4 ± 30.2	85.6 ± 15.3	<0.001

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GLS (%)	-10.2 ± 3.5	-20.1 ± 2.8	<0.001

Table 2: Differentially Expressed miRNAs in HF Patients vs. Healthy Controls

miRNA	Fold Change (HF vs. Controls)	p-value	Regulation
miR-21	3.5	<0.001	Upregulated
miR-29a	2.8	<0.01	Upregulated
miR-133a	0.4	<0.001	Downregulated
miR-1	0.6	0.02	Downregulated
miR-208a	2.2	<0.01	Upregulated
miR-499	1.8	0.03	Upregulated

Correlation with LV Remodeling

miR-21 and miR-29 expression levels were positively correlated with LVEDV and LVMI, suggesting their involvement in LV dilation and hypertrophy (Table 3). In contrast, miR-133a was negatively correlated with LVEF and GLS, indicating its role in impaired systolic function.

Table 3: Correlation Between miRNA Expression and Echocardiographic Parameters

miRNA	LVEF (r)	LVEDV (r)	LVMI (r)	GLS (r)
miR-21	-0.45*	0.52*	0.48*	-0.40*
miR-29a	-0.38*	0.47*	0.42*	-0.35*
miR-133a	0.50*	-0.55*	-0.52*	0.45*

- $p < 0.05$

Discussion

This study comprehensively analyzes miRNA expression profiles in HF patients and their association with LV remodeling. Our findings reveal that specific miRNAs, including miR-21, miR-29a, and miR-133a, are significantly dysregulated in HF patients and correlate with key echocardiographic parameters of LV remodeling. These results highlight the potential of miRNAs as biomarkers and therapeutic targets in HF.

miR-21 was significantly upregulated in HF patients and positively correlated with LVEDV and LVMI, suggesting its involvement in LV dilation and hypertrophy. miR-21 is a well-established regulator of cardiac fibrosis, a key pathological feature of LV remodeling. It promotes fibroblast activation and extracellular matrix (ECM) deposition by targeting anti-fibrotic proteins such as Sprouty1 and PTEN (7, 11). Our findings are consistent with previous studies demonstrating elevated miR-21 levels in

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HF patients with adverse LV remodeling (12). The upregulation of miR-21 in our cohort underscores its role in driving fibrotic processes contributing to LV dysfunction.

miR-29a, another upregulated miRNA in our study, is known to regulate ECM proteins such as collagens and elastin (8). Its positive correlation with LVMI suggests that miR-29a may contribute to LV hypertrophy by modulating ECM turnover. Previous studies have shown that miR-29a is downregulated in the early stages of HF but upregulated in advanced stages, where fibrosis is more pronounced (13). This biphasic expression pattern may reflect its dual role in ECM homeostasis. In our study, the upregulation of miR-29a in HF patients with significant LV remodeling supports its involvement in adverse ECM remodeling.

In contrast to miR-21 and miR-29a, miR-133a was downregulated in HF patients and negatively correlated with LVEDV and LVMI. miR-133a is a key regulator of cardiomyocyte hypertrophy, and its downregulation has been linked to the activation of pro-hypertrophic signaling pathways, such as calcineurin/NFAT and RhoA (9, 14). Our study's negative correlation between miR-133a and LVEF suggests that its downregulation may contribute to impaired systolic function. These findings align with previous reports showing that miR-133a levels are reduced in HF patients and animal models of cardiac hypertrophy (15).

Conclusion

This study demonstrates that specific miRNAs, including miR-21, miR-29a, and miR-133a, are differentially expressed in HF patients and are associated with LV remodeling. These miRNAs may serve as biomarkers for early detection, risk stratification, and therapeutic targets for preventing or reversing LV remodeling in HF. Further research is needed to validate these findings and explore the potential of miRNA-based therapies in HF management.

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