The diagnostic value of circulating microRNAs in heart failure (Review)

YAO-MENG HUANG[1], WEI-WEI LI[1], JUN WU[1], MEI HAN[1] and BING-HUI LI[2]

[1]Hebei Key Laboratory of Medical Biotechnology, Hebei Medical University, Shijiazhuang, Hebei 050017;
[2]Department of Oncological Surgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei 050011, P.R. China

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Abstract. Heart failure (HF) is a complex clinical syndrome, characterized by inadequate blood perfusion of tissues and organs caused by decreased heart ejection capacity resulting from structural or functional cardiac disorders. HF is the most severe heart condition and it severely compromises human health; thus, its early diagnosis and effective management are crucial. However, given the lack of satisfactory sensitivity and specificity of the currently available biomarkers, the majority of patients with HF are not diagnosed early and do not receive timely treatment. A number of studies have demonstrated that peripheral blood circulating nucleic acids [such as microRNAs (miRs), mRNA and DNA] are important for the diagnosis and monitoring of treatment response in HF. miRs have been attracting increasing attention as promising biomarkers, given their presence in body fluids and relative structural stability under diverse conditions of sampling. The aim of the present review was to analyze the associations between the mechanisms underlying the development of HF and the expression of miRs, and discuss the value of using circulating miRs as diagnostic biomarkers in HF management. In particular, miR-155, miR-22 and miR-133 appear to be promising for the diagnosis, prognosis and management of HF patients.

Correspondence to: Professor Mei Han, Hebei Key Laboratory of Medical Biotechnology, Hebei Medical University, 361 Zhongdong Road, Shijiazhuang, Hebei 050017, P.R. China
E-mail: hanmei@hebmu.edu.cn

Professor Bing-Hui Li, Department of Oncological Surgery, Fourth Hospital of Hebei Medical University, 12 Health Road, Shijiazhuang, Hebei 050011, P.R. China
E-mail: lbh58@hebmu.edu.cn

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Contents

1. Introduction

The causes of heart failure (HF) include ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM), hypertension, valvular heart disease, diabetic cardiomyopathy and congenital heart disease (CHD) (1). The pathogenesis of HF is associated with myocardial hypertrophy, fibrosis or necrosis, cardiomyocyte apoptosis, renin-angiotensin-aldosterone system imbalance and collagen changes, as well as several other factors (2-7).

MicroRNAs (miRs) are small (~22 nucleotides in length), single-strand, non-coding RNA sequences derived from precursors that control gene expression in a variety of physiological and developmental processes, which are involved in post-transcriptional regulation of gene expression (8). miR disorders are associated with a number of human diseases, including diabetes, myocardial infarction and cardiovascular disease, obesity and cancer. Several studies have demonstrated that miRs may affect different aspects of the occurrence and development of HF (9-14). The association between miRs and HF is discussed in detail below.

Circulating miRs are increasingly recognized as promising biomarkers, given their stability and resistance to endogenous RNase (15); these miRs, to some degree, may also be used as diagnostic biomarkers for angiocardiopathy. In addition, miRNAs and various types of HF have complex relationships, as described below.

2. Changes and associated mechanisms of miRs in various types of HF

miRs may be involved in several aspects of the occurrence and development of HF, such as cardiomyocyte apoptosis, hypertrophy, fibrosis, inflammation, oxidative damage and

hypoxic damage (9-14), among others. The specific regulatory functions of miRs are indicated in Figs. 1 and 2 and are summarized in Table I (16-66).

3. Circulating miRs as diagnostic biomarkers

HF is primarily caused by cardiomyopathy, hypertension, diabetes and CHD, among other causes (15). The different etiology is associated with several miRs.

miRs associated with cardiomyopathy. The cardiomyopathies leading to HF predominantly include DCM and ICM (67-71). DCM, characterized by left ventricular dilatation, ventricular wall thinning and diffuse myocardial dysfunction, leads to congestive HF (72) and right ventricular dysfunction (73). These pathological changes result in the transition from compensatory hypertrophy to DCM (74). The heart undergoes continuous remodeling of myocardial cells through transduction of intercellular signals and activation of the transcription and transmission pathways (75). Naga Prasad *et al* (76) performed reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis on a set of samples used for miR microarray analysis, and identified that hsa-mir-378 ($P<0.0055$), hsa-mir-001 ($P<0.0001$), hsa-mir-007 ($P<0.0009$) and hsa-mir-29b ($P<0.0087$) were notably decreased in DCM compared with control samples; by contrast, hsa-mir-342 ($P<0.0004$), hsa-mir-214 ($P<0.0001$), hsa-mir-125b ($P<0.0785$), hsa-mir-145 ($P<0.0091$) and hsa-mir-181b ($P<0.0047$) were significantly increased in DCM compared with non-failing controls, and may be used to indicate the stage of HF development. Enes Coşkun *et al* (77) investigated 23 pediatric patients (aged 2-192 months) with isolated idiopathic DCM as the experimental group, and 26 age-matched healthy children with innocent murmur as the control group. Patients with fractional shortening of <25% and with a left ventricular end-diastolic diameter >112% of the predicted dimension were considered to have DCM. The results of RT-qPCR demonstrated that the expression levels of miR-454 and miR-518f were significantly higher in DCM patients compared with those in the control group. Furthermore, the expression levels of 10 miRs (miR-618, miR-875-3p, miR-205, miR-194, miR-302a, miR-147, miR-544, has-miR-99b, miR-155 and miR-218) were notably lower in patients with DCM compared with control subjects, suggesting that they may be used as potential diagnostic biomarkers. Interestingly, Miyamoto *et al* (78) observed that 2 miRs (hsa-miR-636 and hsa-miR-155) were upregulated and 2 miRNAs (hsa-miR-646 and hsa-miR-639) were downregulated in patients with DCM compared with patients with DCM with recovered ventricular function, which indicated that they may serve as diagnostic as well as prognostic biomarkers. However, further research is required to elucidate the specific underlying mechanisms.

Leger *et al* (79) and Zeng *et al* (80) measured left ventricular ejection fraction (LVEF) and the 6-min walk test distance (6MWTD) and CBP/p300 interacting transactivators with ED-rich termini 2 (CITED2), hypoxia-inducible factor-1 (HIF-1) in patients with ICM before and after treatment, and identified that LVEF, 6MWTD, CITED2 and HIF-1 levels were significantly lower in the ICM group compared with those in the control group prior to treatment ($P<0.01$). The N-terminal pro-B-type natriuretic peptide (NT-proBNP), HIF-1 and miR-182 levels in the ICM group were significantly higher compared with those in the control group ($P<0.01$). Following 4 months of treatment, the levels of 6MWTD, CITED2 and LVEF in the ICM group were significantly increased, whereas the levels of plasma NT-proBNP, HIF-1 and miR-182 were significantly decreased ($P<0.01$). Furthermore, the plasma miR-182 level was negatively correlated with CITED2, LVEF and 6MWTD ($P<0.05$) and positively correlated with HIF-1 ($P<0.05$) in the ICM group. Therefore, miR-182 is correlated with several indicators of HF, and may be considered to reflect the severity of the disease. Olson and Rooij (81) and Fichtlscherer *et al* (82) observed upregulation of miR-208a and miR-499 and downregulation of the circulating levels of miR-126, miR-17, miR-92a and the inflammation-associated miR-155 in patients with coronary artery disease compared with healthy controls by qPCR. Similarly, the level of miR-145 in smooth muscle was significantly reduced. By contrast, the levels of cardiac muscle-enriched miRs (miR-133a and miR-208a) tended to be higher in patients with coronary artery disease. Li *et al* (83) demonstrated a decrease of miR-125a, miR-20a and miR-302d levels in ICM using Deep RNA sequencing. Notably, only 55 miRs were indicated to be consistently increased in ICM and non-ischemic cardiomyopathy (NICM), including miR-21-5p, miR-125b-1-3p and miR-106b-5p, among others. However, 38 miRNAs were downregulated in both ICM and NICM (non-ischemic cardiomyopathy), including miR-20a-5p, miR-17-5p and let-7e-5 (83). The findings suggest that miR-182 appears to be a promising new biomarker for the diagnosis of ICM and DCM in clinical research.

miRs associated with hypertension. Hypertension is an independent risk factor for cardiac and cerebrovascular disease (84). It has been reported that at least 50% of patients with long-term hypertension will likely undergo cardiac remodeling, particularly left ventricular remodeling (85). Myocardial cell hypertrophy is among the primary causes underlying the occurrence of HF (86). Notably, it has been demonstrated that miR-208 can induce cardiac hypertrophy and results in the overexpression of β-myosin heavy chain in myocardial fibrosis (87). Several miRs were indicated to be differentially expressed in hypertension, including miR-296-5p, let-7e and human cytomegalovirus (HCMV)-miR-UL112, as encoded by HCMV in previous studies of the hypertension-associated miR spectrum (88-90). Interferon regulatory factor 1, which is involved in the regulation of blood pressure by acting on nitric oxide synthase and vascular angiotensin (Ang) receptor, was demonstrated to be a direct target of HCMV-miR-UL112 (91). However, in hypertension, HCMV titers are considered to reflect the expression level of HCMV-miR-UL 112 (91), which is an independent risk factor for hypertension. HCMV has been reported to inhibit vasodilation by impairing nitric oxide synthase function (92) and causing endothelial cell dysfunction (93). However, further research is warranted due to the elusive association between HCMV infection and endothelial dysfunction.

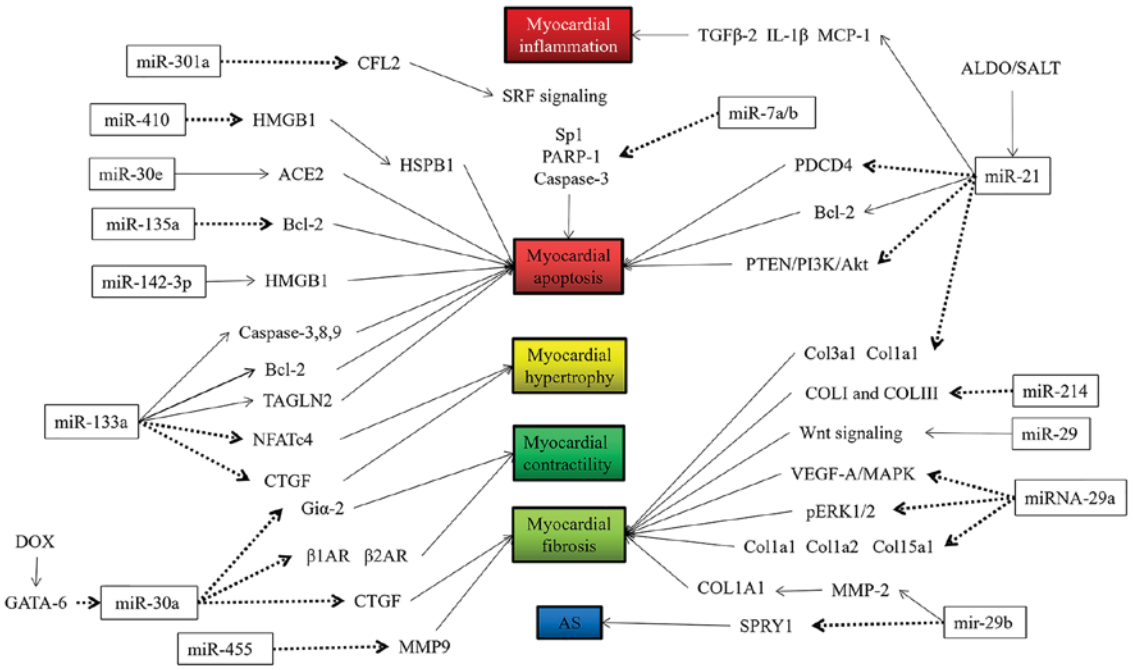

Figure 1. Association between miRs and different pathogenic mechanisms of heart failure. Solid lines represent positive regulation and dashed lines represent negative regulation. The nock of the arrow controls the tip of the arrow, for example miR-7a/b downregulates Sp1, PARP-1 and caspase-3, whereas Sp1, PARP-1 and caspase-3 promote myocardial fibrosis. Therefore, miR-7a/b protects cardiomyocytes against apoptosis. CFL2, Cofilin-2; HMGB1, high-mobility group box 1 protein; HSBP1, Heat Shock Factor Binding Protein 1; ACE2, Angiotensin-convertingenzyme2; Bcl-2, B-cell lymphoma-2; SRF, serum response factor; TAGLN2, Transgelin 2; NFATC4, Nuclear Factor Of Activated T Cells; CTGF, connective tissue growth factor; DOX, Doxorubicin; MMP-9, matrix metalloproteinase-9; β1AR and β2AR, β1-and β2-adrenoceptor; TGF-β, transforming growth factor-β; IL-1β, Interleukin-1β; MCP1, monocyte chemoattractant protein-1; PDCD4, programmed cell death 4; SP1, specific protein 1; PARP1, poly ADP-ribose polymerase; ALDO, aldosterone; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, Protein Kinase B; Col1a1, collagen 1A1; Col1a2, collagen 1A2; col15a1, collagen 15A1; Col III, type III collagen; Col I, type I collagen; MAPK, mitogen-activated protein kinase; VEGF, Vascular endothelial growth Factor; ERK, extracellular regulated protein kinases; MMP-2, matrix metalloproteinase-2; SPRY1, Protein sprouty homolog 1.

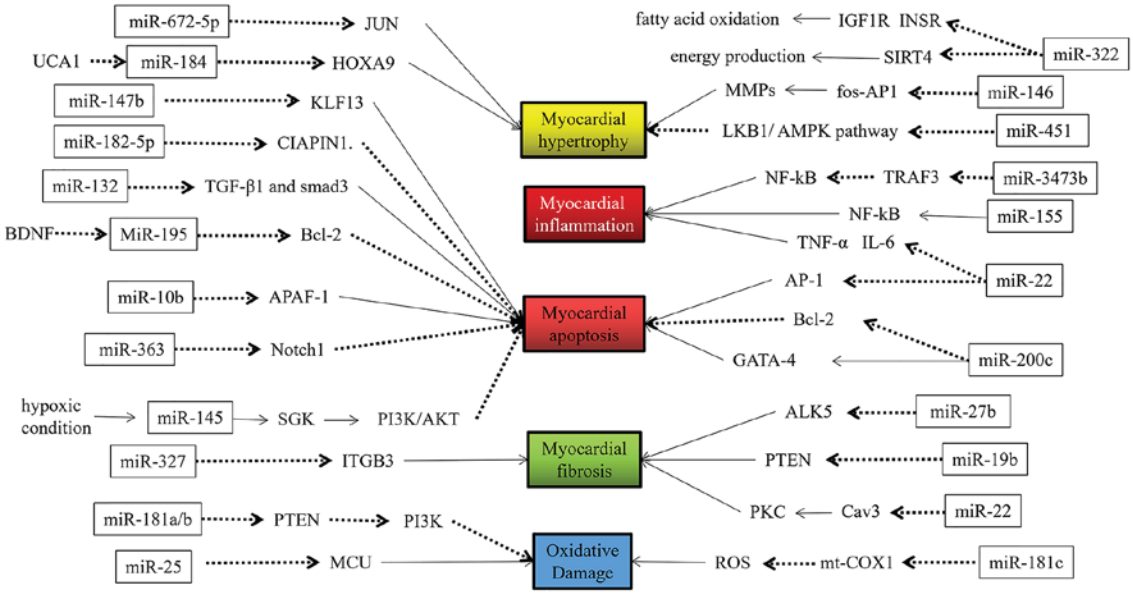

Figure 2. Association between miRs and different pathogenic mechanisms of heart failure. Solid lines represent positive regulation and dashed lines represent negative regulation. The nock of the arrow controls the tip of the arrow, for example miR-451 downregulates the LKB1/AMPK pathway, and the LKB1/AMPK pathway negatively regulates the tendency for cardiomyocyte hypertrophy. Therefore, miR-451 promotes myocardial hypertrophy. JUN, Jun proto-oncogene product which is a subunit of the AP-1 transcription; HOXA9, Homeobox A9; UCA1, urothelial carcinoma-associated 1; KLF13, Kruppel-like transcription factor 13; CIAPIN1, cytokine-induced anti-apoptotic molecule; BDNF, brain derived neurotrophic factor; TGFβ-1, transforming growth factor β-1; Bcl-2, B-cell lymphoma-2; APAF-1, apoptotic protease activating factor-1; SGK, Serum and Glucocorticoid Induced Kinase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; ITGB3, integrin β3; PTEN, phosphatase and tensin homolog deleted on chromosome 10; MCU, mitochondrial calcium uptake; INSR, insulin receptor; IGFR1, Insulin-like growth factor 1 receptor; SIRT4, Sirtuin-4; fos-AP1, Fos-Associated Protein 1; MMP, matrix metalloproteinase; AMPK, adenosine monophosphate-activated protein kinase; LKB1, Liver kinase B1; NF-κB, nuclear factor kappaB; TRAF3, TNF receptor associated factor 3; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; AP-1, activator protein-1; ALK-5, activin-like kinase 5; PKC, protein kinase C; CAV3, Caveolin 3; ROS, reactive oxygen species; COX, cycloxygenase.

Table I. Information on different types of miRs.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
Li *et al*, 2016	miR-7a/b	Sp1, PARP-1 and caspase-3	Binding activity of Sp1 may conditionally mediate the repression of miR-7a/b-regulated PARP-1 and caspase-3 expression, miR-7a/b inhibitors effectively upregulated Sp1, PARP-1 and caspase-3 expression	H9c2 cell line	Western blot, RT-qPCR, luciferase assay and ChIP	(16)
Ball *et al*, 2017	miR-21	ALDO/SALT, TGFβ-2, IL-1β, MCP-1, Col3a1 and Col1a1	miR-21 downregulation attenuated ALDO/SALT-mediated LV inflammatory marker mRNA expression, such as TGFβ-2, IL-1β and MCP-1. miR-21 downregulation exacerbated ALDO/SALT-mediated LV fibrosis marker mRNA expression upregulation, such as Col1a1 and Col3a1	Left ventricle of Control, ALDO, SALT, ALDO/SALT, ALDO/SALT+Eplerenone or ALDO/SALT+AHT. ALDO (0.75 μg/h, Steraloids)	RT-qPCR and northern-blot	(17)
Deng *et al*, 2016	miR-21	PTEN/PI3K/Akt, Caspase-3 Bax and Bcl-2	miR-21 decreased H_2O_2-induced apoptosis by decreasing PTEN/PI3K/Akt signaling. miR-21 downregulated the proapoptosis protein Caspase-3 and Bax, and upregulated Bcl-2	c-kitD CSC	RT-qPCR, western blot and confocal microscopy	(18)
Cheng *et al*, 2016	miR-21	TGF-β1 and p-ERK/ERK	Celastrol attenuated miR-21 upregulation by TGF-β1 and decreased elevated p-ERK/ERK levels in CFs transfected with miR-21	Cardiac fibroblasts	Western blot, RT-qPCR and luciferase reporter assay	(19)
Xiao *et al*, 2016	miR-21	PDCD4	miR-21 inhibited apoptosis pathway through downregulating PDCD4, Restored miR-21/PDCD4 pathway could protect myocardial cells against oxidative stress-related apoptosis	H9C2 cardiac cells	Western blot, RT-qPCR and luciferase activity assay	(20)
Tao *et al*, 2016	miR-29a	VEGF-A and p-ERK1/2	miRNA-29a suppressed cardiac fibrosis and fibroblast proliferation via down-regulating p-ERK1/2 and VEGF-A/MAPK signal pathway	Cardiac fibroblasts	Western blot and RT-qPCR	(21)
Liu *et al*, 2017	miR-29a	APN and collagen I and III	miR-29a has a negative correlation with ANP in atherosclerosis	Blood sample	RT-qPCR and ELISA	(22)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
Lu *et al*, 2018	miR-29b	SPRY1, MAPK, TNF-α, ROS, NADPH oxidase, CCL2 and CCL5	miR-29b suppressed the MAPK signaling pathway through inhibiting SPRY1 at the posttranslational level in atherosclerosis	HUVECS	Western blot, luciferase reporter assay, statistical analysis, RT-qPCR and ROS determination	(23)
Sassi *et al*, 2018	miR-29	Wnt signaling	miR-29 promoted cardiac hypertrophy and fibrosis via derepressesing Wnt signaling	Cardiac fibroblasts, aorta in patients with aortic valve stenosis and aorta in mice induced by TAC	RT-qPCR, immunohistochemical analyses and secretome analysis	(24)
Panizo *et al*, 2017	miR-29b	CTGF, COL1A1 and MMP-2	miR-29b inhibited CTGF, COL1A1 and MMP-2	Cardiomyocytes of the left ventricle	Western blot and RT-qPCR	(25)
Heid *et al*, 2017	miR-29	Col1a1, Col1a2 and col15a1	Upregulation of miR-29 decreased col1a1, col1a2 and col15a1	Human cardiac fibroblasts	Luciferase reporter assay, Masson/ immunohistochemical staining, western blot and RNA sequencing	(26)
Chen *et al*, 2018	miR-30a	CTGF and collagen	miR-30a inhibited CTGF by directly combining with the 3'-UTR of CTGF, thereby reducing collagen and myocardial fibrosis, which improved cardiac function	Young adult and old Nfu hearts	RT-qPCR	(27)
Roca-Alonso *et al*, 2015	miR-30	GATA-6, β1AR, β2AR and Giα-2	miR-30 expression attenuates the contractile response of cardiomyocytes to βAR stimulation (β1AR, β2AR and Giα-2), which reduced cardiomyocyte contractility DOX sustained miR-30 downregulation in cardiomyocytes via improving GATA-6	H9c2 cardiac muscle cell line	NanoString technology, luciferase assays, ROS detection and cAMP accumulation	(28)
Lai *et al*, 2016	miR-30e	ACE2, caspase-3 and Beclin-1	Silencing miR-30e reverses the heart-protective effect of ACE2 and induces primary cardiomyocyte apoptosis Overexpression of ACE2 attenuates doxorubicin-mediated pathological signaling of primary cardiomyocytes	H9C2 cardiomyocytes	RT-qPCR and western blot	(29)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
van Middendorp *et al*, 2017	miR-133a	CTGF	miR-133a negatively regulated CTGF expression SRF and NFATc4, as target genes of miR-133a, did not show significant relation with miR-133a in local hypertrophy	Isolated cardiomyocytes	RT-qPCR and statistical analysis	(30)
Li *et al*, 2010	miR-133a	NFATc4	Silencing of NFATc4 by miR-133a may contribute to miR-133a-mediated anti-hypertrophy	Neonatal rat cardiomyocytes	RT-qPCR, western blot and immunostaining	(31)
Li *et al*, 2015	miR-133a	Caspase-8, caspase-9, caspase-3, Bcl-2 and TAGLN2	miR-133a suppressed caspase-8, caspase-9, and caspase-3, but improved Bcl-2 and suppressed TAGLN2 expression via binding to 3'-UTR of TAGLN2 mRNA	Hypoxic H9c2 cells	Bioinformatics analysis and dual-luciferase reporter analysis	(32)
Rangrez *et al*, 2017	miR-301a	CFL2	Overexpression of Cfl2 or knockdown of miR-301a resulted in the activation of SRF signaling and overexpression of miR-301a reduced Cfl2 expression	NRVCM	RNA isolation, cDNA synthesis, RT-qPCR and microarray analysis	(33)
Dong *et al*, 2016	miR-214	Ang-II, COL-I and COL-III	miR-214 may inhibit collagen synthesis in CFBs induced by Ang II and upregulated miR-214 can inhibit COLI and COLIII Ang II negatively correlates with the expression of miR-214	CFBs	Masson staining, RT-qPCR and western blot	(34)
Chaturvedi *et al*, 2015	miR-455	MMP-9	miR-455 prevented the downstream detrimental effects of MMP9 that lead to fibrosis and myocyte uncoupling	Cardiosomes (exosomes from cardiomyocytes)	Western blot, RT-qPCR and IHC	(35)
Liu *et al*, 2017	miR-135a	Bcl-2	miR-135a positively regulated H_2O_2-induced apoptosis in H9c2 cells via blocking Bcl-2 protein	H9c2 cells	RNA-mediated gene silencing, RNA extraction, RT-qPCR and western blot	(36)
Wang *et al*, 2016	miR-142-3p	HMGB1 and TGF-β1/Smad3	TGF-β1/Smad3 signaling involved in the miR-142-3p/HMGB1-mediated apoptosis and fibrosis of M6200 cells miR-142-3p inhibits H/R-induced apoptosis and fibrosis by the inhibition of HMGB1 expression partly	M6200 cells	Bioinformatics analysis and dual-luciferase reporter assay	(37)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
Yang *et al*, 2017	miR-410	HMGB1 and HSPB1	miR-410 may inhibit mitophagy and apoptosis following cardiac I/R injury by repressing HSPB1 activity via directly suppressing HMGB1	HACMs	Dual-luciferase assay	(38)
Zhang *et al*, 2018	miR-208a	CHD9 and Notch/NFB	CHD9 is a direct target of miR-208a, which was also related with Notch/NFB signal pathway during I/R injury	H9c2 cells	RT-qPCR, dual-luciferase activity and western blot,	(39)
Fan *et al*, 2018	miR-210	HGF	Upregulation of HGF was observed among the AMI rats after receiving miR-210 agonists	HUVEC	RT-qPCR, immunohistochemistry, western blot and statistical analysis	(40)
Zhang *et al*, 2018	miR-182-5p	CIAPIN1	miR-182-5p promoted apoptosis in hypoxia-induced cardiomyocytes via negative regulation of CIAPIN1	H9c2 and 293T cells/primary rat cardiac muscle cells	Bioinformatic analysis and dual-luciferase reporter assay	(41)
Liu *et al*, 2018	miR-132	TGF-β1 and smad3	miRNA-132 decreased the expression of TGF-β1 and smad3 and increased the antioxidant stress and antiapoptotic ability of H9C2 cells	HF patients' blood/H9C2 cell	HE/Masson staining, MTT assay, RT-qPCR western blot and statistical analysis	(42)
Zhou *et al*, 2018	miR-184	HOXA9 and ANP, BNP, PE and UCA1	UCA1 promoted cardiac hypertrophy through competitively binding with miR-184 to enhance the expression of HOXA9. The overexpression of miR-184 lessened the enlarged surface area of cardiomyocytes and the elevated expression of fetal genes (ANP and BNP) induced by PE	Cardiomyocyte isolated from neonatal mice	Plasmid construction and transfection, RT-qPCR, luciferase reporter analysis and western blot	(43)
Rubiś *et al*, 2016	miR-99	Akt-1 and EGR-1	EGR-1 mediated regulation of miR-99 family that serves a key role in determining the fate of cardiac hypertrophy by regulating Akt-1 signaling	Extracellular matrix and serum	Endomyocardial biopsy and RT-qPCR	(44)
Ji *et al*, 2018	miR-327	ITGB3	miR-327 represses integrin (ITG)B3, contributing to its effect on cardiac fibrosis	Cardiac fibroblast	Immunohistochemistry, western blot and RT-qPCR	(45)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
Lu *et al*, 2018	miR-672-5p	JUN	miR-672-5p had suppressive effects on cardiac hypertrophy through inhibiting the expression of Jun in cardiomyocytes	Myocardial cells	RT-qPCR, luciferase assay and western blot	(46)
Wang *et al*, 2018	miR-27b	ALK5 and Smad-2/3 pathway	miR-27b inhibited AngII-induced Smad-2/3 phosphorylation, miR-27b ameliorates AF through inactivation of Smad-2/3 pathway by inhibiting ALK5, a receptor of TGF-β	Myocardial cells	RT-qPCR, luciferase assay and western blot	(47)
Yang *et al*, 2016	miR-22	AP-1, Bcl-2/Bax, TNF-α and IL-6	miR-22 significantly inhibited AP-1 activity, changed Bcl-2/Bax ratio and suppressed TNF-α and IL-6 induced by H/R	Neonatal rat ventricular cardiomyocytes	RT-qPCR, western blot, ELISA and EMSA	(48)
Zhang *et al*, 2018	miR-22	Cav3-PKCε pathway	miR-22 accelerates cardiac fibrosis through the miR-22-Cav3-PKCε pathway and inhibits angiotensin II-mediated excessive collagen deposition through protein kinase C (PKC)ε inactivation	Cardiac fibroblasts from the neonatal SD rats	RT-qPCR, western blot, Masson trichrome staining, luciferase reporter assay and immunofluorescence staining	(49)
Zheng *et al*, 2018	miR-26a-5p	ULK1, LC3-I and LC3-II	miR-26a-5p can reduce the expression of ULK1 and collagen I, and decrease the activation of LC3-I to LC3-II	Primary cardiac fibroblasts	Dual-luciferase reporter assay, western blot and RT-qPCR	(50)
Gu *et al*, 2018	miR-147b	KLF13	miR-147b inhibits cell viability and promotes apoptosis of rat H9c2 cardiomyocytes via downregulating KLF13 expression	H9c2 cells	Luciferase reporter assay and RT-qPCR	(51)
Sun *et al*, 2017	miR-145	SGK1, PI3K/AKT signaling pathway and HIF-1a	miR-145 could be upregulated by HIF-1a in cardiomyocytes under hypoxic conditions, miR-145 overexpression promoted cell viability, inhibited apoptosis and ROS activity and promoted activation of PI3K/AKT signaling pathway via SGK1 upregulation	H9c2 cell line and mouse cardiac muscle cell line	RT-qPCR, western blot and ELISA	(52)
Chen *et al*, 2017	miR-200c	GATA-4 and Bcl-2	miR-200c significantly increased GATA-4 expression. Furthermore, downregulation of miR-200c upregulated the expression of the anti-apoptotic gene Bcl-2	Cardiomyocyte	RT-qPCR, luciferase assay and western blot	(53)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
Meng *et al*, 2017	miR-363	Notch1	Inhibition of miR-363 protects cardiomyocytes against hypoxia-induced apoptosis through promotion of Notch1 expression and activation of Notch signaling	Rat myocardium-derived H9C2 and 293T cells	RT-qPCR, MTT and western blot	(54)
Li *et al*, 2015	miR-10a, miR-139b and miR-206	TNF, IL-1, IL-6, Cx43 and Rho kinase	TNF, IL-1 and IL-6 downregulate the expression of miR-10a, miR-139b, miR-206 and miR-222, and upregulate the expression of Cx43 and Rho kinase in VSMCs. miR-10a, miR-139b, miR-206 and miR-222 could downregulate the expression of Cx43 and Rho kinase	Cardiomyocyte from SD rats fed with a high-fat diet	Statistical analyses, ELISA and RT-qPCR	(55)
Gallego *et al*, 2016	miR-10b	APAF-1	miR-10b inhibition in HL-1 cardiomyocytes induced the overexpression of APAF-1	Cardiomyocytes	TaqMan low density array and RT-qPCR	(56)
Huang *et al*, 2016	miR-195	Bcl-2 and BDNF	miR-195 promotes ischemic apoptosisc by repressing Bcl-2 and inhibits cardiac function of MI rats BDNF abolished the pro-apoptotic role of miR-195, which was reversed by its scavenger TrkB-F	NRVMs	RNA extraction, RT-qPCR, luciferase activity assay and cell viability assay	(57)
Blumensatt *et al*, 2017	miR-208a	AT II	Locked-nucleic-acid-mediated inhibition of miR-208a function reversed the detrimental effects induced by AT II	Primary adult rat cardiomyocytes from Lewis rats	Statistical analysis, and histomorphological and immunohistochemical analysis	(58)
Marchand *et al*, 2016	miR-322	SIRT4, IGF1R and INSR	miR-322 inhibits the insulin pathway/IGF1R and cyclin D, miR-322 downregulates SIRT4, IGF1R and INSR, which thus decreases Akt phosphorylation and insulin action	Cardiomyocytes and heart from C57BL/6 mice fed with high-fat diet (10 weeks)	RNA isolation, RT-qPCR, western blot and luciferase assay	(59)
Zhong *et al*, 2016	miR-19b	PTEN, a-SMS and TGFβRII	miR-19b promotes cardiac fibroblast proliferation and migration by downregulating PTEN, which decreased a-SMS expression by targeting TGFβRII	H9C2 cardiomyocytes	Western blot and RT-qPCR	(60)
Pan *et al*, 2015	miR-25	Oxidative stress pathways/MCU	miR-25 protects cardiomyocytes against oxidative damage by inhibiting the MCU	H9C2 cardiomyocytes exposed to doxorubicin	FACS, TUNEL assay, immunoblotting, luciferase	(61)

Table I. Continued.

Author, year	miRs	Relative gene protein or signaling pathways	Biological effects	Tissue, cells or experimental model	Detection means	(Refs.)
					reporter assay, western blot and RT-qPCR	
Das *et al*, 2017	miR-181a/b	PTEN, PI3K ROS and mt-COX1	miR-181a/b deficiency inhibits PI3K signaling through upregulation of PTEN. miR-181a/b enhanced damage by overproduction of ROS via inhibiting mt-COX1	H9c2 cardiomyocytes	Measurement of sarcomere shortening and Ca^{2+} transients, mitochondrial swelling assay, western blot and statistical analysis	(62)
Palomer *et al*, 2015	miR-146	Fos-AP1, MMPs and collagen	Downregulation of the Fos-AP-1 pathway by miR-146a can inhibit MMP-9 activity and therefore suppresses hypertrophy of cardiomyocytes and fibrosis of the interstitial substance	AC16 cell line (cardiac muscle cells)	Immunoblot analysis, statistical analysis, electrophoretic mobility shift assay and RT-qPCR	(63)
Khamaneh *et al*, 2015	miR-155	NF-κB inflammatory signaling pathways	Activation of inflammatory signaling pathways/NF-κB	Cardiomyocytes from diabetes mellitus type 1 model SD rats administrated with streptozotocin	RT-qPCR and statistical analysis	(64)
Fang *et al*, 2015	miR-3473b	inflammatory signaling pathways/TRAF3-NF-κB	miR-3473 negatively regulates TRAF3, a well-known negative regulator of the NF-κB pathway, to enhance NF-κB pathway	Bacterial infection model with murine macrophages	RT-qPCR and western blot	(65)
Kuwabara *et al*, 2015	miR-451	LKB1/AMPK pathway	Induces activation of lipotoxicity through suppression of the LKB1/AMPK pathway	Neonatal cardiomyocytes from C57BL/6 mice feed with high fat diet (20 weeks)/heart	Dual luciferase reporter assay, western blot, transthoracic echocardiography and statistical analysis	(66)

PDCD4, programmed cell death 4; TGFβ-2, transforming growth factor β-2; MCP-1, monocyte chemoattractant protein-1; CSCs, cardiac stem cells; CFs, cardiac fibroblasts; APN, adiponectin; HUVECs, human umbilical vein endothelial cells; TAC, transverse aortic constriction; col1a1, collagen 1A1; col1a2, collagen 1A2; col15a1, collagen 15A1; ARVCMs, adult rat ventricular cardiomyocytes; DOX, doxorubicin; β1AR and β2AR, β1-and β2-adrenoceptor; NRVCM, neonatal rat ventricular cardiomyocytes; CFBs, cardiac fibroblasts; H/R, hypoxia/reoxygenation; I/R, ischemia-reperfusion; HMGB1, high-mobility group box 1 protein; HUVECs, human umbilical vein endothelial cells; CIAPIN1, cytokine-induced anti-apoptotic molecule; PE, phenylephrine; HOXA9, homeobox A9; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; EGR-1, early growth response protein 1; ITGB3, integrin β3; JUN, Jun proto-oncogene; AP-1, activator protein 1; AF, atrial fibrosis; Bcl-2, B-cell lymphoma-2; Cav3, Caveolin 3; ULK, Unc-51 like autophagy activating kinase; Cx43, connexin 43; APAF-1, apoptotic protease activating factor-1; BDNF, brain derived neurotrophic factor; IGFR1, insulin-like growth factor 1 receptor; PTEN, phosphatase and tensin homolog deleted on chromosome 10; MCU, mitochondrial calcium uptake; MMP-3, matrix metalloproteinase-3; NF-κB, nuclear factor-κB; TRAFs, TNF receptor associated factors; AMPK, adenosine monophosphate-activated protein kinase; TTC, 2,3,5-triphenyltetrazolium chloride; TUNEL, TdT-mediated dUTP nick-end labeling; ELISA, enzyme linked immunosorbent assay; ROS, reactive oxygen species; CFL2, cofilin-2; IHC, immunohistochemistry; HF, heart failure; UCA1, urothelial carcinoma-associated 1; AT, angiotensin; EMSA, electrophoretic mobility shift assay; TNF, tumor necrosis factor; SD, Sprague-Dawley; PKC, protein kinase C; FACS, fluorescence-activated cell sorting; western blot, western blotting analysis; ALDO, aldosterone; SALT, 1.0% NaCl; AHT, triple antihypertensive therapy (240 mg/kg hydralazine + 75 mg/kg hydrochlorothiazide + 1.5 mg/kg reserpine); KLF, Kruppel-like transcription factor; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SGK, serum and glucocorticoid induced kinase; ChIP, chromatin immunoprecipitation assay; COL-I, type I collagen; COL-III, type III collagen.

Kontaraki *et al* (94,95) reported that upregulated miRs included miR-1 and miR-21, whereas downregulated miRs included miR-9, miR-126, miR-133, miR-143 and miR-145 in the hypertension group compared with the healthy control group. In addition, miR-21, miR-143 and miR-145 were negatively correlated and miR-133 was positively correlated with 24-h ambulatory mean blood pressure, mean diastolic blood pressure and mean pulse pressure in the hypertension group. Furthermore, miR-9 and miR-126 were positively correlated with mean pulse pressure, but the association between miR-9 and left ventricular hypertrophy index was positively correlated with the 24-h ambulatory mean blood pressure and mean diastolic blood pressure. Therefore, this miR may reflect the severity of hypertensive HF.

Dickinson *et al* (96) reported that the circulating levels of miR-423-5p, miR-106b, miR-20b, miR-223, miR-16 and miR-93 were markedly increased in hypertension-induced HF, which was confirmed via RT-qPCR analysis of plasma RNA from hypertensive rats. These results indicate that several miRs can reflect disease progression to a certain extent, and may be used as biomarkers of hypertensive HF. This suggests that miRs should be detected pre- and post-treatment to reduce the effects of medication on the results of the experiment. Hou *et al* (97) randomly divided 16 spontaneously hypertensive rats (SHR) into the SHR control (distilled water) and intervention SHR (captopril 10 mg/kg/day) groups. An additional 8 Wistar male rats comprised the normal control groups (captopril 10 mg/kg/day or distilled water for 8 weeks). The expression of miR-137 was detected by RT-qPCR and western blot analysis in rat hearts, and miR-137, Ang II, transforming growth factor (TGF)-β1, Smad3, collagen (Col)-I and Col-III were identified to be more highly expressed in the SHR treatment and SHR control groups than the normal control group ($P<0.01$ and $P<0.05$, respectively); by contrast, the levels of miR-137, Ang II, TGF-β1, Smad3, Col-I and Col-III were significantly lower in the normal control groups compared with the SHR control group ($P<0.01$ and $P<0.05$, respectively). Thus, miR-137 may promote cardiac remodeling in SHR by upregulation of Ang II and the TGF-β1/Smad3 signaling pathway; in addition, captopril intervention can inhibit miR-137 expression. Therefore, miR-137 not only indicates the presence of high blood pressure, it may also reflect its severity.

Li *et al* (98) reported that insulin-like growth factor (IGF)-1 prevented diabetes-induced cardiomyopathy via marked anti-apoptotic and anti-fibrotic effects, which are mediated by miR-1. These findings provide a new paradigm for the endocrine effects of IGF-1 in the heart, and suggest that cardiac-specific miR-1 may be a useful biomarker and therapeutic target for diabetes-induced cardiomyopathy. Yang *et al* (99) observed that miR-505 interfered with the migration of cultured endothelial cells through targeting fibroblast growth factor 18, suggesting that miR-505 may be involved in vascular regeneration. In addition, a group of miRs (miR-92a, miR-130a and miR-195) were demonstrated to be abnormally expressed in hypertensive patients with metabolic syndrome. Notably, miR-92a is differentially expressed in the blood of hypertensive and non-hypertensive patients (100) and may promote miR-mediated intercellular communication (101). Kontaraki *et al* (94,95) confirmed several types of differentially expressed miRs in an animal model: Myocardial hypertrophy was induced by miR-21, miR-208b and miR-499; the anti-myocardial hypertrophy miRs comprised miR-1, miR-26b and miR-133a, of which miR-1, miR-21, miR-208b and miR-499 were upregulated, whereas miR-26b and miR-133a were downregulated in peripheral blood mononuclear cells from patients with hypertension compared with healthy controls. In patients with hypertension, the degree of left ventricular hypertrophy was negatively correlated with the miR-1 and miR-133 indices, whereas the miR-21, miR-26b, miR-208b and miR-499 indices were positively associated with left ventricular hypertrophy.

miRs associated with diabetic HF. Dickstein (102) reported that the occurrence and development of insulin resistance in HF was correlated with overactivation of the renin-angiotensin-aldosterone system (103,104), disturbance of energy metabolism in the myocardium (105), liver pathology, as well as other factors. It was previously demonstrated that the expression of miR-133 and miR-1 increased significantly in myocardial cells following hyperglycemic injury (106). IGF-1 and IGF-1 receptor are the two target genes of miR-1 (107). Previous studies demonstrated an increasing level of miR-133 and decreasing levels of miR-650, miR-222 and miR-338 in hyperglycemic cardiomyocyte injury (108,109). Greco *et al* (110) collected biopsies from the peri-infarctual area (border zone) and the non-ischemic remote zone from patients with diabetic HF (D-HF), non-diabetic HF (ND-HF) and the control group. miR expression was measured using RT-qPCR in left ventricular biopsies from 10 patients with D-HF and 19 patients with ND-HF affected by non-end-stage ischemic cardiomyopathy. A total of 17 miRs were revealed to be differentially expressed in patients with D-HF and/or ND-HF when compared with control subjects; in particular, miR-34b, miR-34c, miR-210, miR-199b and miR-372 were upregulated, whereas miR-650 and miR-223 were downregulated. Therefore, miRs may not only be obtained from the blood or serum, but also from tissue biopsies, when the content in the body fluids is low. Nandi *et al* (111) and Deng *et al* (112) reported that attenuation of miR-133a in diabetic hearts is associated with the induction of autophagy and hypertrophy. In conclusion, attenuation of miR-133a appears to serve a key role in D-HF and contributes to the exacerbation of diabetes-mediated cardiac autophagy and hypertrophy in patients with HF undergoing left ventricular assist device implantation. Chavali *et al* (113) used multiplex RT-qPCR in insulin 2 mutant Akita mouse hearts (a diabetic mouse model with heart disease) and observed marked downregulation of miR-744, miR-142-3p, miR-384-3p, miR-494, let-7a, miR-450, miR-338, miR-130, miR-142-3p, miR-148, miR-338, miR-345-3p, miR-433, miR-451, miR-455, miR-500, miR-542-3p and miR-872. By contrast, miR-295 was upregulated in Akita mouse hearts. Therefore, miR-295 may be used as a mammalian-specific miR in early embryonic stages. Increased miR-295 expression was associated with pathological changes in Akita mouse hearts. miR-223, as an anti-inflammatory miR, may reflect the progression of diabetic $Ins2^{+/-}$ Akita heart

Table II. Expression of miRs in different types of heart failure.

Author, year	Heart failure type	miR expression level	Detection means	Source	(Refs.)
Leger *et al*, 2013	ICM	miR-361 ↑ in ICM group	RT-qPCR	Serum	(79)
Zeng *et al*, 2017	ICM	miR-182 ↑ in coronary artery disease group compared with the healthy control group	RT-qPCR	Plasma/serum	(80)
Olson and Rooij, 2014	ICM	miR-208 and miR-499 ↑ in ICM group	RT-qPCR	Serum	(81)
Fichtlscherer *et al*, 2010	ICM	miR-126, miR-17, miR-92 and miR-155 ↓ in ICM	RT-qPCR	Serum and blood	(82)
Li *et al*, 2018	ICM	miR-125a, miR-20a and miR- 302d ↓ only in ICM	RT-qPCR and deep RNA sequencing	Serum	(83)
Li *et al*, 2018	ICM	miR-20a-5p, miR-17-5p and let-7e-5 ↓ in ICM and NICM	RT-qPCR and deep RNA sequencing	Serum	(83)
Li *et al*, 2018	ICM	miR-21-5p, miR-125b-1-3p and miR-106b-5p ↑ in ICM and NICM	RT-qPCR and deep RNA sequencing	Serum	(83)
Naga *et al*, 2017	DCM	hsa-miR-214, hsa-miR-342, hsa-miR-125b, hsa-miR-181b and hsa-miR-145 ↑ in the DCM compared with controls	RT-qPCR	Serum	(76)
Naga Prasad *et al*, 2017	DCM	hsa-miR-1, hsa-miR-29b, hsa-miRNA-7, hsa-miR-378 ↓ in the DCM compared with controls	RT-qPCR	Serum	(76)
Enes Coşkun *et al*,	DCM	miR-454 and miR-518f ↑ in DCM	RT-qPCR	Serum	(77)
Enes Coşkun *et al*, 2016	DCM	miR-618, miR-875-3p, miR-205, miR-194, miR-302a, miR-147, miR-544, has-miR-99b, miR-155 and miR-218 ↓ in DCM	RT-qPCR	Serum	(77)
Miyamoto *et al*, 2015	DCM	hsa-miR-636 and hsa-miR-155 ↑ in the DCM	RT-qPCR	Serum	(78)
Miyamoto *et al*, 2015	DCM	hsa-miR-639 and hsa-miR-646 ↓ in the DCM	RT-qPCR	Serum	(78)
Ding *et al*, 2017	HHF	miR-296-5p, let-7e and hcmv-miR-UL112 ↑ in the HHF group	RT-qPCR	Serum	(91)
Kontaraki *et al*, 2013	HHF	miR-1, miR-21, miR-208b and miR-499 ↑ in the HHF group	RT-qPCR	Serum	(94)
Kontaraki *et al*, 2013	HHF	miR-26b, miR-133a, miR-9, miR-126, miR-133, miR-143 and miR-145↓ in the HHF group	RT-qPCR	Serum	(95)
Dickinson *et al*, 2013	HHF	miR-16, miR-20b, miR-93, miR-106b, miR-223 and miR-423-5p ↑ in the HHF group	RT-qPCR	Plasma/serum	(96)
Hou *et al*, 2016	HHF	miR-137 ↑ in SHR treatment group vs. SHR control group/SHR control group compared with the normal control group	RT-qPCR	Serum	(97)
Latronico *et al*, 2007	Diabetic heart failure	miR-133 ↑ in diabetic heart failure compared with control	RT-qPCR	Serum	(109)

Table II. Continued.

Author, year	Heart failure type	miR expression level	Detection means	Source	(Refs.)
Latronico *et al*, 2007	Diabetic heart failure	Level of miR-650, miR-222 and miR-338 ↓in diabetic heart failure	RT-qPCR	Serum	(109)
Greco *et al*, 2012	Diabetic heart failure	miR-650 and miR-223 ↓in diabetic heart failure	RT-qPCR	Body tissue	(110)
Greco *et al*, 2012	Diabetic heart failure	miR-34b-34c, miR-210, miR-199b and miR-372 ↑ in D-HF and ND-HF compared with control group	RT-qPCR	Body tissue	(110)
Nandi *et al*, 2015	Diabetic heart failure	miR-133a ↓ in diabetic heart failure introduced by insulin2 mutant (Ins2+/61) Akita heart disease	RT-qPCR	Serum	(111)
Deng *et al*, 2017	Diabetic heart failure	miR-24 ↓ in diabetic heart failure	RT-qPCR	Serum	(112)
Chavali *et al*, 2014	Diabetic heart failure	miR-295 ↑ in Akita	RT-qPCR	Serum	(113)
Chavali *et al*, 2014	Diabetic heart failure	miR-126, miR-222, miR-130a, miR-142-3p, miR-148, miR-338, miR-345-3p, -miR-384-3p, miR-433, miR-450, miR-451, miR-455, miR-499, miR-500, miR-542-3p, miR-744 and miR-872 ↓ in diabetic heart failure	RT-qPCR	Serum	(113)
van Solingen *et al*, 2012	Diabetic heart failure	miR-126 ↓ in diabetic microvascular tissues	RT-qPCR	Diabetic microvascular tissues	(116)
Fichtlscherer *et al*, 2010	Diabetic heart failure	miR-126 ↑ in patients with coronary atherosclerosis	RT-qPCR	Serum	(117)
Škrha *et al*, 2015	Diabetic heart failure	miR-29a, miR-1, miR-373, miR-143 and miR-20a ↓ in diabetic heart failure	RT-qPCR	Serum	(118)
Škrha *et al*, 2015	Diabetic heart failure	miR-195, miR-199a-3P, miR-700, miR-142-3p, miR-24, miR-21, miR-22, miR-499-3p, miR-208a and miR-705 ↑ in diabetic heart failure	RT-qPCR	Serum	(118)
Li *et al*, 2018	CHD	miR-29 ↑ in patients with CHD	RT-qPCR	Serum	(83)
Mukai *et al*, 2017	CHD	miR-486-3p, miR-155-5p and miR-486-5p ↑ in congenital cyanotic heart disease	RT-qPCR and microarrays	Serum	(125)
Mukai *et al*, 2017	CHD	miR-133a-2, let-7e-5p and miR-1260a ↓ in congenital cyanotic heart disease	RT-qPCR and microarrays	Serum	(125)
Chen and Li, 2017	CHD	miR-19a, miR-198, miR-130a and miR-27b ↑ in patients with CHD	RT-qPCR	Serum	(129)

miR, microRNA; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; HHF, hypertensive heart failure; DCM, dilated cardiomyopathy; CHD, congenital heart disease; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; SHR, spontaneously hypertensive rats; D-HF, diabetic heart failure; ND-HF, nondiabetic heart failure; ↓, downregulation; ↑, upregulation.

disease or D-HF. In another study, miR-1 and miR-133A were demonstrated to act as regulators of glucose homeostasis *in vitro* (113). Notably, miR-133a/b can reduce the expression of glucose transporter 4 and inhibit the uptake of glucose by insulin-induced myocardial cells (114). Furthermore, miR-133a/b targets Kruppel-like transcription factor 15, which is directly involved in this process (108). Two other target genes of miR-133a/b are the human ether-a-go-go-related gene and KCNQI, and these two genes are involved in the regulation of cardiac K^+ channels and the presence of long QT syndrome in patients with diabetes (115). The decrease of miR-126 in diabetic microvascular tissues may indicate the severity of diabetic vascular complications (116); however, the expression of miR-126 did not decrease, but was rather significantly increased in patients with coronary atherosclerosis (117). In a mouse model of type 1 diabetes mellitus established by streptozotocin (118), 15 miRs were differentially expressed in the myocardium, among which 10 miRs (miR-195, miR-199a-3P, miR-700, miR-142-3p, miR-24, miR-21, miR-22, miR-499-3p, miR-208a and miR-705) were upregulated, whereas 5 miRs (miR-29a, miR-1, miR-373, miR-143 and miR-20a) were notably downregulated. Histological examination revealed hypertrophy of the myocardial cells in type 1 diabetes mellitus group mice compared with the control group, with a disorderly arrangement and enlarged nuclei. Notably, the prediction of associated target genes primarily involves cell growth, differentiation, proliferation, collagen fiber growth, apoptosis and angiogenesis.

miRs of HF in CHD. CHD is a multi-gene genetic disease resulting from structural or functional cardiovascular abnormalities present at birth that are caused by congenital abnormalities (119). Disrupted miR expression may result in CHD via specific protein regulation. miR-133 and miR-1 are present in the same transcription unit (120); miR-1 is the most abundant miR and is highly conserved in human myocardial cells (121). Mature miR-1-1 and miR-1-2 have the same gene sequence; the miR-13 family includes miR-133a-1, miR-133a-2 and miR-133b (122,123). During heart development, the deletion or mutation of the essential gene Hand2 of muscle precursor cells in early embryonic development may lead to cardiac hypoplasia and even cardiac arrest (124). Mukai *et al* (125) revealed that miR-486-3p, miR-155-5p and miR-486-5p were increased in patients with cyanotic heart disease compared with those without heart disease. Furthermore, let-7e-5p and miR-1260a were decreased in patients with early-stage acyanotic heart disease compared with those without heart disease, suggesting that these miRs may be used for early diagnosis.

Zhao *et al* (126) reported that the expression of miR-1-2 was upregulated in myocardial and skeletal muscle cells. Overexpression of miR-1 during cardiac development may inhibit ventricular myocyte dilatation. It was also demonstrated that miR-1-2 targets the Hand2 gene, which may block Hand2 protein synthesis and regulate cardiac morphogenesis (127); its abnormal expression may even lead to CHD (127). Another study reported that the mouse phenotypes were almost normal with deletion of either miR-133a-1 or miR-133a-2, but the synchronous lack of these two miRs led to a fatal ventricular septal defect in approximately half of the mice during the embryonic period (128). Thus, miR-133 can promote myoblast proliferation, and miR-1 can stimulate myogenic differentiation. Therefore, miR-1 and miR-133 exhibit a dialectical association, and abnormalities may lead to the development of CHD.

Chen and Li (129) quantified the levels of miR-19a by RT-qPCR in the plasma of 30 patients with CHD, and changes in the levels of miR-19a, miR-130a and miR-27b were also confirmed using RT-qPCR. The levels of miR-19a, miR-198, miR-130a and miR-27b were significantly increased in patients suffering from pulmonary arterial hypertension induced by CHD. These observations suggest that circulating miR-19a may be a novel biomarker for the diagnosis of pulmonary arterial hypertension induced by CHD.

The abovementioned data summarize the differences in expression of miRs in patients with HF (including cardiomyopathy, hypertension, D-HF and CHD). Their clinical significance as HF biomarkers were analyzed (Table II).

Limitations of miRs as biomarkers of HF. Establishing an accurate, reliable circulating miR system for HF diagnosis, prognosis and prediction of response to treatment is challenging, from sample collection and processing to data analysis. First, overlapping between various failure mechanisms leads to difficulties in assessing which mechanisms underlie the expression changes in circulating miRs. Second, serum or plasma are the first choices for sample selection and handling, but the level of circulating biomarker miRs was low, which to some degree impedes the detection of miRs (130). Serum hemolysis may result in waste of samples (131). Furthermore, the serum level of miRs was higher than for circulating plasma, indicating that serum samples can prevent potential interference caused by platelets and leukocytes during sample preparation (132). Therefore, use of the same type of material and synchronous sampling is important for the patient and control groups, as well as a standard scheme to avoid sample hemolysis, minimizing differences between patient selection and classification. Third, some studies have reported fluctuation of miR levels in patients with HF following treatment (133,134). Blood samples were collected at three stages, namely prior to, during and following treatment. A fourth factor was the choice of measurement platform for miR. As indicated in Fig. 2, all research techniques have advantages and disadvantages, but the most commonly used method is RT-qPCR. This method is more sensitive and more cost-effective compared with other methods, but its primary limitation is the inability to detect new miRs. In addition, the standardization of miR expression level may be difficult, as the expression levels of miRs fluctuate with changes in physiological and pathological conditions. Therefore, standard methods are commonly used for the experiments, including the use of equal amounts of starting material (such as serum or plasma), which is more reliable for endogenous miRs for data normalization.

As observed in the present study, the clinical manifestations of HF caused by expression changes of different miRs are similar, and the changes in miR expression caused by

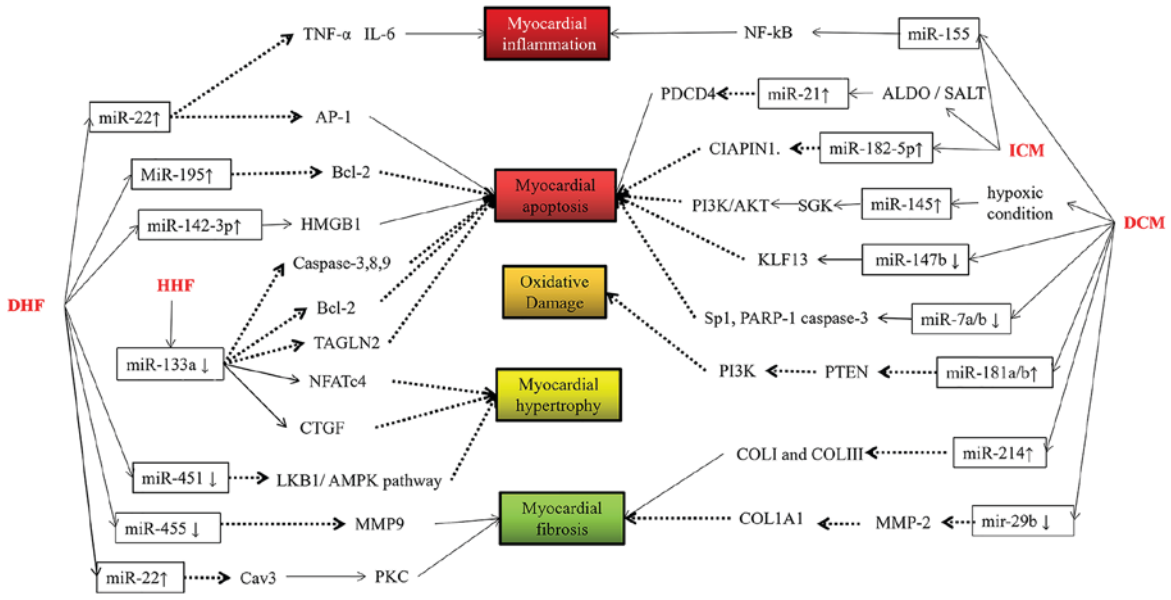

Figure 3. MiRNAs in different heart failure have different regulatory mechanisms for pathogenesis of heart failure. Solid lines represent positive regulation and dashed lines represent negative regulation. The nock of the arrow controls the tip of the arrow, for example, upregulation of miR-22 in diabetic heart failure alleviated myocardial inflammation through inhibiting tumor necrosis factor-α or interleukin-6 expression. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; AP-1, activator protein-1; HMGB1, high-mobility group box 1 protein; Bcl-2, B-cell lymphoma-2; TAGLN2, Transgelin 2; NFATC4, Nuclear Factor Of Activated T Cells; LKB1, Liver kinase B1; AMPK, adenosine monophosphate-activated protein kinase; MMP-9, matrix metalloproteinase-9; CAV3, Caveolin 3; PKC, protein kinase C; PDCD4, programmed cell death 4; ALDO, aldosterone; CIAPIN1, cytokine-induced anti-apoptotic molecule; KLF13, Kruppel-like transcription factor 13; SGK, Serum and Glucocorticoid Induced Kinase; SP1, specific protein 1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10; MMP-2, matrix metalloproteinase-2; Col1a1, collagen 1A1; Col III, type III collagen; Col I, type I collagen; PARP 1, poly ADP-ribose polymerase 1.

different types of HF may also be similar, reflecting the complexity of miR biology.

4. Conclusion

As described in Fig. 3, the expression of miR-145 was upregulated and the expression of miR-147 and miR-7 was downregulated in DCM, ultimately inhibiting cardiomyocyte apoptosis. The upregulation of miR-181 inhibited oxidative stress. Furthermore, upregulation of miR-214 and downregulation of miR-29b attenuated cardiomyocyte fibrosis, which may be a late regulatory mechanism. By contrast, upregulation of miR-155 promotes cardiomyocyte inflammation, which may be an early regulatory mechanism. The above-mentioned miRs appear to be promising potential candidate markers associated with DCM.

In ischemic HF, upregulation of miR-155 intensified cardiomyocyte inflammation, and upregulation of miR-182 promoted apoptosis, which may be an early indicator of this condition. Upregulation of miR-21 alleviated apoptosis via negative feedback regulation. Thus, miR-21 may be a late-age indicator in ischemic HF.

In hypertensive HF, downregulation of miR-133 inhibited cardiomyocyte hypertrophy and promoted cardiomyocyte apoptosis, which may be a late-stage decompensation.

In D-HF, upregulation of miR-22 reduced cardiomyocyte fibrosis, apoptosis and inflammation, and downregulation of miR-455 restrained cell fibrosis, which may be a late indicator of diabetic heart failure, whereas the upregulation of miR-195 and miR-142 aggravated apoptosis and miR-451 downregulation exacerbated cardiomyocyte hypertrophy, which may be an early indicator.

In conclusion, miR-155, miR-22 and miR-133 appear to be promising markers of the development, diagnosis and prognosis of HF. However, further research is required to determine whether there is an efficient miR template for application in clinical oncology practice.

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Availability of data and materials

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Authors' contributions

MH and BHL designed and conceived the study. YMH, WWL and JW provided advice and assistance. YMH wrote the manuscript. All the authors have contributed to and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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