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DIAGNOSTIC PROGNOSTIC AND THERAPEUTIC ROLE OF MICRORNA IN CARDIOVASCULAR DISEASES

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Abstract:

Cardiovascular diseases are the main cause of death in the global world and are associated with increasing financial expenses. By the availability of next-generation sequencing technologies since the early 2000s, non-coding RNAs such as microRNAs, long non-coding RNAs and circular RNAs have been recognized as therapeutic target for many diseases, including cardiovascular diseases. In this Review, we will summarize current approaches to screen for novel coding and non-coding RNA candidates with diagnostic and therapeutic potential in cardiovascular disease, including next-generation sequencing, functional high-throughput RNA screening and single-cell sequencing technologies. We highlight viral-based delivery tools that have been widely used to evaluate the therapeutic utility of both coding and non-coding RNAs in the context of cardiovascular disease. Finally, we discuss the potential of using oligonucleotide-based molecular products such as modified RNA, small interfering RNA and RNA mimics/inhibitors for the treatment of cardiovascular diseases. The number of potential RNAs diagnostic and therapeutic targets for cardiovascular diseases will continue to expand for years to come.

Keywords: *microRNA; cardiovascular diseases; myocardial infarction; atherosclerosis; heart failure*

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INTRODUCTION:

Cardiovascular disease (CVD) is one of the leading causes of death in the world, especially in developed countries. As such, there is an urgent need to identify new prognostic and diagnostic biomarkers for the prevention and treatment of CVD. With the advance of precision medicine and next generation sequencing, microRNAs (miRNAs) have become potential markers for this disease. miRNAs are endogenous, conserved, single-stranded, small (~22 nucleotides) non-coding RNAs that influence most, if not all biological processes. miRNAs are critical regulators of cardiovascular function and play important roles in almost all aspects of cardiovascular biology [1-4]. This review provides an overview of the biology, therapeutic and diagnostic potential, as well as the limitations of miRNAs in the diagnosis and treatment of CVD. Heart failure (HF) is one of the major causes of mortality in the US, responsible for ~30% of patient deaths annually. Heart failure is the final manifestation of CVD and cardiac injury, as well as less common but important etiologies including cardiomyopathies, valvular heart disease, prolonged arrhythmias, myocarditis, infections and exposure to cardiotoxic drugs [18]. Circulating miRNAs have been identified as potential biomarkers of HF. Mounting evidence suggests that miRNAs are involved in the development and progression of HF. Changes, both increases and decreases in the levels of almost 30 circulating miRNAs have been associated with HF and comorbid pathologies Declining levels of circulating miRNAs, including miR-18a, miR-27a, miR30e, miR-26b, miR-199a, miR-106a and miR-652, are found in patients with HF. Reductions in circulating miRNAs let-7i, miR-18b, miR-18a, miR-223, miR-301a, miR-652 and miR-423 have been reported within 48 h after acute HF admission, and are associated with an increased risk of 180-day mortality. miR-21 is upregulated and miR-1 downregulated in patients with symptomatic Medical interventions are also associated with changes in miRNA levels. Compared to stable HF patients, individuals with advanced HF with left ventricular (LV) assist device. miR-208b and miR-499 are released in the coronary sinus after cardioplegia and reperfusion to markedly higher levels than that present prior to surgery.

Myocardial microRNAs

miR-1 is the most abundant miRNA specific for cardiac and skeletal muscle and functions as a regulator of differentiation and proliferation during cardiogenesis as well as a regulator of cardiomyocyte growth in the adult heart. At the same time miR-1 is considered pro-apoptotic in myocardial ischemia. In a rat model miR-1 levels significantly increased in the myocardium 12 hours after coronary artery occlucion . In human hearts of patients who had died of MI miR-1 was upregulated in remote myocardium as compared to infarcted tissue or healthy adult hearts.

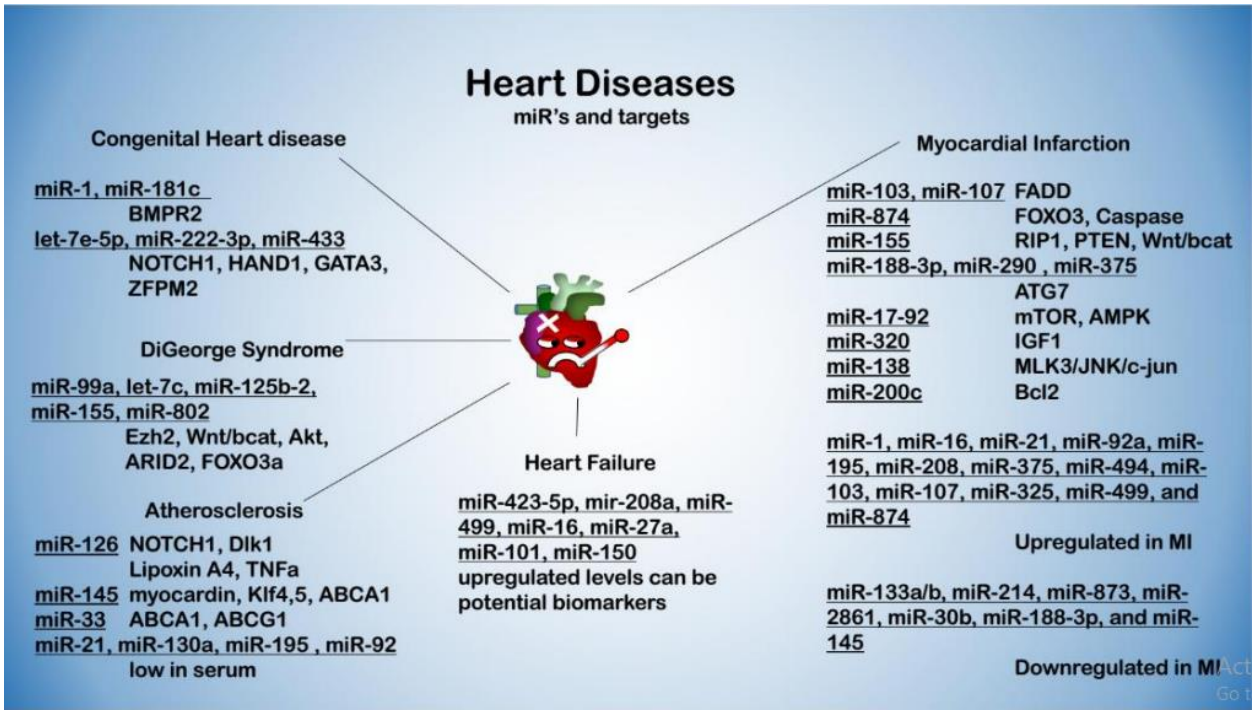
miR-133, which is transcribed from the same chromosomal loci as miR-1, enhances myoblast proliferation and thus is involved in cardiomyocyte proliferations. Interestingly, though, while miR-1 supports apoptosis in oxidative stress, miR-133 was found to repress caspase-9 expression and thus has anti-apoptotic effects.

miR-21 is upregulated in cardiomyocytes shortly after initiation of ischemia before during cell death its concentration decreases. However, increased expression of miR-21 in fibroblasts enhances their proliferation suggesting a role of miR-21 in remodeling.

As shown in a mouse model miR-208 is exclusively expressed in cardiomyocytes and consequently released during cardiomyocyte death in MI .

Members of the miR-29 family are downregulated in the region adjacent to MI areas in mice and humans. The authors discuss the role of miR-29 as a regulator in cardiac fibrosis and a potential target of tissue fibrosis.

Levels of miR-126 were up regulated in the non-infracted areas after induced MI in rat hearts. At the same time a different group reported significantly reduced survival rates in miR-126 knock-out mice after permanent coronary artery occlusion compared with wild-type mice. The authors hold defective angiogenesis in miR-126-null mice responsible for this effect. miR-126 is supposed to be mainly involved in the reparative phase after myocardial injury by enhancing angiogenesis.



REVIEW

The effect of ischemia-reperfusion on miRNAs in the rat heart was evaluated by Tang *et al*. . The authors found that levels of miR-1, miR-126 and miR-208 were increased while miR-21, miR-133 and miR-195 levels had decreased. Botjancic and colleagues analyzed cardiac tissue samples of 50 patients who had died from MI as well as eight formerly healthy trauma victims. The authors found miR-208 upregulated in infarcted tissue whereas miR-1, miR-133a/b was downregulated compared with healthy controls.

microRNAs in prediction and prognosis of CAD and MI .

Beside their diagnostic value circulating miRNAs are also evaluated as potential predictive biomarkers with respect to cardiovascular disease and CAD and MI in particular.

Plasma levels of miR-133a and miR-208b were significantly associated with the risk of death in univariate and age- and gender-adjusted analyses of 444 ACS patients. Hoekstra *et al*. detected a miRNA signature consisting of three miRNAs (miR-134, -198 and -370) with the power to discriminate unstable from stable angina pectoris suggesting a potential to identify patients at risk for future cardiovascular events pointing out the possibilities of miRNAs as a prognostic tool in clinical disease outcome. The finding of miR-370 as a potential prognostic biomarker in risk stratification for acute coronary events is backed up by analogous results in an earlier study in mice. Increased miR-370 expression levels had been found in response to induced ischemia . In a study involving 424 patients with suspected MI elevated plasma levels of miR-208b and miR-499-5p were strongly associated with increased risk of mortality or heart failure within 30 days. Although the association was lost after adjustment for troponin T the study provides evidence of an association of altered levels of circulating miRNAs with outcome after MI. Recently, in a screening and validation approach miR-652 was found to be significantly associated with post-MI readmission for heart failure while in combination with NT-proBNP and left ventricular ejection fraction this miRNA even improved risk stratification after MI . Similar results concerning the risk stratification of mortality or heart failure within 6 months after MI were described for miR-328 and miR-134 in a study population of 359 acute MI patients compared with 30 healthy volunteers.

So far, the only known prospective population-based cohort study examining the predictive value of circulating miRNAs with respect to MI included 820 people from the Bruneck study. In multivariable Cox regression analysis, the authors found a signature of three miRNAs (miR-126, miR-197 and miR-223) involved in the prediction of MI. miR-126 levels were positively while miR-197 and miR-223

inversely associated with future MI. These are promising data for the use of circulating miRNAs in the field of population-based risk assessment for CAD.

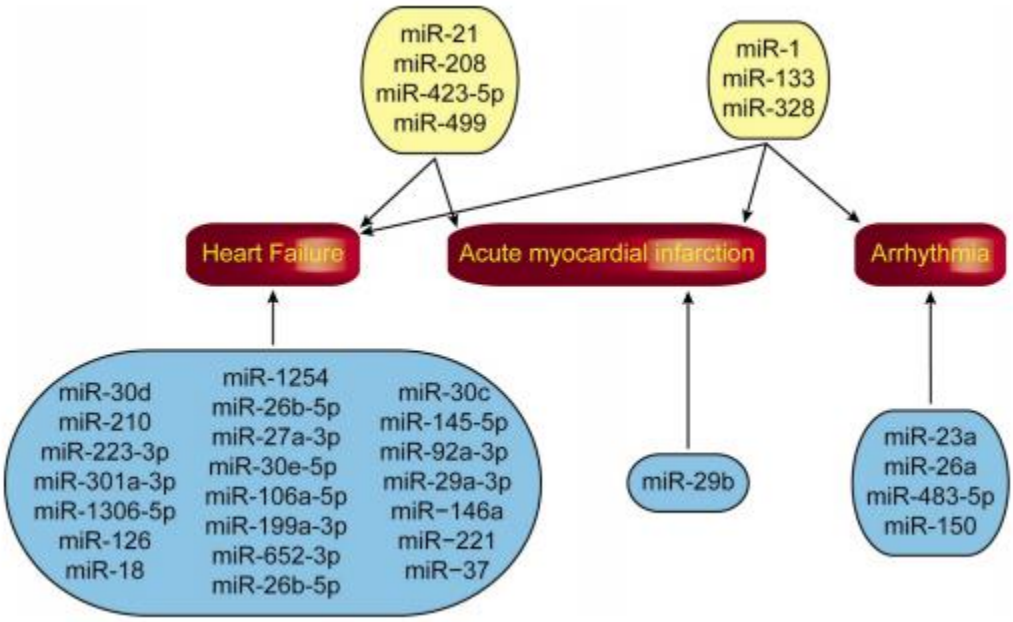


Figure: miRNAs associated with the diagnosis and prognosis of heart failure, acute myocardial infarction and arrhythmia.

Arrhythmia

It is defined as group of symptoms where heart beat changes from its normal pattern. The symptomatic pattern can be irregular (dysrhythmia), too fast (tachycardia) or too slow (bradycardia). Changes in the levels of several circulating miRNAs have been associated with arrhythmia. Changes in the levels of several miRNAs have been linked to AF. Deregulation of miR-29; which targets mRNAs encoding fibrosis-promoting proteins has been found to contribute to AF via regulating the genes involved in cardiac fibrosis and apoptosis. miR-208b upregulation was documented in cardiac tissue from human and animal AF samples. The risk of post-operative AF can be predicted from elevated serum levels of miR483. Circulating miR-23a and miR-26a may be involved in the underlying biology of post-operative AF development.

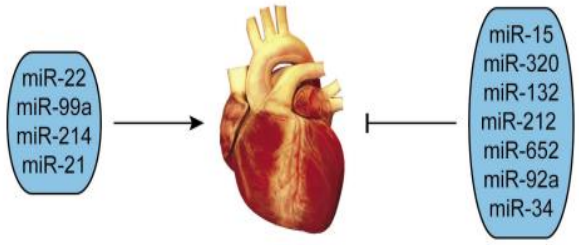
Figure: mRNA in Arrythmias

miRNA ID	Change in expression	Purpose	Pathology (number of subjects)*	Reference
miR-1	↓	Diagnosis: SVT	TACH (24)	[38]
miR-133	↑	Diagnosis: VT	TACH (24)	[39]
miR-328	↑	Diagnosis: AF		[80]
	↑	Diagnosis: AF	AF (122)	[79]
miR-23a	↓	Diagnosis: POAF	POAF (24)	[77]
miR-26a	↓	Diagnosis: POAF	POAF (24)	[77]
miR-483	↑	Predict: POAF	CABG (34)	[76]
miR-150	↓	Diagnosis: AF	HF (41)	[87]

microRNAs as therapeutic targets for cardiovascular diseases:

Changes in the circulating serum levels of many miRNAs are associated with several CVDs, suggesting that they may be potential therapeutic targets. In recent years, numerous miRNA mimics and anti-miRs; synthetic oligonucleotides that block miRNA function; have been evaluated in animal models for the treatment of various CVDs by targeting different aspects of cardiac pathology; apoptosis and autophagy or hypertrophy. In older animals, miR-22 is elevated and suppresses cardiac autophagy. Consequently, administration of miR22 anti-miRs activates cardiac autophagy to prevent postinfarction remodeling and improve cardiac function in older mice[2]. miR-99a targets the mTOR/p70 ribosomal protein S6 kinase signaling pathway to prevent apoptosis and increase autophagy.

Overexpression of miR-99a in a murine model of MI improved both cardiac function and survival by increasing these activities. In addition, overexpression of miR-99a ameliorated hypoxia-mediated apoptosis to improve cardiac function in ischemic heart of mice undergoing MI. Intra-myocardial injection of mice with miR-99a improved LV function and survival 4 weeks after the MI. Similarly, adenovirus -delivered miR-214 or miR-21 improved LV remodeling and decreased myocardial apoptosis in a rat model of AMI or ischemia-reperfusion injury, respectively.The magnitude of cardiac hypertrophy and autophagy in cardiomyocytes is regulated by the miR-212/132 family, which targets the anti-hypertrophic and pro-autophagic FoxO3 transcription factor. While hypertrophic stimuli increase the levels of miR-212 and miR-132 expression, inhibition of miR-132 with anti-miRs rescues cardiac hypertrophy and HF in mice. In a mouse model of hypertrophy and cardiac dysfunction, inhibition of Jagged1/Notch signaling by the administration of a locked nucleic acid anti-miR-652 resulted in attenuation of cardiac hypertrophy. Improved heart function was associated with reduced cardiac fibrosis. These studies suggest that anti-miR-212, anti-miR-132 or anti-miR-652 may be promising agents for the treatment of pathological remodeling during HF and could be used as part of cardiac failure therapies.



CONCLUSION:

Numerous studies reported miRNAs as new diagnostic and prognostic biomarkers in the field of cardiovascular diseases. The application of circulating miRNAs as biomarkers represents a potential additional module in disease diagnosis and prognosis complimentary to established protein-based biomarkers. *In vitro* testing and animal models have depicted pathophysiological pathways and authors have developed miRNA-based methods to interfere with disease progression and complications. The use of miR-mimics and antagomirs in the cardiovascular field has not yet found its way into clinical trials but promising study results reflect potential future applications of miRNA therapeutics in this field.

REFERENCES:

1. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993;75:843-54
2. Lagos-Quintana M, Rauhut R, Lendeckel W, et al. Identification of novel genes coding for small expressed RNAs. Science 2001;294:853-8
3. Reid G, Kirschner MB, van Zandwijk N. Circulating microRNAs: Association with disease and potential use as biomarkers. Crit Rev Oncol Hematol 2011;80:193-208
4. Chandrasekaran K, Karolina DS, Sepramaniam S, et al. Role of microRNAs in kidney homeostasis and disease. Kidney Int 2012;81:617-27
5. Fan HM, Sun XY, Guo W, et al. Differential expression of microRNA in peripheral blood mononuclear cells as specific biomarker for major depressive disorder patients. J Psychiatr Res 2014;59:45-52
6. Elbashir SM, Lendeckel W, Tuschl T. RNA interference is mediated by 21- and 22-nucleotide RNAs. Genes Dev 2001;15:188-200]
7. Fichtlscherer S, De Rosa S, Fox H, et al. Circulating microRNAs in patients with coronary artery disease. Circ Res 2010;107:677-84
8. Small EM, Frost RJ, Olson EN. MicroRNAs add a new dimension to cardiovascular disease. Circulation 2010;121:1022-32
9. Corsten MF, Dennert R, Jochems S, et al. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. Circ Cardiovasc Genet 2010;3:499-506
10. Gomes da Silva AM, Silbiger VN. miRNAs as biomarkers of atrial fibrillation. Biomarkers 2014;19:631-6.
11. Lau NC, Lim LP, Weinstein EG, et al. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science 2001;294:858-62.
12. Reinhart BJ, Weinstein EG, Rhoades MW, et al. MicroRNAs in plants. Genes Dev 2002;16:1616-26.
13. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97
14. Ambros V, Bartel B, Bartel DP, et al. A uniform system for microRNA annotation. Rna 2003;9:277-9.
15. Farh KK, Grimson A, Jan C, et al. The widespread impact of mammalian MicroRNAs on mRNA repression and evolution. Science 2005;310:1817-21.
16. Kozomara A, Griffiths-Jones S.miRBase: annotating high confidence microRNAs using

deep sequencing data. Nucleic Acids Res 2014;42:D68-73
17. Friedman RC, Farh KK, Burge CB, et al. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009;19:92-105
18. Bushati N, Cohen SM. microRNA functions. Annu Rev Cell Dev Biol 2007;23:175-20519. van Rooij E.The art of microRNA research. Circ Res 2011;108:219-34.
20. Bauersachs J, Thum T.Biogenesis and regulation of cardiovascular microRNAs. Circ Res 2011;109:334-47
21. Creemers EE, Tijsen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? Circ Res 2012;110:483-95
22. Dzikiewicz-Krawczyk A.MicroRNA polymorphisms as markers of risk, prognosis and treatment response in hematological malignancies. Crit Rev Oncol Hematol 2015;93:1-17.
23. Mishra PJ, Bertino JR. MicroRNA polymorphisms: the future of pharmacogenomics, molecular epidemiology and individualized medicine. Pharmacogenomics 2009;10:399-416
24. Salzman DW, Weidhaas JB. SNPing cancer in the bud: microRNA and microRNA-target site polymorphisms as diagnostic and prognostic biomarkers in cancer. Pharmacol Ther 2013;137:55-63
25. Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A 2008;105:10513-8.
26. Weber JA, Baxter DH, Zhang S, et al. The microRNA spectrum in 12 body fluids. Clin Chem 2010;56:1733-41
27. Zampetaki A, Willeit P, Tilling L, et al. Prospective study on circulating MicroRNAs and risk of myocardial infarction. J Am Coll Cardiol 2012;60:290-9.
28. Contu R, Latronico MV, Condorelli G. Circulating microRNAs as potential biomarkers of coronary artery disease: a promise to be fulfilled? Circ Res 2010;107:573-4.
29. Wu AH, Jaffe AS. The clinical need for high-sensitivity cardiac troponin assays for acute coronary syndromes and the role for serial testing. Am Heart J 2008;155:208-14.
30. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361:868-77.]
31. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999-3054.
32. Li C, Pei F, Zhu X, et al. Circulating microRNAs as novel and sensitive biomarkers of acute myocardial Infarction. Clin Biochem 2012;45:727-32.
33. Wang R, Li N, Zhang Y, et al. Circulating microRNAs are promising novel biomarkers of acute myocardial infarction. Intern Med 2011;50:1789-95.
34. Kuwabara Y, Ono K, Horie T, et al. Increased microRNA-1 and microRNA-133a levels in serum of patients with cardiovascular disease indicate myocardial damage. Circ Cardiovasc Genet 2011;4:446-54.
35. Jaguszewski M, Osipova J, Ghadri JR, et al. A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction. Eur Heart J 2014;35:999-1006.
36. Suárez Y, Fernández-Hernando C, Pober JS, et al. Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells. Circ Res 2007;100:1164-73
37. Kuehbacher A, Urbich C, Zeiher AM, et al. Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. Circ Res 2007;101:59-68.
38. Schroen B, Heymans S.Small but smart--microRNAs in the centre of inflammatory processes during cardiovascular diseases, the metabolic syndrome, and ageing. Cardiovasc Res 2012;93:605-13.
39. Jovanović I, Zivković M, Jovanović J, et al. The co-inertia approach in identification of specific microRNA in early and advanced atherosclerosis plaque. Med Hypotheses 2014;83:11-5.
40. Menghini R, Stohr R, Federici M.MicroRNAs in vascular aging and atherosclerosis. Ageing Res Rev 2014;17:68-78.
41.Urbich C, Kuehbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. Cardiovasc Res 2008;79:581-8.