Detection of Myocardial Injury Using miRNAs Expression as Genetic Biomarkers in Acute Cardiac Care

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ABSTRACT
Cardiovascular disease is a leading cause of death globally. At present, there are many ways to diagnose this pathophysiology. The greatest disadvantages related to current biomarkers are their low specificity, low selectivity and low accuracy. A new method, extensively studied recently, is the expression of miRNAs, used as genetic biomarkers for the early diagnosis of cardiovascular diseases. This paper presents an update of miRNAs species expression that can serve as early diagnostic biomarkers and for the continuous monitoring of patients with cardiovascular disease.

Keywords: microRNA, acute myocardial infarction, acute cardiac care

BACKGROUND
Cardiovascular disease is one of the leading causes of death globally. An important reason for the increased rates of morbidity and mortality in these patients is the late diagnosis of complicated cases that progress to cardiovascular emergencies.¹⁻³ In acute cardiac settings, a number of methods are used currently for evaluation based on biochemical–humoral biomarkers, such as cardiac troponin (TNC), creatine kinase–myocardial band isoform (CK–MB) and brain natriuretic peptide (BNP).⁴⁻⁷ Unfortunately, these biomarkers show low selectivity and specificity, and can often display false positive results due to their association with multiple pathophysilogies. A potential future biomarker, intensively studied lately, is the genetic expression of miRNAs. Essential features that make it the ideal candidate for use as a biomarker are its high selectivity and specificity. Moreover, investigation methods for miRNAs are noninvasive and inexpensive.⁸⁻¹⁰

In this update paper, genetic and epigenetic modifications of miRNAs in cardiovascular emergencies are pre-
miRNA biosynthesis takes place in the cell nucleus. The mechanisms that lead to the formation of miRNAs begin with the attack of RNA polymerase II on specific genes (Figure 1). Following the transcription reactions, the first pri-miRNAs are formed. After these events, the RNase II endonuclease, also known as Drosha, attacks the pri-miRNAs species together with the DiGeorge Syndrome Critical Region 8 (DGCR8) enzymatic cofactor, leading to the formation of pre-miRNAs. Pre-miRNAs are transported from the nucleus into the cytoplasm by coupling with the Exportin 5 transporter protein. Inside the cytoplasm, the pre-miRNAs are combined with RNase III endonuclease, also known as Dicer, resulting in mature miRNAs. The RNA-binding trans-activator protein cofactor (TRBP) is involved in the formation reactions of mature miRNAs, which will be embedded in the RNA-induced silencing complex (RISC) for its transport outside the cell.

The miRNA species formed in this manner are exported from the cells into the extracellular space in different configurations, such as exosomes, microvesicles, or apoptotic bodies.

miRNA EXPRESSION IN MYOCARDIAL INJURY FOLLOWING ACUTE MYOCARDIAL INFARCTION AND REPERFUSION SYNDROME

Ischemic heart disease is a leading cause of death among patients with cardiovascular disease. A pathophysiological effect secondary to ischemic heart disease is the inflammatory effect induced by ischemia and reperfusion syndrome (IR), which occur in cases of acute myocardial infarction immediately after repermeabilization of the acutely occluded coronary artery. Yao et al. (2016) showed significant changes in miRNA-26 in patients with IR. Moreover, they reported that miRNA-26 caused inhibition of the high mobility group box 1 (HMGB1), thus significantly reducing IR. Wu et al. (2016) identified an alteration of the expression of miRNA-613 in cases of IR syndrome. Gidlöf et al. (2013) conducted a similar study on the expression of miRNAs in patients with IR syndrome or with ST elevation myocardial infarction (STEMI). They reported a rapid increase in miRNA-1, miRNA-133a and miRNA-208b. Regarding miRNA changes in patients with STEMI, an increase of miRNA-1 and miRNA-133a was observed. A similar study on the expression of miRNAs in patients with STEMI was conducted by D’Alessandra et al. (2010), who reported an altered expression of miRNA-1, miRNA-133a, miRNA-499-5p, miRNA-122 and miRNA-375.

miRNA EXPRESSION IN ACUTE HEART FAILURE AND CARDIAC HYPERTROPHY

Vegter et al. (2016) studied the expression of miRNAs in acute heart failure. The study showed statistically significant changes for several miRNAs. Moreover, it was reported that there was a number of statistical correlations between the altered expression of miRNAs and the clinical outcome. Furthermore, they identified changes in the expression of miRNA-16–5p, miRNA-106a–5p, miRNA-223–3p, miRNA-652–3p, miRNA-199a–3p and miRNA-18a–5p.
Another common cardiac pathophysiology is cardiac hypertrophy. From a pathophysiological point of view, cardiac hypertrophy is an important compensatory mechanism that initially aims to reduce cardiac wall stress, but also to preserve and ensure contractile performance. Unfortunately, once it becomes chronic, this pathology leads to severe cardiac dysfunction that can rapidly deteriorate and progress to acute cardiac failure. Recent studies have reported several changes in the expression of miRNAs in the case of this pathology, which can serve as a biomarker for an early diagnosis. These included miRNA-133, miRNA-1, miRNA-208, miRNA-21, miRNA-18b, miRNA-195 and miRNA-199, miRNA-23, miRNA-24, miRNA-27 and miRNA-9.24

**miRNA EXPRESSION IN CORONARY ARTERY DISEASE AND SUDDEN CARDIAC DEATH**

Coronary artery disease (CAD) is a cardiac pathology frequently associated with sudden cardiac death. Li *et al.* (2016), in a study on the expression of miRNAs in cases of CAD, reported significant growth for miRNA-126–5p. A similar study was conducted by Liu *et al.* (2016), who identified changes in the expression of miRNA-208a and miRNA–370 in patients with CAD.26 Mehta *et al.* (2016) also reported a decrease in the expression of miRNA-132 and an increase in miRNA–143 expression in patients with CAD. A similar study was conducted by Sun *et al.* (2012), who identified a significant decrease of miRNA-126, strongly correlated statistically with the decreased concentration of low-density lipoprotein (LDL) cholesterol in patients with CAD.28 Fichtlscherer *et al.* (2010) reported a decrease in the expression of miRNA-17, miRNA-92a miRNA-126, miRNA–145, and miRNA–155 in patients with CAD.29

**PANELS OF miRNA EXPRESSION IN ACUTE MYOCARDIAL INFARCTION**

One of the most common syndromes associated with CAD is acute myocardial infarction (AMI). In practice, the best-known biomarker for AMI is cardiac troponin I (cTnI). A major disadvantage of cTnI is the false positives that can occur in patients with atrial fibrillation, chronic kidney disease or septic shock. Wang *et al.* (2013), in a study on the changes of miRNA expression in patients with AMI, showed a significant increase for miRNA-133a.30 Wang *et al.* (2010) also reported an increase for the expression of miRNA–1, miRNA–133a, miRNA–208a and miRNA–499 in patients with AMI.31 A similar study conducted by Cheng *et al.* (2010) highlights an increase in the expression of miR-NA–1 in patients with AMI.32 Meder *et al.* have also studied the expression of miRNAs in the case of AMI, reporting an increase of miRNA–30c and miRNA–145. Moreover, they identified a decrease in the expression of miRNA–663b and miRNA–1291 in the case of AMI.33

**CONCLUSION**

Cardiovascular diseases represent one of the leading causes of death. Early evaluation and monitoring at this moment shows no increased specificity and selectivity. An ideal biomarker for evaluating these patients may be genetic expression of miRNAs. In a conducted study, we can say that certain species of miRNAs can bring important answers about the pathophysiology of the heart. However, further studies are needed to strengthen a panel of miRNAs with expressions of high accuracy specific for cardiac pathophysiologies.

**CONFLICT OF INTEREST**

Nothing to declare.

**REFERENCES**


