

# Which future for circulating microRNAs as biomarkers of acute myocardial infarction?

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Cardiovascular disease remains the first cause of death and disability around the world according to the World Health Organization ([http://www.who.int/cardiovascular\\_diseases](http://www.who.int/cardiovascular_diseases)). An estimated 31% of deaths worldwide are due to cardiovascular disease and, in many countries, cardiovascular disease is responsible for more than twice as many deaths as cancer (1). Coronary heart disease and stroke are especially devastating and, among coronary heart disease, acute myocardial infarction (AMI), known as “heart attack”, is the most common and the most deadly condition. Obstruction of a coronary artery leads to AMI and to the necrosis of a part of the heart due to rupture of blood supply. An early diagnosis of AMI in patients presenting with chest pain is necessary to rapidly restore blood flow to the heart to limit the extent of myocardial necrosis, which largely impacts patient outcome. Currently, AMI diagnosis is based on electrocardiogram findings and measurements of blood biomarkers of myocardial damage, among which cardiac troponins (cTns) are the most widely used. High-sensitivity troponin assays have been developed, but they suffer from a lack of specificity since elevation of cTn levels can be due to non-cardiac causes. Therefore, there is an unmet need for novel, early and specific biomarkers of AMI.

In the early 2000's, a new class of RNA molecules called microRNAs (miRNAs) emerged. miRNAs are small 20–22 nucleotides-long single-stranded non-coding RNAs able to down-regulate the expression of protein-coding genes, either through inhibition of the translation of target messenger RNAs or induction of their degradation (2). In the heart, miRNAs are widely expressed and regulate multiple physiological and pathological pathways such as

apoptosis, fibrosis or angiogenesis (2).

The discovery by Mitchell and co-workers that miRNAs are present and stable in the bloodstream (3) triggered a wealth of investigations of their biomarker potential. Of note, circulating miRNAs can be either released by dying cells or be actively secreted by living cells, acting as paracrine factors. The former possibility led to the hypothesis that circulating miRNAs emanating from dying cardiomyocytes after AMI might constitute a novel class of biomarkers of AMI. This hypothesis was tested by multiple groups and led to the publication of many reports since 2010 [reviewed in (2)]. From animal studies and small-scale studies conducted in humans, it appeared that many miRNAs are indeed released from dying cardiomyocytes after AMI. In patients with hypertrophic obstructive cardiomyopathy, circulating levels of muscle-enriched miR-1 and miR-133a were significantly increased 15 mins after transcatheter ablation of septal hypertrophy (4), supporting the hypothesis that heart-derived miRNAs may constitute early diagnostic biomarkers of AMI. The excitement around the diagnostic potential of miRNAs for AMI was tempered by large-scale studies in AMI patients and patients with chest pain reporting that circulating miRNAs fail to provide an incremental diagnostic value over traditional markers including cTns (2,5). This disappointing result was nevertheless limited by the fact that patients in these retrospective studies were initially diagnosed with cTns. Additional prospective studies might bring back some hope, such as a recent study from Wang and colleagues reporting that plasma levels of miR-19b-3p, miR-134-5p and miR-186-5p reached a peak in the 4 hours

after admission for AMI, while cTnI showed a peak only after 8 hours (6). All three miRNAs had a robust diagnostic capacity and a 3-miRNA panel discriminated AMI patients from controls with an area under the curve close to 0.90 at admission. However, this study is limited by a low sample size (18 AMI and 20 controls) and the absence of multivariable analyses to address the added diagnostic value of miRNAs on top of existing markers.

While the benefit of using circulating miRNAs for the diagnosis of AMI may be limited, mostly due to the accuracy and rapidity of high-sensitivity cTns assays, there might exist a window of opportunity for prognostication purposes. Indeed, predicting outcome after AMI is still a challenging task. The heart failure biomarkers brain natriuretic peptides (BNPs) are poor predictors of the adverse left ventricular remodelling process leading to heart failure, mainly due to fluctuating plasma levels in the few hours following AMI (7). In two independent groups of AMI patients, plasma levels of miR-150 at admission predicted left ventricular remodelling and provided an added prognostic value over a multivariable clinical model (8). A 4-miRNA panel including miR-150 improved outcome prediction in a cohort of 150 AMI patients (9). In a recent case/control study with 198 patients, circulating levels of miR-22 were independent predictors of cardiovascular mortality in patients with systolic heart failure from both ischemic and nonischemic origin (10).

While the use of circulating miRNAs as prognostic biomarkers after AMI holds some promise, more remains to be done before these relatively novel markers can reach clinical application. Candidate miRNAs have to be extensively validated; they have to provide very accurate predictions at an early stage after AMI; they have to be stable enough in the blood to be reliably detected; they have to be insensitive to medications and other confounding factors such as age or sex; and finally their methods of detection have to be critically improved to be applicable in a clinical setting. A point-of-care device integrating miRNA measurements in a multifactorial computational model delivering a diagnosis in a relatively short period of time would constitute an attractive “New concept in patient stratification” (Horizon 2020 Work Program 2016–2017. Health, demographic change and well-being. SC1-PM-02-2017) towards personalized healthcare.

In conclusion, although circulating miRNAs are still attracting some interest as diagnostic biomarkers of AMI, the majority of studies conducted so far concluded that miRNAs will have a hard time outperforming the sensitivity and rapidity of high-sensitivity cTn assays. On the other

hand, past and recent studies support the use of circulating miRNAs to aid in risk stratification after MI. Future technological developments are needed to translate these research findings into clinical application. Also, more efforts are required before circulating miRNAs can aid controlling the growing burden of heart failure.

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*Comment on:* Wang KJ, Zhao X, Liu YZ, *et al.* Circulating MiR-19b-3p, MiR-134-5p and MiR-186-5p are Promising Novel Biomarkers for Early Diagnosis of Acute Myocardial Infarction. *Cell Physiol Biochem* 2016;38:1015-29.

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