

# Circulating extracellular vesicles containing miRNAs may have utility as early biomarkers for cardiac injury

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Through advancements in prevention, awareness, detection, and treatment modalities, rates of myocardial infarction (MI) have decreased over time. However, MI still remains a significant cause of morbidity and financial burden within the United States, with approximately 3.2 per 1,000 individuals hospitalized per year, corresponding to an estimated 11.3 billion dollars in societal costs (1). The universal definition of MI specifies that patients must have a rise and fall of cardiac biomarkers as well as ischemic symptoms for diagnosis. Currently, circulating biomarkers in plasma including creatinine kinase MB (CK-MB) and cardiac troponin remain the gold standard for detection and validation of type 1 MI. Although assays using high sensitivity troponin are able to detect MI as early as 2–3 hours after cardiac injury with good sensitivity and specificity (2), in certain patients the initial assay may be negative. Because early recognition of MI is associated with improved outcomes, decreased hospital length of stay, and decreased cost (3–6), there is interest into novel diagnostic methods for MI. Beyond diagnosis of MI, improving the detection and etiology of myocardial injury using novel biomarkers may enhance the management of a variety of cardiac conditions.

It is in this context that Deddens and coauthors (7) present a study investigating the possible utility of quantification of microRNAs (miRNAs) and extracellular vesicle (EV) release to assist in early determination of myocardial injury. Using mouse and porcine models, their study demonstrates that circulating EVs as well as miRNAs are significantly increased in animals with induced MI as compared with sham controls early after ischemia. The authors demonstrate that after ligation of the LAD in mice to induce myocardial ischemia, followed by reperfusion

(n=3), the amount of EVs released are significantly greater than the sham arm (n=1) in mice at 150 minutes. Moving to porcine models, the authors serially sample plasma to determine the level of circulating miRNA at different time points. They demonstrate that the circulating miRNAs previously demonstrated to be increased in plasma after MI in humans are also increased in animal models with a significant increase demonstrated in cases as compared to controls 2.5–3.5 hours after ischemia. The authors found that significantly elevated miRNAs include miRNA-1, -208, and -499 but not miRNA-21 or miRNA-146a, and that these levels are higher in EV than in plasma.

Although limited by small study size, the study offers interesting opportunities for translational medicine. Because miRNAs are involved in gene expression at a post translational level, the ability to understand the role of miRNA in pathological processes may also provide possible therapeutic targets (8). Although the purpose of the analysis by Deddens and colleagues was not to determine the exact mechanism and significance of miRNA elevation after MI, identification of key miRNAs after ischemia is an important step in better understanding the physiologic process that occurs when myocardium becomes ischemic.

The importance of miRNAs in the post transcriptional regulation of gene expression is increasingly recognized (9). Prior studies have identified certain miRNAs as markers of cardiac ischemic/reperfusion injury with both regulatory, protective, and diagnostic utility (10–12). In addition to modifying myocardial gene expression in response to injury, miRNA are secreted in a regulated manner into the circulation by EVs as part of intercellular communication (similar to hormones). The presence of EVs in the circulation provides an important “window”

into the injured myocardium that is otherwise inaccessible in the clinical setting. EVs package miRNA in specific proteins (e.g., Ago2 or HDL) which render miRNA highly resistant to degradation. Unlike most extracellular RNA which is rapidly degraded in the absence of RNase inhibitors or strict handling conditions, EV miRNA is robust to degradation under most conditions. This feature coupled with the ability to readily measure RNA in clinical laboratories make EV miRNA an attractive platform for a clinical biomarker.

In addition to detection of myocardial necrosis, miRNA quantification and assessment may be of utility in elucidating the mechanism of myocardial injury, assisting in the prognostic and diagnostic capabilities in acute MI. This highlights possible future avenues of translation into clinical practice, with possible benefit in distinguishing between MI, heart failure, myocarditis, and other processes involving myocardial injury upon patient presentation. Additional potential applications include myocardial monitoring for cardiac allograft rejection, chemotherapy induced cardiomyopathy, asymptomatic severe valvular disease, and risk stratification during exercise stress testing.

Excitingly, miRNAs are also emerging as potential therapeutic targets, thus better understanding of their utility, function, and targets are a priority for investigation (13). EV miRNA are also being developed as therapeutic targets as the extent of their increase has been shown to be associated with worsened myocardial injury (14). Studies have demonstrated improvement in hepatitis C viremia in primate studies (15) and colon cancer (16), however the full potential of miRNA as therapeutic agents is only beginning to be fully realized.

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### Footnote

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