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# Circulating MicroRNAs in Cardiovascular Disease

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MicroRNAs (miRNAs) are short, single-stranded, non-coding, highly conserved posttranscriptional regulators found in a variety of tissues including circulating blood.[1] MicroRNAs regulate gene expression posttranscriptionally through inhibiting translation from and/or inducing degradation of specific RNAs.[2] Certain miRNAs are expressed and function cell-type specifically or in association with particular physiological processes. MicroRNAs contribute to cardiac development and remodeling, and miRNAs found in cardiac tissue show dynamic changes in the setting of heart disease, suggesting their involvement in the regulation of cardiovascular disease (CVD). Mouse and human studies have emphasized the importance of individual miRNAs in different forms of CVD, including myocardial infarction (mirR-1, miR-133a, miR-208a, and miR-499), atrial and ventricular arrhythmias (miR-1, miR-133, and miR-328), fibrosis (miR-21 and miR-29), and ventricular hypertrophy (miR-208 and miR-133).[3–7]

Remarkably, miRNAs can be detected circulating in blood plasma or serum as a result of cellular damage or secretion.[8] In contrast to intracellular miRNAs and other extracellular disease mediators, circulating miRNAs have ideal characteristics as risk markers because they are stable and easily detectable (miRNA are comprised of nucleic acids, and their sequences can be amplified).[9] Circulating miRNAs have been associated with CVD risk factors (eg, hypertension and diabetes mellitus), and there is an emerging literature associating specific miRNAs with coronary artery disease, myocardial infarction, and heart failure.[8,10–12] Although the cellular secretion of specific miRNA suggests process specificity, the source of circulating miRNAs associated with CVD remains unclear in many cases. In the current issue of *Circulation*,[13] De Rosa et al fill a major gap in our knowledge by investigating whether or not circulating miRNAs associated with acute coronary syndrome (ACS) are produced by the human heart. In 57 patients undergoing cardiac catheterization for suspected ACS, they measured the transcoronary concentration gradients of vascular, leukocyte, and platelet-enriched miRNAs (Figure). They report that circulating levels of cardiomyocyte-enriched miR-499, miR-133a, and miR-208a are elevated and correlate with troponin levels in patients with troponin-positive ACS compared with patients with coronary artery disease.

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None.

De Rosa et al also report that levels of cardiomyocyte-enriched miRs-499 and 133a increase across the coronary circulation in patients with troponin-positive ACS and that this is not seen in patients without elevated troponin levels. In demonstrating that miRNA levels differ in plasma obtained directly from the coronary venous sinus and proximal aorta (Figure) of patients with a troponin-positive ACS, De Rosa et al confirm and extend the findings of a study by Widera et al involving 444 patients with ACS, in which patients with myocardial infarction were shown to have higher circulating levels of miR-1, miR-133a, and miR-208b compared with patients who had unstable angina.[14] Although the present study does not determine whether or not increased expression or release are responsible for the observed transcoronary miRNA gradients, another study by Kuwabara et al suggests that cardiomyocyte injury promotes increased secretion of exosomes containing miRNAs 133a and 499.[15]

Intracellular levels of miRNAs provide information about regulatory pathways involved in mediating the cardiomyocyte injury response. MicroRNA 133a, for example, has been shown to target the ion-channel–encoding genes *HCN2* and *HCN4*.[6,16] mir-208a is encoded in the intron of the $\alpha$-myosin heavy chain gene and indirectly influences $\beta$-myosin heavy chain and connexin-40 expression,[17] and mir-499 is intronic to the myosin gene *Myh7b*.[17] Intronic miRNA are coded within a host gene, often regulating pathways similar to those of the protein encoded by that gene and frequently acting to regulate a single biological process.[18] Whether circulating miRNAs such as miR-133a and miR-499 function as signaling molecules or are simply released after cardiomyocyte injury remains unknown, but the functional redundancy of miRNAs would suggest that miRNAs help to mitigate biological perturbations such as occur during an ACS.[19] Although De Rosa's findings firmly establish that miR-133a and miR-499 are produced by the heart and are specific to an ACS, important questions remain unanswered, such as whether or not secreted miRNAs serve to influence gene regulation in other parts of the heart (eg, in peri-infarct or noninfarcted zones) or in other organs.

As evidenced by the authors' surprising finding that miR-126 levels decrease across the transcoronary circulation (Figure), much remains unknown about the acute processes regulating circulating miRNA levels, especially in the setting of an ACS. The authors propose that the negative miR-126 transcoronary gradient may be explained by the secretion of proteases and/or RNases by injured or ischemic myocytes. Although nonspecific degradation of circulating proteins conjugated to miRNAs or miRNAs themselves may explain the negative miR-126 transcoronary gradient, an alternative hypothesis is that miRNAs such as miR-126 function as signaling molecules and are taken up by injured cardiomyocytes in a specific fashion. More information is needed about the biochemical composition of important circulating miRNAs and how this relates to miRNA stability and uptake.[20]

Modulation of miRNAs has opened exciting opportunities for miRNA-based therapies in the treatment of CVD.[21] Indeed, miRNA mimics and anti-miRs are currently under development and have been advanced to clinical trials.[19] Further study is warranted of circulating miRNA secretion, clearance and potential function in patients with CVD. In addition to the potential role of miRNA as biomarkers, miRNAs will provide new insights into CVD pathogenesis and new applications for CVD prevention and treatment in the near future.

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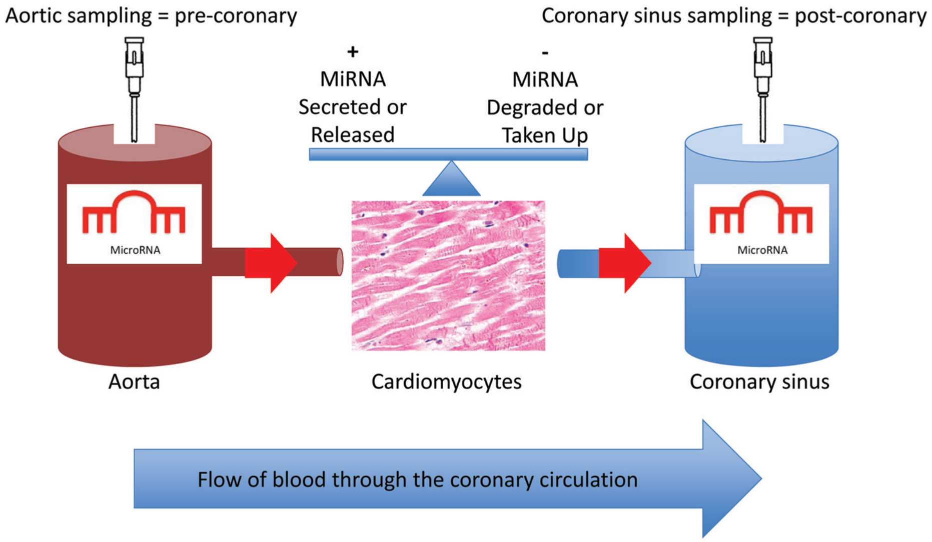

**Figure.**

Experimental scheme: transcoronary concentration gradients of circulating microRNA. miRNA indicates microRNA.