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Novel Biomarkers for Acute Myocardial Infarction: Is MicroRNA the New Kid on the Block?

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Guests:
Dr. Joshua Raizman is from the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital in Toronto. Dr. Katey Rayner is from the Cardiometabolic microRNA Laboratory and the University of Ottawa Heart Institute.

Bob Barrett: This is a podcast from C*linical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Early detection of acute myocardial infarction is crucial for deciding the course of treatment to preserve and prevent further damage to the myocardial tissue. During the last several years there has been a burgeoning interest in circulating microRNAs as potential novel biomarkers for acute myocardial infarction.

Recent animal and clinical studies have demonstrated increased microRNA in the plasma shortly after the onset of a coronary event.

In a Question and Answer feature appearing in the June 2014 issue of *Clinical Chemistry,* four microRNA experts with an interest in coronary artery disease help shed light on the utility of circulating microRNA and testing for acute myocardial infarction.

Dr. Katey Rayner of the Cardiometabolic microRNA Laboratory and the University of Ottawa Heart Institute, and Dr. Joshua Raizman of the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital in Toronto, participated in that Q&A session and they are our guests in today's podcast.

And Dr. Raizman, we will start with you, cardiac troponins are currently the best blood test to help diagnose a heart attack. What are the advantages and limitations of troponin testing, and why is there a push to find new circulating markers?

Dr. Joshua Raizman: Well, one of the major advantages of high sensitivity troponin assays are their improved analytical sensitivity at lower levels. So improved analytical sensitivity allows these assays to detect and even quantify smaller concentrations of troponins than the older conventional assays.

What this means is that troponins can be detected earlier when there is myocardial injury, but the lower threshold also means that troponins will be detected in a healthy population as well.

And that's because the criteria for high sensitivity are that they must be detectable below the 99th percentile and above the assay limit of detection in at least 50% of the reference population, so half of the reference population must have detectable levels.

So what does this mean for the clinician? Well, it means that high sensitivity assays will actually diagnose more people with acute myocardial infarctions.

Furthermore, high sensitivity troponin assays can identify at-risk patients sooner, and improvement in precision at low concentrations allows for reliable serial monitoring, which can detect small changes evolving from low concentrations within the reference interval, to small increases above the 99th percentile value.

Now, being able to detect small changes within a window of one to three hours can help to guide medical decisions making diagnosis sooner and thus preventing future coronary outcomes.

However, as the question applies, the major challenge of these high sensitivity assays is that now they are detecting levels in patients with myocardial infarction. Elevated troponins reflect myocardial injury, but they do not necessarily indicate the mechanism or cause of that injury. And also, they are detected in conditions such as congestive heart failure, renal failure, myocarditis, pulmonary embolism and even strenuous exercise in healthy individuals. And those latter conditions require a different treatment from treating a patient with myocardial infarction.

Even more, patients with advanced age and cardiovascular risk factors tend to have elevated troponin levels at baseline, so the improvement in analytical performance has indeed lowered the threshold for diagnosing myocardial injury, but really the gains in diagnostic sensitivity are at the cost of reduced clinical specificity for MI.

In recent years these limitations and challenges of using high sensitivity troponin assays in diagnosis of myocardial infarction has been a hotly debated topic.

Now acute care physicians have been challenged to interpret, detect the troponin levels in their patients in the context of the clinical picture. So physicians are being

challenged on how to best use the test to risk-stratify their patients and rule in or out acute illness.

As you could expect, an ideal biomarker for rapid and reliable diagnosis of acute MI is still lacking, unfortunately. However, much research in the cardiovascular field has focused on finding novel biomarkers of acute myocardial infarction that are both specific for ischemia, but sensitive enough for early detection, and one such biomarker which shows promise is microRNA.

Bob Barrett: Dr. Rayner, let's go to you. There has been a lot of recent interest in understanding the role of microRNA and cardiovascular disease. A few questions, what is microRNA, what functions do they have, and how are they released from the heart into circulation?

Dr. Katey Rayner: Well, a microRNA is sort of like a gene and the word micro just kind of means small. It's sort of a modifier of our gene. So we have it in our DNA, they get made in our cells, and then they can turn on or off a particular expression of a gene. So they mainly bind our genes and turn them off.

What they do basically is they can dial up or dial down a particular cellular response, so we call them sort of the real stats of our genome.

So really these things are small, like the name implies, microRNA, they are about 20-22 nucleotides long, and ultimately they function to regulate our genes and how our cells function.

How they are released from the heart is sort of an open question. So during a heart attack the blood supply to the heart muscles causes cells to die, and that could release the microRNAs just simply by cells sort of dying and exploding their contents. That might be one way that the microRNAs are released into the circulation.

But probably there is a more kind of controlled and active process within the cells that are sending these microRNAs out into the bloodstream as sort of a signal, as a stress signal or a help me signal, that kind of thing, but how that's actually happening, we are not really sure yet.

Bob Barrett: In your opinion, what makes microRNA the next kid on the block for detecting heart attack?

Dr. Katey Rayner: Well, a lot of people have found very, very strong associations between the levels of particular microRNAs in patients who are suffering from a heart attack. So miR-133, for example, or miR-208, so various microRNAs have been shown to be in the bloodstream when somebody is having a

heart attack, and this has been sort of reproduced many, many times.

The sort of challenge that we are facing at this point is, at this stage those tests that we would have to test whether or not a microRNA is in the blood during a heart attack are not really improved compare to cardiac enzyme tests that are currently used.

So if a patient goes into the ER and is suspected to be having an MI, the blood tests that are currently used are pretty good and pretty fast for determining whether or not somebody is actually having a heart attack.

So is the microRNA going to improve that? Possibly, but maybe not likely. Where microRNAs are really coming on the scene when it comes to heart disease is more before a patient has a heart attack.

So let's say you have a lot of risk factors or perhaps you are having some symptoms or some kind of chest pain or something like that, microRNAs may be the kind of blood test -- the kind of biomarker test -- that could be used to predict whether or not you are at risk for heart attack in the near future.

So, I don't think that they are going to be any better than the current test available for figuring out if a patient is having or has just had a heart attack, those tests are very, very good right now. But I think that where the excitement really lies is in their use to predict who is at the highest risk, especially for heart attacks, especially for the big massive heart attacks that are often deadly.

So that's I think where a lot of the research is going and where a lot of the excitement for microRNAs as biomarkers in the blood is actually going, is their predictive value rather than currently diagnosing a heart attack.

Bob Barrett: And finally Dr. Raizman, back to you, given that diagnosing myocardial infarction quickly is so critical for clinical decisions and patient management, how could microRNA be measured to maintain similar turnaround time as troponins, and what type of technology improvements are needed to make this happen?

Dr. Joshua Raizman: Well, in acute care settings time is of the essence, or as they say in the clinic time is myocardium. When a patient comes to the emergency department with a clinical suspicion of an MI, rapid recognition and detection of an ischemic event is crucial to prevent adverse outcomes associated with myocardial ischemia, and part of this care means that high sensitivity troponin assays must have a

quick turnaround time to meet the needs of this acute care setting.

Now, amino assays for troponins have turnaround times of under one hour. The current methods to measure microRNA however involve real-time PCR-based assays and these assays can take upwards of three hours.

So you can see this is time consuming and would not meet the turnaround time demands to adequately diagnose myocardial infarction and limit myocardial damage in the emergency department situation.

These PCR techniques are sensitive specific and reproducible, but they are also difficult to standardize.

There are also other powerful technologies being developed like NanoString microarrays, mass spectrometry or next-gen sequencing that can accurately detect genetic material.

However, practically speaking, the issues of time are less than ideal in those methods and are better suited for more chronic conditions.

Now, rapid genetic tests need to be developed if microRNA will ever go prime time in the clinical world. Interestingly, the recent use of the Point-of-Care Rapid Gene Test to genotype patients with a specific CYP Allele to guide antiplatelet therapy during coronary intervention is a step in the right direction in developing point-of-care tests to measure circulating microRNA and improve turnaround times.

However, more work is needed to improve this technology for rapid detection of microRNA, but with the current drive to find novel biomarkers this really shouldn't be long ways off.

Bob Barrett: Dr. Joshua Raizman is from the Department of Pathology and Laboratory Medicine, Mount Sinai Hospital in Toronto. Dr. Katey Rayner is from the Cardiometabolic microRNA Laboratory and the University of Ottawa Heart Institute. They have both been our guests in this podcast from C*linical Chemistry*. I am Bob Barrett. Thanks for listening.