A Novel Technology for Measuring Cumulative Cardiac Biomarker Exposure over Time: What Happened When We Weren't Looking?

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I'm Bob Barrett.

In the past, a diagnosis of acute myocardial infarction involved testing for peak levels of cardiac troponin concentration during hospitalization. With the advent of high-sensitivity cardiac troponin assays, detectable troponin concentrations can now be detected in much of the general population depending on the patient's age. These low-level increases may not be benign in these seemingly asymptomatic individuals because such increases may be associated with an increased risk of adverse cardiovascular events including myocardial infarction.

Although cardiac imaging can provide some insight into the cardiac pathology underlying a persistent biomarker increase, it's not always certain that an increase is related to another myocardial infarction.

In the January 2012 issue of *'Clinical Chemistry'*, Dr. Christopher deFilippi, Associate Professor of Medicine at the University of Maryland School of Medicine and Cardiologist at the Maryland Heart Center reviewed a new technology first presented by researchers at Harvard that continuously measures concentrations of the biomarkers that are present in these post-myocardial infarction patients.

Dr. deFilippi is our guest in this podcast. Doctor, clinicians and laboratorians are familiar with measuring cardiac biomarkers in the acute care setting for diagnosis and prognosis. Why is there now an interest in evaluating chronic exposure?

Dr. Christopher deFilippi: There had been hints over the past 10-15 years that in the absence of an acute presentation, there can be elevation of biomarkers such as cardiac-specific troponins, which are the diagnostic tests for acute myocardial infarction. This is seen in disease states, the prototypical one being end-stage renal disease, and it has been recognized for about ten years that elevations in the absence of symptoms can indicate a poor prognosis from a cardiovascular standpoint with respect to cardiovascular death or cardiovascular hospitalization.

Recently with the introduction of these new highly sensitive cardiac troponin assays, which are often tenfold order of magnitude more sensitive than the conventional tests currently being used in the United States, we've recognized that in some instances even in the general population, the majority of individuals

will have detectable troponin levels and that the presence of a detectable troponin level can often indicate a poor prognosis with respect to developing symptoms of heart failure and hospitalizations for heart failure, cardiovascular events including myocardial infarctions and even cardiovascular death.

However, even with these highly sensitive assays, we are only able to measure at one, two, or three time points in individuals who might be considered at risk. And therefore, one does at times want to know what has happened in between these measures because as we increasingly recognize that there can be chronic elevations of a marker such as the cardiac troponin, different amounts of release over time may indicate different forms of pathology.

Bob Barrett: So would measuring a cardiac biomarker at two or maybe three time points in an at-risk individual, provide all the information a clinician might need?

Dr. Christopher deFilippi: Probably not, perhaps a very chronic setting in individuals where you're suspicious that they may be at risk of heart failure, this may be appropriate. But even though there is the ability to get some element of the trajectory, we really don't know the cumulative amount of biomarker exposure these individuals have.

An analogy would be blood glucose where measuring blood glucose at two or three time points gives you a snapshot into that individual's risk for diabetes, but ultimately looking at a marker that shows a cumulative exposure to high glucose levels such as Hemoglobin A1c may provide more insight and help direct management of that disease.

Bob Barrett: When you talk about cumulative cardiac biomarker exposure, what do you mean by that?

Dr. Christopher deFilippi: Well, so what we would like to know ultimately is what is the mean concentration of the biomarker over a period of time. As we know with a disorder such as an acute coronary syndrome, there is going to be a rise and then a subsequent fall in levels of cardiac troponin for example. And ultimately over that period of time, there would be a high mean level for cardiac troponin.

In contrast, someone who may have sort of the early forms of cardiomyopathy or be on their way to developing symptomatic heart failure may have a

very chronic low-level release. In other words, their mean cardiac troponin level may be reflected by the troponin level measured at one or two time points. And their prognosis and how we might manage that patient may be very different.

Bob Barrett: Tell us about the technology you wrote about that can measure cumulative biomarker exposure?

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Dr. Christopher deFilippi: This is really quite intriguing. It represents departure for, I think, laboratory and then certainly departure for clinical cardiologists such as myself and how we would consider the measurement of a biomarker.

So this technology which I discussed in a recent perspective piece in *'Clinical Chemistry'* was based on a publication by Ling et al. from *'Nature Biotechnology'* last year.

And what they do is they developed a subcutaneous implantable receptor that uses a new class of nanoparticle-based magnetic resonance contrast agents. And these are superparamagnetic iron oxide nanoparticles that act great around an analyte molecule and alter the transverse relaxivity surrounding water protons. The particles can be used to detect small molecules including proteins, nucleic acids, oligonucleotides, peptides, receptors, ligands, and antibodies.

This technology is capable of quantifying small molecules that occur in blood and concentration as low as the picogram per milliliter range. So at the range of some of our most highly sensitive troponin assays for example are able to make these measurements.

And in this proof of concept experiments that they did, they showed that they were able in mirroring the models to measure markers of myocardial injury that included Myoglobin, Creatine Kinase Isoenzyme MB, and also Cardiac Troponin I, and they were able to do this by implanting these devices subcutaneously they contain the nanoparticles within the semipermeable membrane that they placed in the animal's flank.

And they were able to quantify the biomarker levels either by explanting the sensor or perhaps even more intriguingly, they were able to do in situ interrogation for a minimal invasive measurement of

the cumulative dose of the biomarker present at different time points.

And that's particularly intriguing because one could recognize that you could potentially implant a sensor that may be able to last even a period of several months and make measurements at different time points.

Bob Barrett: Well, Doctor, you are clinical cardiologist, so in your opinion, would a device like this be accepted in the cardiology community?

Dr. Christopher deFilippi: I think that it could be well-accepted. We're becoming increasingly comfortable and familiar with device implantation, of course, for therapeutic uses that includes the widespread use of pacemakers for many years, but also now more recently the implantation of implantable cardiac defibrillator devices. They have also been a host of implantable subcutaneous diagnostic devices, those that can monitor for arrhythmias individuals who have intermittent syncope.

There are experimental devices that are in place that can measure hemodynamic parameters such as pulmonary artery pressure that can perhaps be used to guide therapy for heart failure management.

So it wouldn't be much of a leap to say that there could be good acceptance for the use of a device that can measure cumulative biomarker exposure, particularly if we're looking at an at-risk population such as those that we're concerned may have a silent or an atypical presentation for a myocardial infarction that may go clinically unrecognized.

Bob Barrett: Well finally, Doctor, are there additional groups of patients that other than those at high risk for another myocardial infarction that might benefit from cumulative cardiac biomarker evaluation?

Dr. Christopher deFilippi: I think there are and that's also these are a couple intriguing and important groups, that are in fact, maybe even larger than looking at patients let's say post-myocardial infarction where we're maybe concerned that they might have another silent myocardial infarction and we'd like to catch cumulative biomarker exposure.

The two groups I think that this could be most applicable to would be those with chronic heart failure. Recently there was a publication in the

'Journal of the American College of Cardiology' that represented perhaps the cumulative experience of multiple biomarker studies looking at natriuretic peptides to guide chronic therapy. What they found is that with frequent visits in patients with chronic heart failure and measurements of the biomarker N-terminal proBNP that this could be used to guide a therapy effectively to reduce hospitalizations and also improve left ventricular function.

Now it may be a bit of a leap but one could see that if you could measure cumulative natriuretic peptide release over a period of time, for example, like going in and having the sensor interrogated every several weeks that that might be an even better guide for therapy and of course that would have to be tested in a clinical trial.

Another group that may be particularly relevant to look at that was mentioned in Ling's article are individuals who are undergoing chemotherapy with agents that are potentially cardiotoxic.

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The time course of cardiotoxicity isn't completely clear and the best way to monitor this for the continuation of particular chemotherapeutic agents is still under study.

But one could imagine that if one could look at cumulative release of a marker such as a cardiac troponin after receiving chemotherapy from potentially cardiotoxic drugs such as Herceptin that this might be able to guide an oncologist's dosing strategy.

Bob Barrett: Dr. Christopher deFilippi is an Associate Professor of Medicine at the University of Maryland School of Medicine and a Cardiologist at the Maryland Heart Center. He has been our guest in this podcast from *'Clinical Chemistry'*.

I'm Bob Barrett, thanks for listening!

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