Myocardial Ischemia on Exercise Stress Echocardiography Testing Is Not Associated with Changes in Troponin T Concentrations

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Guest: Dr. Alexander Limkakeng, associate professor and director of Acute Care Research at Duke University.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Patients that present to the Emergency Department, or ED, with symptoms of potential acute coronary syndrome but have no significant changes in cardiac biomarkers and electrocardiograms that are non-diagnostic fall into the so-called gray zone. It's not appropriate that these patients be sent home from the ED, but it also might not be appropriate for them to be admitted to the cardiology service.

Now, current guidelines recommend such patients undergo cardiac stress testing in order to determine whether they have inducible myocardial ischemia.

In the March 2017 issue of JALM, an article entitled "Myocardial Ischemia on Exercise Stress Echocardiography Testing is Not Associated with Changes in Troponin T Concentration" investigated whether there were significant changes in Troponin T concentrations from before and after stress testing in recently symptomatic ED patients with myocardial ischemia compared to those without ischemia.

The first author of this article is Dr. Alexander Limkakeng, associate professor and director of Acute Care Research at Duke University, and he's our guest for today's podcast. Welcome, Dr. Limkakeng.

Dr. Limkakeng: Thank you so much, Randye, for this opportunity and thank you to the journal.

Randye Kaye: To start with, can you explain the study and tell us what's different about this study?

Dr. Limkakeng: Sure. I'd like to start by first, of course, acknowledging the work of my collaborators and colleagues who are co-authors as well as the role of the sponsor which is detailed in the article. There have been previous studies that measure cardiac troponin concentrations in patients undergoing stress tests, however these exclusively enrolled outpatients

and largely they've been done by folks like cardiologists who see these patients on an outpatient basis.

I'm an emergency physician and so I found this opportunity to enroll a slightly different population, that being patients who had come to our emergency department with symptoms. And then we have what's called an ED-based observation unit. So these are folks who are staying up to 24 hours in order to get stress testing in our emergency department, rather adjacent to it. So we had a slightly different population because all of these folks were really recently symptomatic, so that was one difference.

I think our study was slightly different because my interest in this whole concept wasn't just academic, but I'm really interested in developing this, what I call stress delta concept into a usable clinical test. And so that informed our decision to try to capture downstream outcome events in the patients be enrolled. So we follow them up, up to 90 days and to see if they had any bad events like heart attacks or needed to have what's called coronary artery bypass surgery. So that's a significant outcome.

And then, although there were a few, I think that are cited in our paper that used what we call high-sensitivity troponin assays, most of the prior studies predated high-sensitivity assays and so they didn't use them. So that's another difference in our paper.

Randye Kaye: Okay, that sounds very essential. Why might this be considered controversial?

Dr. Limkakeng: One of the citations in our article point to many, and who really prominent in this field, have called for what's called requiem of this entity we called unstable angina. And so there's this prevailing thought that the new generation or high-sensitivity troponin assays are going to be able to detect any element of myocardial ischemia, and that's because they are able to detect much lower, an order of magnitude lower, level of cardiac troponin concentrations in the serum.

I was at a convention where a very experienced emergency cardiology researcher said at much that if you don't have any elevation in your troponin "It's not cardiac in nature." And so, our work seems to contradict that prevailing thought, that actually it's possible to have objectively demonstrated myocardial ischemia without changing your troponin concentrations. So, some might consider that a little bit different than the current thought on this.

Randye Kaye: I see. Wow! That's interesting. Where do you see this line of research going?

Dr. Limkakeng: As I said, the bigger idea was to try to develop what I call a biomarker stress test. So traditionally, a stress test had two components, right? There's the provocative or stressor element where people either run on a treadmill or get a medicine, and the idea is that we're trying to induce ischemia. So we're trying to increase the patient's heart demand for oxygen by doing that.

And then there's an assessment component which traditionally in all the forms of stress test that we do now is essentially some form of an imaging. So things like echocardiography or what's called SPECT or nuclear studies. Sometimes people use what's called Cardiac MRI. So we're interested overall in trying to determine whether lab tests, or biomarkers, could identify ischemia in the same way that imaging does within a stress test. As an emergency physician, that would be a real boon for us clinically simply because our laboratory friends are always available to us 24 hours a day, whereas those imaging components currently aren't in most health systems. So that would be a huge clinical advantage if we were able to develop a biomarker stress test.

So having demonstrated that troponin doesn't change under this paradigm, we're going to look at other specific biomarkers and try systems biology approaches, things like metabolomics and transcriptomics, and to see if there are changes in metabolites or other molecules that we can identify.

Randye Kaye: Now, how do you see this maybe impacting the introduction of high-sensitivity troponin assays in the United States?

Dr. Limkakeng: Well, it's really timely that we're having this conversation and the publication of this paper. Of course I couldn't have known that. The FDA just recently approved use of a high-sensitivity troponin assay for clinical use in the United States. Our paper doesn't change the fact that the new assays are going to be valuable and have the ability to identify some patients who are going to have concentrations so low that their risk of acute coronary syndrome is probably negligible. So I don't think it's going to dampen the enthusiasm for these assays because we've been wanting them for a long time and nor should it, but I think our paper does inform us a little bit about how to use these assays appropriately and that's going to be the bigger question for the introduction of these assays.

Randye Kaye: One more question for you, how would you apply these findings to your clinical practice?

Dr. Limkakeng: We certainly need to be thoughtful about how we do this. Say that we need to incorporate high-sensitivity troponin assays and their values into a full clinical assessment, and so not use the troponin assay deterministically, and also not to use them dichotomously. There is the temptation to say even in our language where it's positive or negative. We're going to need to shift our mindset a bit into thinking about the value, the actual concentration as a number that we use sort of continuously as a piece of information that we incorporate into our overall evaluation into patients in the emergency department.

I think that our work shows that it's possible to have even brief myocardial ischemia that is not reflected by elevation of troponin concentrations, and that's consistent with prior literature even establishing in Europe, the use of high-sensitivity troponin assays, that there were still some folks who were going to be in that gray zone.

So it won't change the overall value that there's going to be value to having the assays, but I think it also confirms -- our work confirms that there will probably remain a role for stress testing in some selected patients. But we're going to be able to reduce the number of those patients by using better assays, at least that's the hope.

Randye Kaye: Wow! That sounds great. One final question I usually like to ask, is there anything we haven't covered here in these questions that you want to add, or you think we're pretty much covered it?

Dr. Limkakeng: As I talk to people in trying to do this study, these are sort of the questions that have come to me. I'd like to acknowledge the role of the sponsors and my co-authors and I just want to thank Duke University for providing an outstanding environment for us to conduct this work. And thank you to the *Journal of Applied Laboratory Medicine* for giving us a chance to talk about this work.

Randye Kaye: Well, it's been our pleasure. Thank you so much for joining us today.

Dr. Limkakeng: Thank you Randye.

Randye Kaye: That was Dr. Alexander Limkakeng from Duke University talking about the JALM article, "Myocardial Ischemia on Exercise Stress Echocardiography Testing is Not Associated with Changes in Troponin T Concentration" for this podcast. Thanks for tuning in for "JALM Talk." See you next time and don't forget to submit something for us to talk about.