Clinical Chemistry

Longitudinal Studies of Cardiac Troponin I in a Large Cohort of Healthy Children

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Guest:
Dr. Peter Hickman is the Director of Chemical Pathology at the Canberra Hospital and Associate Professor of Pathology at the Australian National University.

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

When it comes to measuring cardiac troponins, the 99th percentile is well-established as an essential component of the definition of myocardial infarction. It's clear that in adult populations with both conventional and high-sensitivity assays that individuals with troponin concentrations above the 99th percentile are at a markedly increased risk of death from myocardial infarction, but what about studies of troponin in children?

In the December 2012 issue of *Clinical Chemistry*, Australian and U.S. researchers described just such a study. Joining us today is lead author of that paper, Dr. Peter Hickman. He is the Director of Chemical Pathology at the Canberra Hospital and Associate Professor of Pathology at the Australian National University.

Dr. Hickman, studies of troponins in children are unusual. Tell us about the Lifestyle of Our Kids (LOOK) study.

Dr. Peter Hickman: Right, kids, is that an American slang term too for young children?

Bob Barrett: Absolutely!

Dr. Peter Hickman: Okay. Yeah, Lifestyle Of Our Kids, this study started in 2005, when the kids were eight years old, and we followed them through to the end of 2009, when they were 12. We started with 830 and we finished with 590, and the dropouts were mostly because the kids have moved away from their school where they were enrolled.

I should tell you that all of the studies have being done on the children in their school, everything including the bloods we collected from them.

We are hoping that we will be able to follow them up next year, in 2013, when they are age 16, and if we can get finance for it, we would like to follow them up again every decade so that we can see the influence of early lifestyle on later quality of life.

Our study was funded by the Commonwealth Educational Trust. They gave us on the order of $500,000 every year for four years. And in addition, there was an organization called The Bluearth Institute, who are interested in physical education and they provided some support with qualified instructors.

The LOOK study really covered a wide range of things. There were 11 major areas of research interest and they covered all sorts of things, ranging from physical fitness, through psychology, right through to academic performance, and we were involved in the sections on blood biomarkers, diabetes, and cardiovascular fitness.

Bob Barrett: Well, I thought troponin was about cardiac risk and cardiac disease. Isn't looking at a marker of heart disease in children just a bit pointless?

Dr. Peter Hickman: You'd certainly think so, wouldn't you, at first sight, but the point is we just don't know. In adults, we know that asymptomatic people with high troponins are at risk of future cardiovascular disease. No one has ever looked at children in this way before, so we don't know whether high troponins in children may say something about future cardiac risk. We potentially will have to follow these children for decades to get the answer to that question.

However, I suspect myself that the children who have the high troponins aren't at increased cardiac risk, principally because each time we collected blood, we found that different children had the high troponins, and I think if this was a reflection of hidden cardiac disease, we would expect the same children to have the high troponins. So we think something else is going on to give relatively transient troponin increases in these children.

So to get back specifically to your question, is it pointless measuring troponin in children? I don't think so. The main purpose of measuring troponin in adults is to look at possible cardiac disease. With these new assays, we find there is always some troponin present, so we have got to relearn what troponin means.

We have got to learn about this background troponin so we can understand what's a significant change when you've got an adult presenting to the emergency department, and what better population to get a feel for this background information than the population that we think is effectively free of cardiac disease?

Bob Barrett: You make the point that most children show very little change in their measured troponin, but a small number show a rather large change. Now, what is that telling us?

Dr. Peter Hickman: Okay. Look, I have got to make a little detour here to answer this question, so bear with me for a minute. I have got to refer to another paper we've published earlier this year. In this other paper we measured the other cardiac marker, troponin T, in the same group of children. Now, this assay isn't as sensitive as the troponin I assay we reported results on in our *Clinical Chemistry* paper.

For the troponin T assay, quite a few of the children, approximately 80%, had no detectable troponin in their blood. So what we did was we scored the children as troponin T present or troponin T absent, and we found a quite striking result. We found large numbers of troponin T present children in a particular school, in a particular year, but when we came back two years later, a much smaller number of children had troponin T present.

We talked to a colleague who is a very senior and very capable statistician and he got really involved in this, and he found this appearance of troponin and disappearance to be highly significant. It looked for all the world like an infective disease pattern, appearing in one place, spreading through a group, and then disappearing.

And to relate that study or that data to our *Clinical Chemistry* data, we think the small number who had the big changes belong to this group who had this external effect on them, which caused the troponin rise.

And can I just emphasize that these were well children, they had their blood samples collected at school, and every person who has been a parent knows that if their child is feeling unwell, they would tell mom and dad in pretty uncertain terms that they don't want to go to school.

Bob Barrett: Well, you also make the point in your paper that there is physiological as well as pathological release of troponin. Now, clarify this for our listeners.

Dr. Peter Hickman: Okay, physiological as well as pathological. Ten years ago, assays for troponin were relatively poor quality and almost no healthy persons had detectable troponin in their blood. If

they did have detectable troponin, experience told us that this person was at an increased risk of having a heart attack of some sort. So ten years ago, just the presence of troponin was always pathological.

Things have changed dramatically since the new high-sensitivity assays have become available. Even in children, we are finding nearly everyone has troponin present.

Let me give an example from the children which I think explains some things when I say physiological. When the kids were eight years old, only 87% of them had detectable troponin present in their blood, but when they were 12 years old, nearly all of them, greater than 98%, had detectable troponin.

Now, this study was a very detailed study and every two years, these children had sound waves, pictures of their heart taken, that's called echocardiography, and one of the things you can get from that is you can measure the amount of muscle that's present in the heart, and when they went from 8 years to 12 years old, their median left ventricular muscle mass increased by 65%. This isn't proof, but it does suggest that the bigger your heart, the more troponin you will release without cardiac disease being present.

And another little interesting variant on this is that in all studies that are being published, healthy men nearly always have higher troponin than apparently healthy women. So to me this implies that there is a background of physiological troponin release on top of which we then have to use troponin in the way that we want to use it, which is looking at people who are potentially having a heart attack.

Bob Barrett: Well, finally, Dr., do these studies with children have any direct application in our understanding of cardiac disease in adults?

Dr. Peter Hickman: Yeah, I believe so, and I can give you a couple of items for you to consider. I have already mentioned that ten years ago assays weren't as good as they are today, so when troponin was presently new, there was pathology present.

Okay, enough said about that. But studying an effectively cardiac disease free group, such as the children, has shown this background of troponin in nearly all of them, and that to me demonstrates there is a background of troponin in everyone.

I think one great power of our study is that we collected samples on more than one occasion, and most studies in adult looking at cardiac risk are cross-sectional. We found that most of the children had low concentrations on all the

occasions they were bled, but some had an occasional high result.

If we apply this finding to adults potentially, we might find that a person might have an occasional high result and this might not be an index of future likelihood of cardiovascular disease. But perhaps what our study is saying is that when you are looking at adults, who are the people of interest for cardiac disease, perhaps those persons with a high troponin result might need to be re-bled to see whether the result remains high. This may well improve the predictive value of troponin for future cardiac disease.

So when it comes to adults, I think it means that simply detecting troponin in blood no longer indicates cardiac disease. It might be this physiological background troponin or it might be as a result of the heart attack or some damage to the heart. So I think this implies a change in emphasis is required. Simply looking for troponin concentration above a cutoff is insufficient.

I should add that most persons have very little variation in troponin on a day-to-day basis. We found this with the children and it has been found in some studies in adults too. And it's possible to have a significant increase in troponin while the concentration is still below the cut point.

So I feel this emphasizes the need to make two measurements to look for a significant change, and it's also terribly important that we have a good clinical assessment of the patient. It's the combination, I think, of two measurements and a careful clinical assessment that is the message from our study.

Bob Barrett: Dr. Peter Hickman is the Director of Chemical Pathology at the Canberra Hospital and Associate Professor of Pathology at the Australian National University. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!