

**Article:**

Paul Collinson.

Macrotroponin—Analytical Anomaly or Clinical Confounder.

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Guest: Dr. Paul Collinson is Professor of Cardiovascular Biomarkers and honorary Consultant Cardiologist at St George's University Hospitals National Health Service foundation trust and St George's University of London.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

The cardiac troponins are critical diagnostic biomarkers for detecting myocardial injury. However, cardiac troponin autoantibodies can contribute to the significant discrepancies observed among troponin assays. Endogenously occurring antibodies form large complexes with circulating troponin and these are referred to as "macrotroponin." Macrotroponin, similar to macro enzyme complexes, may reduce the clearance of troponin from circulation, leading to increased concentrations.

The October 2022 issue of *Clinical Chemistry* published a paper where the investigators examined the effects of macrotroponin and repeat testing by different high-sensitivity troponin I assays in a cohort of community patients with elevated troponin levels. The same issue had an accompanying editorial that asked the question whether macrotroponins are analytical anomalies or clinical confounders.

The author of that editorial is Dr. Paul Collinson. He is Professor of Cardiovascular Biomarkers and Honorary Consultant Cardiologist at St George's University Hospitals National Health Service Foundation Trust and St George's University of London. We're pleased to have Professor Collinson as our guest in this podcast. So, first of all, are these macrotroponins common and how does the laboratory find them?

Paul Collinson:

Well, anecdotally macrotroponins are in fact quite rare. They usually turn up when a clinician rings you in a state of some high fever saying he's got a patient who he's usually done lots of investigations on because they've got a troponin that's really high and they can't find anything wrong with their coronary arteries. What do I do now? What do I do now? And then we do some tests in the lab and we say "well actually, the troponin you're looking at is a really genuine true false positive. It's called a macrotroponin." And they get really so delighted about it. They write up a case study and

that, so most of them get into the press. That's really what makes this paper really quite so very interesting. Because when they did their study, they found that about 99 out of 188 cases of elevated troponin that they screened had a macrotroponin present. So, this is actually quite an interesting finding.

Bob Barrett: So, do you find it surprising that the rate reported by Lam and co-workers is so high?

Paul Collinson: Well, also that is both yes and no. The real problem is that no one's ever done a systematic study to find out how much macrotroponins are present because as I've said they're usually anecdotal. Someone finds one and they get it confirmed and no one ever really sat down and said, "Alright, how many of them have we got all the time?" But the important thing about this study is you need to see it in the context under which they performed it. Essentially what they did was they took a large community population who were having troponins measured. They screened 4,641 tests. They identified 188 elevations where they had a sample and full clinical information, and then they found 99 troponins there.

So, you're looking at a relatively small proportion of the total number that they screened with an elevation who actually had a macrotroponin, and the median troponin was typically about twice the upper reference limit. In the majority of cases, it's actually less than five times the upper reference, similar to the assay. Although interestingly enough, if there were patients who had a cardiac history, it tended to be slightly higher.

Most of the macrotroponin reports I've come across, the troponin results are really very high. We're talking about hundreds of multiples of the upper reference limit. So I think that the findings, while they're really, really interesting, represent a combination of two things. It's combination of case selection and the fact that majority of the macrotroponins here are not really very high.

Bob Barrett: Do you think that this will cause diagnostic confusion?

Paul Collinson: Well, in the case report series, including a couple of my own, it certainly has called diagnostic confusion, and usually clinical diagnostic confusion rather than anything else. But that seems to be the exception rather than the rule. The evaluations which have been performed of troponin methodologies have not really shown up anything that suggests there's something wrong with troponin assays in general. And this really suggests to me that the diagnostic impact is actually going to be minimal and the reason of this is it probably represents the fact that the majority of elevation

seen in clinical diagnostic studies are, in fact, quite large. We're not talking about things which are sort of only two or three times the upper reference limit; it's usually much much higher. The other factor I think, is that the diagnosis of myocardial infarction depends upon the demonstration of a delta.

So, we're looking at serial troponin measurements and large changes. My experience in my review of the literature is that macrotroponins tend to be stable. So if you've got just a single elevated troponin and you repeat it and it's pretty much the same, you're not going to say, well, it's not an MI. We'll call it something else entirely. It's the fact that these patients re-present with a higher troponin that brings them to the clinician's attention and often these people have had multiple previous admissions and a lot of imaging done in the past.

Bob Barrett: So, are you saying we can just ignore macrotroponins then?

Paul Collinson: No, not at all. I think the important finding in this study, that there's a high prevalence of modest troponin elevation, and this appears to have generated in this study a little bit diagnostic confusion in that the patients who they document tended to have slightly longer hospital admissions, they had few more tests done, and this is really pretty much in keeping with the previous studies, which have occurred with the individual case reports, which are characterized by a lot of investigations on individual patients before they finally say "Well, we can't find anything wrong with their coronary arteries or their heart."

But one thing which I think is quite intriguing here is that as troponin measurements become more sensitive, there's been this terrible term largely coined by largely frustrated emergency doctors about troponitis because they say 'well, we see all these slightly elevated troponins in the emergency department [ED] and does this mean your test is rubbish and it's much better in the good old days when you just had a high one or none at all?' I sympathize with that. It may well be that this finding of macrotroponins contributing substantially to slight troponin elevations is in fact a part of the cause of this.

Bob Barrett: So finally Doctor, what are the research priorities looking forward?

Paul Collinson: Well, I think what we really need here to try and really find out if this troponitis, which is the doldrums of the ED physicians, is actually real and really due to these macrotroponins, rather than as we suppose at the moment, because troponin elevation is extremely common due to coincident comorbidities and essentially a large study with systematic evaluation of troponins, the ED population with

serial sampling and screening for macrotroponin to see if this diagnostic confusion really exists. It may well be that this actually helps relieve the excitement of ED physicians going forward because they'll say, "Oh well, one troponin is elevated, we'll repeat it. The other troponin is also a bit -- oh, this may well be a macrotroponin." But we don't know at this moment in time and that's just I think the next study which I hope someone will be doing and publishing in *Clinical Chemistry*.

Bob Barrett:

That was Paul Collinson, Professor of Cardiovascular Biomarkers and honorary Consultant Cardiologist at St George's University Hospital's National Health Service Foundation Trust and St George's University of London. He has been our guest in this podcast on macrotroponin. His editorial, as well as an original scientific paper on macrotroponin in a cohort of community patients with elevated cardiac troponin, appears in the October 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.