# Cardiac Troponin T Degradation in End-Stage Renal Disease Patients Appears to Occur in Vivo

**Article:**
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**Guest:** Ellen Denessen is a fourth year Ph.D. candidate at the Central Diagnostic Laboratory at the Maastricht University Medical Center in the Netherlands.

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

The advent of high-sensitivity cardiac troponin assays has generally allowed for faster rule-in and rule-out of acute myocardial infarction. This brings opportunities to reduce missed cases and unnecessary hospital admissions. However, the analytical improvements may also cause non-specific elevations of high-sensitivity troponin concentrations in other conditions, including end-stage renal disease, making diagnosis and clinical decision-making difficult in this patient population. Previous research has demonstrated that the relative abundance of different circulating cardiac troponin T forms may vary in patients with myocardial infarction as compared to end-stage renal disease [ESRD] patients without myocardial infarction.

The September 2023 issue of *JALM* features a Letter to the Editor describing a study that investigates in vivo cardiac troponin T forms in hirudin plasma of end-stage renal disease patients. The findings of the study suggest that newer cardiac troponin T methods may be able to offer increased specificity for the acute phase of myocardial infarction.

Today, we're joined by the editorial's first author, Ellen Denessen. Ellen is a fourth year Ph.D. candidate at the Central Diagnostic Laboratory at the Maastricht University Medical Center in the Netherlands. Together with Dr. Alma Mingles, the corresponding author of the letter, Ellen researches cardiac biomarkers in various patient populations, with a primary interest in cardiac troponins. Welcome, Ellen. We know that cardiac troponins are the standard biomarkers for diagnosing myocardial infarction. So why did you decide to study cardiac troponin T in patients with end stage renal disease?

Ellen Denessen: Thank you for the introduction and thank you for the question. So, as you mentioned in the introduction, there are patient populations with elevated baseline cardiac troponin

concentrations, as with end-stage renal disease. So this could potentially confuse cardiologists when diagnosing myocardial infarction.

In the current guidelines to diagnose MI, algorithms are described to detect the rise and fall of cardiac troponin. However, then two blood withdrawals are needed, either one, two, or even three hours apart. Thus, it takes more time to make the correct diagnosis and delaying treatment. Therefore, we wanted to know whether we could improve the specificity of the current cardiac troponin TSA and exploit potential differences in circulating cardiac troponin forms between patients with either acute myocardial damage or patients with chronic diseases like end-stage renal disease.

Randye Kaye: All right, thank you. Now, we often think of troponins as being divided into the different markers of troponin T and troponin I, but it seems it's not as widely known that there are actually different circulating forms of each. Could you elaborate on the different forms of cardiac troponin T that you measured in your study?

Ellen Denessen: Of course. So for cardiac troponin T, previous studies have identified four forms. Form one is intact, or truncated, cTnT in complex with cardiac troponin I and troponin C. Then we have a second form, which is intact cTnT. The third form is cTnT that is cut to a 29-kilodalton protein. And the fourth forms are the small fragments degraded at both sides of the protein. Intriguingly, in serum of ESRD patients, mainly the smaller forms were observed, while in MI patients, larger forms were seen. So that would be the TIC complex, either intact or truncated, or the intact or 29-kilodalton cTnT. And this suggests that larger cTnT forms are more specific for the acute phase of MI.

Randye Kaye: I understand. Thank you. So your paper mentions that previous studies have already demonstrated that the blood of patients with end-stage renal disease mainly contains the smaller cardiac troponin T fragments. So what would you say is the additional value of this current study?

Ellen Denessen: Yeah, so in the previous study of ESRD patients, we found only the small fragments in their serum blood, while in MI patients serum showed a time-dependent degradation pattern, which was dependent on symptom onset. It turned out that thrombin has an important role in troponin degradation.

Thrombin is activated in a serum blood tube, resulting in troponin degradation caused by the serum blood tube. Therefore, we investigated hirudin in plasma of ESRD patients, as hirudin inhibits thrombin and therefore excluding in vitro effects of the blood tube on cTnT. We indeed showed

that with these hirudin blood tubes, still mostly small cTnT fragments were found in the circulation of ESRD patients.

Randye Kaye: Can you elaborate on the hirudin blood tube that you're talking about that you used for sample collection in your study? What exactly is hirudin and why did you use it instead of the lithium heparin tube that most of the audience is likely more familiar with in their clinical laboratories?

Ellen Denessen: Hirudin is a direct thrombin inhibitor and we showed that indeed, it completely stops the cTnT degradation in the blood tube, while lithium heparin is an indirect thrombin inhibitor and still might have a limited effect on cardiac troponin T. And as we wanted to be certain that there would be no additional fragmentation of cTnT in the blood tube, therefore, we chose to use the hirudin tube.

Randye Kaye: I see. Now, finally, what are the clinical implications of your study, and what additional research do you think remains to be performed in this area prior to any major changes in clinical practice?

Ellen Denessen: We observed a clear difference in the cTnT forms present in the blood of ESRD patients versus MI patients when using this blood tube, in which the in vitro fragmentation was not possible. So this difference may possibly lead to a new biomarker for acute myocardial damage, in which potentially one blood withdrawal will suffice, resulting in faster diagnosis and treatment. So the current cTnT assay can identify all forms of cTnT. So the use of a specific blood tube that inhibits the in vitro degradation of cTnT comes into play when designing a new assay, which can only detect the larger cTnT forms.

We have now validated the difference in cTnT forms between MI and ESRD, but potentially more populations with increased cTnT baseline concentration should be added to definitively conclude that the cTnT forms which are present during acute myocardial damage are actually different from chronic cardiac strain.

Randye Kaye: Ellen Denison, thank you so much for joining us on *JALM* Talk.

Ellen Denessen: Thank you for having me.

Randye Kaye: That was Ellen Denessen from Maastricht University Medical Center describing the *JALM* editorial "Cardiac Troponin T Degradation in End-Stage Renal Disease Patients Appears to Occur in Vivo." Thanks for tuning into this episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.