Cardiac Tropinin T in End-Stage Renal Disease Patients Undergoing Chronic Maintenance Hemodialysis

To the Editor:

Hafner et al. compared the serum concentrations of cardiac tropinin T and cardid troponin I in patients with end-stage renal disease (ESRD) undergoing chronic maintenance hemodialysis; they reported concentrations of cardiac troponin T of 0.01–3.7 μg/L and troponin I concentrations of 0.00–4.77 μg/L (1). Since then, Bhayana et al. (2) also reported discordance between results for troponin T and troponin I in nine patients with acute and chronic renal disease.

We have observed increased concentrations of cardiac troponin T (>0.2 μg/L) in 15 of 51 patients (29%) on chronic hemodialysis. The cause of the increase in this patient population is at present not clear. Although cardiac troponin T (39 kDa) has a slightly higher molecular mass than troponin I (26.5 kDa), the observed differences in the serum concentrations of these proteins are unlikely to be explained solely by different dialysis clearances. It has been suggested (3) that the cardiac isoform of troponin T, which in adults is ordinarly expressed exclusively in the heart, may be reexpressed in injured or diseased skeletal muscle, as has been observed in animals (4) and in humans with polymyositis (5). At present, it is unknown whether cardiac troponin T is expressed in skeletal muscle during uremia.

Another possibility is that cardiac troponin T is a more sensitive marker than troponin I, such that circulating cardiac troponin T may reflect repetitive episodes of minor myocardial cell necroses in this patient population, given that a substantial proportion of patients with ESRD also have coronary artery and hypertensive heart disease (6, 7). Our own prospective investigations into the possible causes of cardiac troponin T increases in ESRD patients indeed appear to indicate a correlation between the presence of coronary artery disease and increased steady-state concentrations of troponin T (Haller et al., unpublished observations).

However, we have some methodological concerns on the report by Hafner et al.: They imply that cardiac troponin I may be more specific and therefore superior to cardiac troponin T in this group of patients. However, the data provided do not permit this conclusion. The diagnostic utility of a test depends on the discriminator values used and on the definition and accuracy of the clinical diagnosis. The discriminator values and clinical diagnostic criteria used by Hafner et al. merit critical discussion.

Selection of discriminator values: For cardiac troponin T Hafner et al. used a cutoff value of 0.1 μg/L, whereas we and others have used 0.2 μg/L (8–11). Although 0.1 μg/L might be a more efficient discriminator value in patients with suspected myocardial infarction (11), using a 0.1 μg/L discriminator value in patients with chronic renal failure must reduce the specificity of the cardiac troponin T assay. For cardiac troponin I Hafner et al. use a discriminator value of 2.1 μg/L. The question then arises as to the source of troponin I values between 0.0 and the selected discriminator value of 2.1 μg/L. Is it all analytical noise, or is it the result of selecting a high discriminator value so as to have a high specificity? The same group has previously reported a cardiac troponin I discriminator value of 1.0 μg/L in patients without ESRD, less than half that used in the present study (12). Hence, we cannot exclude the possibility that the comparative evaluation of the two tests may be skewed by the chosen discriminator values.

Clinical diagnostic criteria: To test specificity, Hafner et al. examined 6 of the patients with high cardiac troponin T by two-dimensional echocardiography to detect abnormalities in regional wall motion. However, echocardiography is certainly not sufficiently sensitive to prove or exclude such minor myocardial cell damage that would produce cardiac troponin T concentrations in the reported range. Furthermore, it is necessary to know whether the ultrasound scans were analyzed in a blinded fashion, whether the quality of the scans allowed assessment of all myocardial wall segments, how hypokinetic or akinetic areas were differentiated, and finally what the reproducibility of the ultrasound scans were. The single patient with increased cardiac troponin I reported had a documented clinical history of unspecified cardiovascular disease, but no echocardiographic data were provided.

Thus, while we agree with Hafner et al. that care must be taken in interpreting slight increases in cardiac troponin T values in patients with ESRD as being indicative of acute myocardial infarction (WHO criteria), we argue that the conclusion regarding the superior specificity of cardiac troponin I over cardiac troponin T needs more critical discussion.

Reference

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nin T is not substantiated by the reported data. Moreover, in addition to specificity and sensitivity, the clinical application of diagnostic tests must take into account the prevalence of a given diagnostic marker in the patient population to be examined. In this context, the high prevalence of cardiovascular disease in the dialysis population underscores the negative predictive value of the cardiac troponin T assay.

At present, the cause of the increased cardiac troponin T in ESRD patients remains unclear. A more thorough investigation is needed to understand the significance of slightly increased cardiac troponin T values in some patients with ESRD. Meanwhile, comparative analyses of cardiac troponin T and I must be performed with well-defined assays, discriminator values, and appropriate clinical diagnostic criteria. Without fulfilling these minimum quality requirements, any statements on the comparative validity of the cardiac troponin T and cardiac troponin I assays are uninterpretable.

References

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The authors of the Letter referred to respond:

To the Editor:

Katus et al. corroborate our finding of increased troponin T in patients with chronic renal failure undergoing hemodialysis treatment (15 of 51 patients). Unfortunately no information is given as to whether above-normal troponin T concentrations (>0.2 μL/L) fluctuated in their patients over time, as one would expect if troponin T is derived from cardiac ischemia. In our study (1) we observed constantly increased plasma troponin T values without clinical evidence of myocardial ischemia over a period of 6 months with no significant concentration changes in the respective individual patients (7 of 18). These increases were seen independently of the membrane material (four Hemophan, three Polysulfone) used. Neither in our study nor in a study conducted by another group (2,3) with a similar cohort of patients was an increase in troponin I observed.

Katus et al. argue that increases of troponin T could result simply from having chosen an inappropriate discriminator value in the troponin T assay. However, the cutoff value we applied is that given in the manufacturer's package insert (Boehringer Mannheim, Mannheim, Germany). Even at Katus' recommended cutoff of 0.2 μL/L, troponin T was increased in 30% of all samples (20 of 67).

The troponin I assay we used—unlike the troponin T assay—was a noncommercial test still in the development phase. Because during the development of the assay different batches of microtiter plate plastic materials had to be used, with slightly differing binding characteristics, the cutoff value was determined separately for these particular batches. The cutoff value used for our renal failure patients was 2.1 μL/L. The results obtained are very similar to those reported by Adams et al., who used a different assay configuration (2); we therefore think it unlikely that the cutoff was set inappropriately in our study.

We agree with Katus et al. that echocardiography has lower diagnostic sensitivity than invasive methods such as coronary angiography. The echocardiographic investigations were performed in a blinded fashion. All investigations were of diagnostic quality so that wall segments could be analyzed completely two-dimensionally in the parasternal long and short axis view, in the apical four-chamber and twochamber view, and in the apical RAO-equivalent. In the parasternal views, wall motion was visualized additionally in m-mode. Differentiation of regional wall motion abnormalities was achieved in a conventional and standardized manner. A hypokinesia was defined as a systolic reduction of increase in wall thickness and in the inward movement of the wall. An akinesia was defined as the absence of both findings (4). Comparisons between echocardiography and cineventriculography demonstrated excellent correlation and reproducibility in the assessment of myocardial contractility of even small regions (5,6). On the other hand, we have found troponin T concentrations as high as 37 times the cutoff value of 0.1 μL/L (or 18.5 times the discriminator value suggested by Katus et al.), which would suggest severe myocardial events. It is difficult to conceive, though, that echocardiography would have totally failed to detect any evidence of cardiac disease in patients persistently presenting with high cardiac-derived troponin T.

Taken together, our data and those of others (2,3) still indicate that troponin T measurements in renal disease should be interpreted with caution. It is not surprising, therefore, that an improved troponin T assay with higher specificity has been announced by the manufacturer (7). Whether this new assay version will overcome the problems discussed remains to be seen.