

Cardiac Troponin T and I in End-Stage Renal Failure

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Background: In patients suffering from end-stage renal failure, cardiac troponin T (cTnT) and I (cTnI) may be increased in serum without other signs of acute myocardial damage. Whether these increases are specific to myocardial injury or nonspecific is not completely clear.

Methods: We investigated time courses of cTnT and cTnI over 1 year and the clinical outcome over 2 years in 59 patients with end-stage renal failure undergoing chronic hemodialysis. At the start of the study, we divided the patients into two groups, group 1, without history of cardiac failure, and group 2, with history of cardiac failure, and looked for differences between the groups in later adverse outcome. cTnT was measured using the Enzymun[®] troponin T assay on an ES 700 analyzer (Roche). cTnI was measured on a Stratus[®] II analyzer (Dade Behring). Creatinine and blood urea nitrogen were measured on a Vitros[®] 950 IRC (Ortho).

Results: Dialysis acutely increased cTnT ($P < 0.01$) and decreased cTnI ($P < 0.001$) regardless of the dialysis membrane used. Although statistically not significant, cTnT but not cTnI was increased more frequently in group 2 than in group 1, in some cases over the whole study period. Five patients (8.5%) died of cardiac complications within 2 years; all of them had mostly increased cTnT and, in one or more samples, increased cTnI.

Conclusions: Dialysis alters measured cTnT and cTnI concentrations in serum. In patients suffering from end-stage renal failure, sporadic or persistently increased cTnT and cTnI appear to predict cardiac complications. Because of the effects of the dialysis procedure on troponin values, we recommend that blood be collected before dialysis.

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Cardiac troponin T (cTnT)³ and I (cTnI) are specific markers of myocardial damage (1–4). Patients with end-stage renal failure undergoing chronic hemodialysis have a high incidence of cardiac events (5) and of false-positive increases in myoglobin as well as creatine kinase and its MB isoenzymes (6, 7). cTnT and cTnI may be increased in these patients without evidence of ischemic myocardial damage (8, 9). The increase is not correlated with creatinine concentration (10), and its etiology remains uncertain. The choice of troponin assays may be important. Early reports of frequent increases of cTnT used an assay with cross-reactivity with skeletal muscle troponin T (1). A second-generation cTnT assay shows cross-reactivity <0.01% with skeletal muscle troponin T (3, 11).

Various cTnI assays are available (12, 13). In patients with end-stage renal failure, cTnI is increased less frequently than cTnT (8). cTnI may be more specific for detection of myocardial injury than cTnT (14).

In our study, we measured cTnT with the second-generation assay and cTnI on a Stratus analyzer in multiple blood samples from 59 patients on chronic hemodialysis and compared the results with clinical outcomes 2 years later.

Materials and Methods

We studied 59 patients with end-stage renal failure undergoing chronic hemodialysis three times per week. Each patient was informed and agreed to participate in the study. At the beginning of the study, all patients were examined by electrocardiography and two-dimensional echocardiography. Three patients underwent coronary angiography. Based on the examination results, we divided the patients into two groups. Group 1 consisted of 31 patients without evidence of myocardial injury, but 14 patients showed concentric left ventricular hypertrophy. Group 2 consisted of 28 patients with any myocardial discomfort or heart disease: 11 patients with histories of

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³ Nonstandard abbreviations: cTnT and cTnI, cardiac troponin T and I; AMI, acute myocardial infarction; and CAD, coronary artery disease.

acute myocardial infarction (AMI), 14 patients with signs of coronary artery disease (CAD; T-wave inversion, ST-segment depression, wall dyskinesia), and 3 patients with dilated cardiomyopathy and heart failure.

Blood was collected from the patients, after a 3-day interval of non-dialysis, at the onset of the study, and 4 weeks, 3 months, 6 months, and 1 year later. Each time, 10 mL blood was collected before and after dialysis and centrifuged within 1 h of collection. The serum samples were stored at -20 °C until analysis.

Follow-up examination was done 2 years later at the end of the observation period. The clinical examinations were made without knowledge of the troponin results.

cTnT was measured with the Enzymun[®] Troponin T on an ES 700 analyzer (both from Roche Diagnostics) according to the recommendations of the manufacturer. The upper reference limit was 0.1 µg/L. The reported intraassay and interassay imprecision (as CVs) in this range is 3% and 6%, respectively (11).

cTnI was measured on a Stratus[®] II analyzer (Dade Behring) according to the recommendations of the manufacturer. The results were considered pathological when concentrations were ≥0.4 µg/L (15). The intraassay CV in this range is 13.6%, and the interassay CV is 6.6% (12).

Creatinine and urea were measured on a Vitros[®] 950 IRC (Ortho Clinical Diagnostics). For statistical analysis, we used the Wilcoxon matched-pairs signed-rank test for comparing the values before and after dialyses, the Wilcoxon Mann-Whitney *U*-test for differences between groups 1 and 2, the Kruskal-Wallis test to compare the diagnoses, and the Spearman test for correlation. ROC curves and areas under the ROC curves were calculated for cTnT and cTnI.

Table 1. Results of cTnT and cTnI measurements for all 59 patients at each time point.^a

Time point	cTnT			cTnI			
	Mean, µg/L	Maximum, µg/L	P	Mean, µg/L	Maximum, µg/L	P	
1	Before	0.07	0.49	<0.0001	0.3	1.2	<0.0001
	After	0.08	0.67		0	0.7	
2	Before	0.07	0.57	<0.0001	0.2	0.9	<0.0001
	After	0.09	0.8		0	0.5	
3	Before	0.04	0.46	<0.0001	0.2	0.8	<0.0001
	After	0.07	0.62		0	0.8	
4	Before	0.04	0.44	<0.0001	0.3	0.8	<0.0001
	After	0.06	0.49		0	0.3	
5	Before	0.09	2.07	0.04	0.1	1	0.002
	After	0.1	1.89		0.1	0.9	

^a Shown are mean, maximum, number of increased values, and the statistical differences between mean values in the blood specimens collected before and after dialysis.

Results

In the 566 serum samples obtained from the 59 patients, cTnT was above the upper reference limit in 16.6% and cTnI in 12%. The mean cTnT increased with dialysis, but the mean cTnI decreased markedly (Table 1). Thus, cTnT was increased more frequently in postdialysis samples (14% and 20% of pre- and postdialysis samples, respectively), whereas the opposite was observed for cTnI (increased in 21% of predialysis and 2% of postdialysis samples; Fig. 1). No significant correlation between cTnT and cTnI was found before (*r* = 0.139) or after dialysis (*r* = 0.1754).

Because of the effects of dialysis on cTnT and cTnI, we examined the membranes used for dialysis. Dialysis was

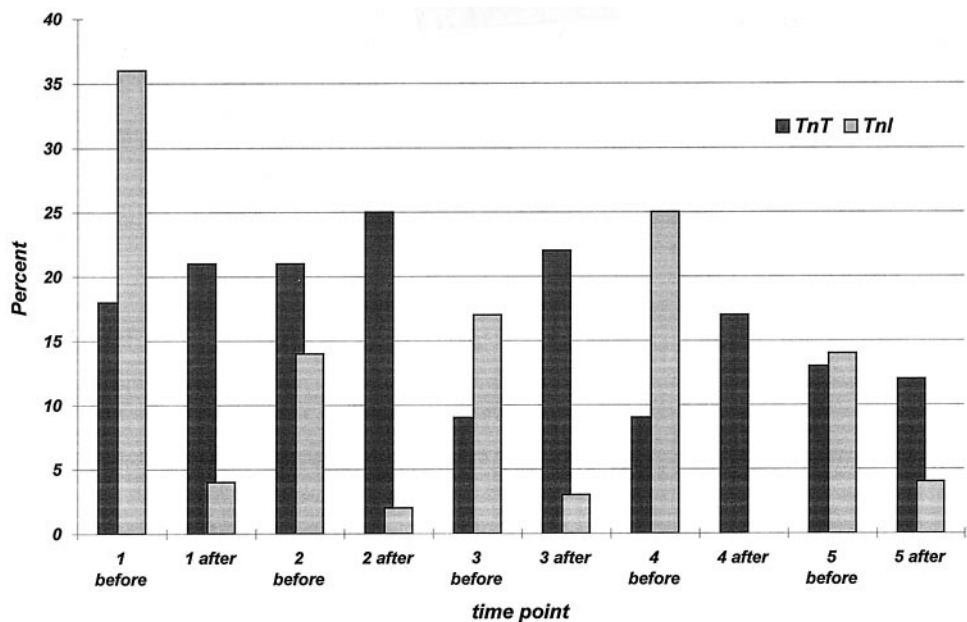


Fig. 1. Percentage of patients with increased cTnT and cTnI at each time point before and after dialysis.

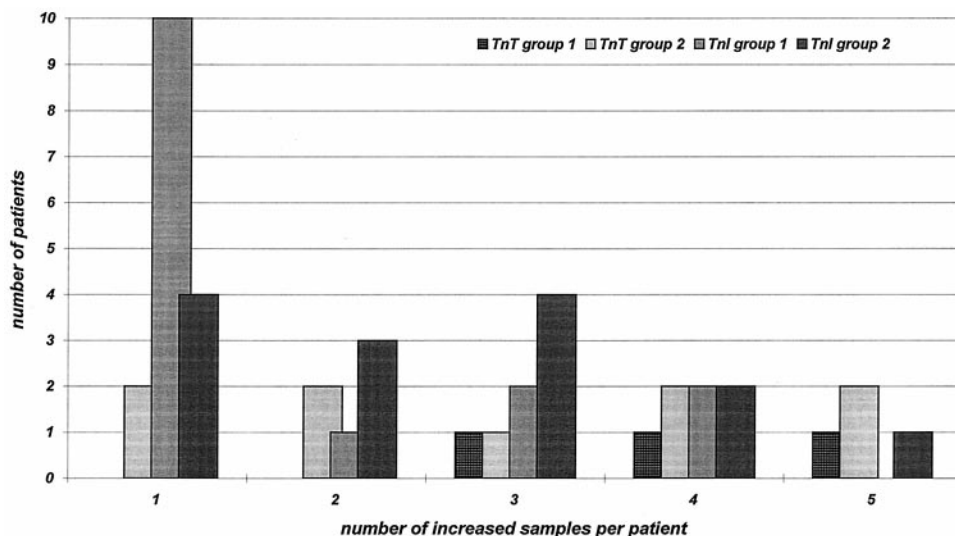


Fig. 2. Number of increased cTnT or cTnI samples for all patients with increased values before dialysis.

done with the high-flux membrane Polysulfon in 29% of patients and with low-flux membranes in 76% (cellulose membrane in 22%, Hemoephon in 35.5%, and Cuprophon in 18.6%). cTnT was increased in 10% of patients before dialysis and in 14% after dialysis by high-flux membrane and in 0–29% of patients before and 3–37% after dialysis by low-flux membranes. Dialysis, regardless of membrane, decreased cTnI by up to 81–86%. These discrepancies in pre- and postdialysis cTnT and cTnI values indicate some influences of the dialysis procedure itself on the cTnT and cTnI values. To avoid discrepancies attributable to the dialysis procedure, we used only the results from the predialysis samples for further comparison.

The frequency of increases of cTnT and cTnI was not predictable based on the underlying disease (Table 2).

RESULTS IN PATIENTS WITH AND WITHOUT CARDIAC SYMPTOMS OR DISEASE

The patients with cardiac symptoms or disease (group 2) were older (67.3 ± 10.3 years) than those of group 1 (51 ± 11.2 years; $P < 0.001$), whereas the mean creatinine concentration before dialysis was higher in group 1 ($1034 \pm 160 \mu\text{mol/L}$) than in group 2 ($795 \pm 164 \mu\text{mol/L}$; $P < 0.001$). The duration of end-stage renal disease treated by dialysis did not differ significantly.

In group 1 (non-cardiac), the mean cTnT concentration

in all samples was $0.06 \mu\text{g/L}$ (range, <0.01 – $2.07 \mu\text{g/L}$), and three individuals (10%) had increased cTnT values at some time. The mean cTnI was $0.2 \mu\text{g/L}$ (range, 0.0 – $1.1 \mu\text{g/L}$), and cTnI was increased in 15 (48%) patients at some time.

In group 2 (cardiac), the mean cTnT was $0.07 \mu\text{g/L}$ (range, <0.01 – $0.52 \mu\text{g/L}$). Nine patients (32%) had increased values. For cTnI, the mean value was $0.2 \mu\text{g/L}$ (range, 0.0 – $1.2 \mu\text{g/L}$), and cTnI was increased in 14 (50%) patients. The frequencies of increased results per patient are shown in Fig. 2. Significant differences between the two groups were found only at the fourth time point, with higher cTnT in group 2 than in group 1.

CARDIAC TROPONINS AND PATIENT OUTCOMES

Five (8.5%) patients died during or shortly after the study: From group 2, one death was attributed to heart failure, one to sudden cardiac death, one to myocardial infarction, and one to cardiac failure in combination with a severe stenosis of the aortic valve. The fifth patient was from group 1, and death was attributed to septicemia following endocarditis. Four of the patients who died had increased cTnT in two to four samples and increased cTnI in one or more samples (Table 3). Only the patient with endocarditis showed a progressive increase of cTnT and cTnI during the study. The patient with severe stenosis of the aortic valve consistently had cTnT concentrations within the reference range, whereas cTnI was increased in three of five samples (Table 3).

Two other patients (one from group 1 and one from group 2) developed unstable angina with coronary vessel disease demonstrated by coronary angiography. Both had troponin values within the reference limits throughout the study (Table 3).

We prepared ROC curves for cTnT and cTnI (Fig. 3), using the values of the initial specimen before dialysis and a composite endpoint of cardiac death or development of

Table 2. Increased cTnT and cTnI values and the underlying renal diseases.

Diagnosis	No. of patients	M/F	cTnT positive, %	cTnI positive, %
Glomerulonephritis	22	13/9	18	46
Tubulointerstitial nephritis	9	3/6	22	33
Pyelonephritis	5	1/4	40	40
Polycystic kidney	6	3/3	0	33
Diabetic nephropathy	8	6/2	37.5	75
Others	9	4/5	11	67

Table 3. Clinical findings and cTnT and cTnI values in patients with mostly increased values or with adverse outcome.^a

Patient	Diagnosis	Group	No. of samples with increased cTnT	Median (range), $\mu\text{g/L}$	No. of samples with increased cTnI	Median (range), $\mu\text{g/L}$	Clinical findings ^b
D61	Glomerulonephritis	1	5	0.34 (0.14–0.8)	0	0.1 (0–0.2)	8, 9, 10, LAH ^c
D67	Diabetic nephropathy	1	0	0.2 (0–0.05)	4	0.8 (0.3–1.1)	8, 9, 10, 11
D15	Tubulointerstitial nephropathy	2	5	0.17 (0.15–0.21)	3	0.4 (0.2–0.8)	7, 5, 10, pacemaker
D45	Glomerulonephritis	2	5	0.44 (0.38–0.82)	4	0.5 (0.3–0.9)	3, 6, 10, dyspnoe, COPD
D41 ^d	Glomerulonephritis	1	0	0.0 (0.01–0.03)	0	0.1 (0.1–0.3)	unstable AP, CHD
D72 ^d	Tubulointerstitial nephropathy	2	0	0.02 (0–0.04)	0	0	1, 2, 4, unstable AP, CHD
D43 ^e	Glomerulonephritis	1	4	0.12 (0.1–2.07)	1	0.1 (0–1)	6, endocarditis
D64 ^e	Glomerulonephritis	2	4	0.12 (0.08–0.14)	1	0 (0–0.4)	1, 2, 3, 10, 11
D56 ^e	Pyelonephritis	2	4	0.17 (0.1–0.39)	2	0.1 (0–0.5)	1, 3, 6, 10
D71 ^e	Other	2	2	0.125 (0.08–0.13)	1	0.25 (0.1–0.5)	1, 2, 10
D33 ^e	Glomerulonephritis	2	0	0.04 (0.03–0.06)	3	0.4 (0–0.5)	2, 3, 6, 8

^a Adverse outcome defined as development of unstable angina or death.

^b Clinical findings: 1, state after myocardial infarction; 2, angina pectoris-like clinical signs (stable); 3, repolarization disorders; 4, wall dyskinesia; 5, left ventricle pump failure; 6, left ventricular hypertrophy; 7, left ventricular dilatation; 8, atrial dilatation; 9, hyperhydration; 10, hypertonus; 11, diabetes.

^c LAH, left anterior bundle hemiblock; COPD, chronic obstructive pulmonary disease; AP, angina pectoris; CHD, coronary heart disease.

^d Patient developed unstable angina.

^e Patient died.

unstable angina within 2 years after initial sampling. Using the recommended cutoff of 0.1 $\mu\text{g/L}$ for cTnT, ROC analysis showed a sensitivity of 57% with a specificity of 88%. For cTnI, the sensitivity and specificity were 57% and 67%, respectively, at 0.4 $\mu\text{g/L}$. The areas under the curves were 0.703 for cTnT and 0.477 for cTnI. The difference between the areas under the curves between cTnT and cTnI was not significant ($P = 0.213$). Using the results of the other time points (pre- and postdialysis samples), we obtained similar results without significant differences between the areas under curve (data not shown).

Discussion

The first results dealing with unexpected increases in cTnT and cTnI in patients with end-stage renal failure were published in 1994. Using the nonspecific first-generation assay for cTnT (1) with $\sim 2\%$ cross-reactivity with skeletal muscle troponin T, Hafner et al. (8) found that up to 46% of all patients showed increased values, whereas for cTnI, only 1.5% had increased values. Using an improved cTnT assay with a cross-reactivity $< 0.01\%$, we found increased cTnT values in 16.6% of all sera at a cutoff of 0.1 $\mu\text{g/L}$. Similar results were obtained by McLaurin et al. (16), who used the 0.2 $\mu\text{g/L}$ cutoff, which was

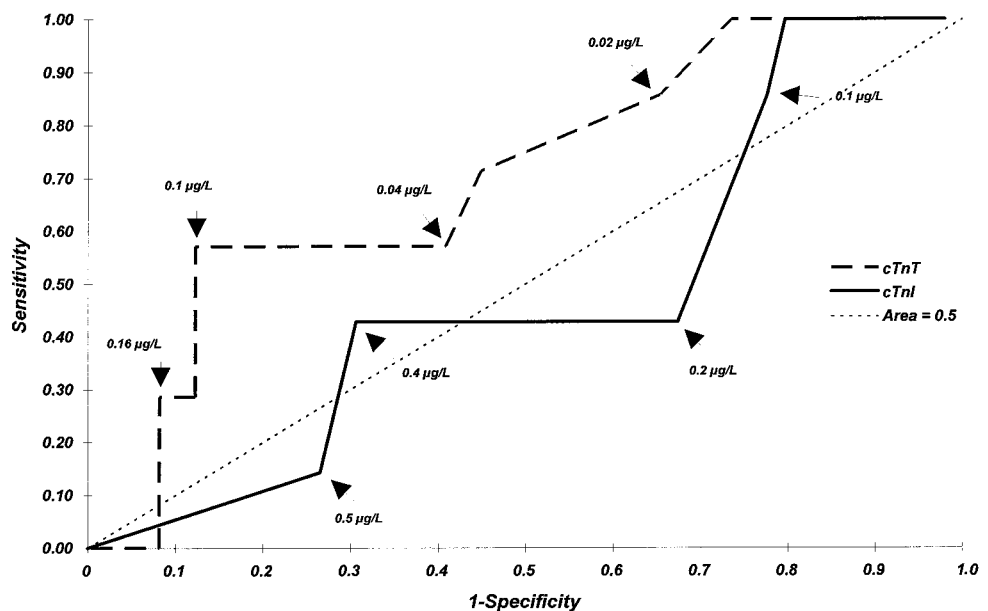


Fig. 3. ROC curves for cTnT and cTnI, using the samples collected at the first time point and cardiac death or unstable angina as the endpoint.

recommended for patients with possible myopathy (11). For cTnI, the cutoffs for discrimination differ much more. Fixing the cutoff at $0.8 \mu\text{g/L}$, McLaurin et al. (16) found increased values in $\sim 4\%$ of all serum samples. In contrast, using the cutoff of $0.4 \mu\text{g/L}$, we found increased values in 12% of all serum samples. The results obtained by Apple et al. (17) were similar, with increased values in 18% of their serum samples.

As shown in the *Results*, the correlation between cTnT and cTnI is poor. This is in agreement with Möckel et al. (18), who also found no significant correlation. This discrepancy may in part be attributable to differences in the precision at the lower end of the measuring range of the assays used. The imprecision of the cTnT assay in the lower end of the measuring range is better (6%) than that of the cTnI assay (13%). Another explanation may be the different effects of dialysis on cTnT and cTnI and the use of serum samples drawn before and after dialysis for comparison. cTnT is increased after dialysis because of concentration effects, whereas cTnI is decreased. Similar results have been described by others (19).

Because dialysis procedures use several different dialysis membranes, we first blamed the type of dialysis membranes for the differences between cTnT and cTnI. Two types of clearance (diffuse clearance and convective clearance) and two types of membranes (high-flux and low-flux membranes) can be differentiated (20). With high-flux membranes, diffuse clearance removes molecules up to 15 kDa, whereas with low-flux membranes, only molecules up to 5 kDa are removed. Convective clearance removes molecules up to a high molecular mass when high-flux membranes are used, but only molecules up to 9 kDa with low-flux membranes. In our study, one high-flux (Polysulfon) and three low-flux (Cuprophan, Hemeophan, and cellulose) membranes were used. We found no differences in cTnI removal attributable to the membrane type; therefore, clearance cannot be the reason for the reduced cTnI concentrations after dialysis (results not shown). It seems more likely that adsorption of cTnI onto the membrane may be the reason for the significant reduction after dialysis because free cTnI is hydrophobic and likely bind to other proteins and surfaces (21). Another explanation may be that modifications of the cTnI molecule by dialysis changes the epitope recognized by the cTnI antibody used in the assay, thus leading to false-negative results (21). Therefore, to achieve reliable values for clinical decision, it is necessary to take blood samples before dialysis. Only then can a correct comparison be carried out.

As shown in the ROC curve in Fig. 3, when a major cardiac event or cardiac death is used as the endpoint, the sensitivities of both cTnT and cTnI are similar at their specific cutoffs, but the specificity is better for cTnT. This may be explained by the higher imprecision of the cTnI assay in the lower end of the measuring range in contrast to cTnT. Our cutoff of $0.4 \mu\text{g/L}$, which was recommended to detect patients with minor myocardial injury (15), is

quite similar to the lower detection limit ($0.36 \mu\text{g/L}$) of the assay. In this range, the imprecision is 13.6% (12). This may produce false-positive as well as false-negative results and may explain why we often found only one increased cTnI value per patient during the year. In contrast, the imprecision of the cTnT assay is only 6% at $0.24 \mu\text{g/L}$ (11). Therefore, the results obtained by the cTnT assay are more reliable than those obtained by the cTnI assay.

On the other hand, areas under the ROC curves indicate that CAD may not be the only reason for increased cTnT and cTnI values in our patients. Not only arteriosclerotic effects, but also nonarteriosclerotic effects (concentric and eccentric hypertrophy, water overload, myocardial fibrosis, decreased arterial compliance, intima-media hypertrophy) may lead to a decrease of myocardial blood flow, causing minimal ischemic lesions. This can lead to the release of small amounts of intracellular proteins such as troponin into the blood of hemodialyzed patients (22). This is in agreement with Frankel et al. (23), who showed that increased myocardial lengthening and congestive cardiomyopathy led to increases in cTnT in 18% of their patients.

For cTnI, the mean value and the number of patients with increased values were similar in both groups. Only the number of samples with increased cTnI per patient was higher in group 2 (Fig. 2); the patients in group 1 often had only one sample with an increased value. The mean cTnT values for both groups were almost identical. However, the number of patients with increased values was remarkably higher in group 2 (32%) than in group 1 (9%). In our population, nearly all patients who died during the study had multiple cTnT values over the upper reference limit, and all had one or more pathological cTnI values. These findings are in agreement with those of Porter et al. (24), whose patients with adverse cardiac outcomes all had increased cTnT, with most having increased cTnI concentrations. In another 1-year outcome study, Apple et al. (17) showed similar results, but in that study, the patients who died were those with the highest cTnT and cTnI values. We could not confirm this because in our study, the amount of troponin did not correlate with the outcome (Table 3). None of the pathological values correlated with acute cardiac symptoms, except for the patient with endocarditis. But considering the pathological troponin values without acute signs of myocardial injury, which often were followed by an adverse outcome later, one must consider minor myocardial injury as the cause of the release of the troponins from the myocardium. The cTnT discrimination limit of $0.1 \mu\text{g/L}$ marks only minor myocardial injury (25); for major cardiac events, the cutoff value is $0.4 \mu\text{g/L}$. For cTnI, the discrimination limit for myocardial infarction is $1.5 \mu\text{g/L}$. Ninety-seven percent of our cTnT values were $<0.4 \mu\text{g/L}$, and all cTnI values were $<1.5 \mu\text{g/L}$, both indicating minor myocardial injury in our patients.

The troponin concentrations of the patient with endocarditis were remarkable. Because isolated endocarditis

does not cause the release of proteins from myocardial cells, the infection must have also affected the myocardium. Some studies have described pathological cTnT and cTnI values in patients with myocarditis (26). Unfortunately, no further examination such as myocardial biopsy was done in our patients to confirm this, but the remarkable increases in troponin (2.07 $\mu\text{g/L}$ cTnT and 1.0 $\mu\text{g/L}$ cTnI) support our assertion.

Other, noncardiac reasons for increases in the troponins, especially cTnT, have been suggested. It has been postulated that myopathic skeletal muscle produced by uremia reexpresses cTnT (16, 27). But Haller et al. (28) demonstrated in patients suffering from end-stage renal failure neither mRNA nor the cTnT protein itself. Therefore, the cTnT values in the blood of dialysis patients measured with the Enzymun cTnT assay do not seem to be of skeletal muscle origin.

In conclusion, sporadic or permanently increased values for cTnT and cTnI can be seen in patients suffering from end-stage renal failure and undergoing chronic hemodialysis. These increases are not always specific for acute CAD. In patients without signs of acute CAD, it seems rather to be an indicator for minor myocardial damage. The correlation between the troponins is poor. This can be explained by the different effects of dialysis on cTnT and cTnI concentrations or by the high imprecision of the cTnI assay in the lower end of the measuring range. Because of the different effects of dialysis on cTnT and cTnI values, we recommend that blood samples be collected before dialysis.

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