Impact of kidney function on plasma troponin concentrations after coronary artery bypass grafting

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Abstract

Background. To date, there have been no studies reliably showing an influence of the kidney on the concentration of troponins. We therefore analysed the concentration curves in patients after coronary artery bypass grafting (CABG) according to their dependence on renal function.

Methods. We determined cardiac troponin I (cTnI), cardiac troponin T (cTnT) and creatinine in plasma in 28 patients after CABG. Discrimination into patients with normal (n = 13) and impaired (n = 15) renal function was based on creatinine clearance (Crea-Clear). The curves for cTnI and cTnT, as recorded by post-operative measurements, were approximated using mathematical functions. The curve parameters peak maximum (P_max), peak position (P_pos), half-height breadth (HHB) and area under the curve (AUC) were established after this. Assuming an exponential function, the half-life (t_1/2) of cTnI was determined from the declining part of the curve.

Results. For both, cTnI and cTnT, significant differences in P_max, P_pos, HHB and AUC were detected after curve approximation. The t_1/2 values of cTnI were 25.1 h (22.0–35.3) for the group with normal renal function and 38.4 h (35.9–51.9) for patients with impaired renal function (P = 0.001). An influence of diabetes mellitus (Dm), renal replacement therapy or the age of the patients could not be verified.

Conclusion. The results of this study clearly demonstrate that kidney function has an impact on plasma troponin concentrations. In everyday clinical practice this has to be considered when interpreting elevated plasma troponin concentration in patients with impaired renal function.

Keywords: coronary artery bypass grafting; curve approximation; half-life; troponin I; troponin T; renal function

Introduction

Many previous studies have assessed the kinetics of cardiac troponins in the plasma of patients after acute myocardial infarction (AMI) or cardiac surgery [1–4], whereas the clearance of troponins has not been studied extensively [5]. Studies by Katus and colleagues [1] suggested a t_1/2 value of 2 h for cardiac troponin T (cTnT). The t_1/2 value of cTnI after MI ranged between 7.3–6.4 h in non-Q-wave-infarction and 24.2–8.9 h in Q-wave-infarction [6]. In patients suffering from end-stage renal disease (ESRD) t_1/2 of cTnI was found to be 1.48 ± 0.77 d as compared with 1.08 ± 0.63 d in patients without renal impairment [7].

The molecular weights of cardiac troponin I (cTnI) (23 kDa) and cTnT (37 kDa) suggest a renal elimination mechanism, but this mechanism has not been proven yet [7–10]. Increased levels of troponins are common in patients with impaired renal function [9]. ESRD patients commonly show increased cTnT and normal cTnI results without evidence of MI or acute coronary syndrome (thoracic pain or
electrocardiographic abnormalities). Nevertheless, it has become apparent that cTnT is a predictor for mortality in ESRD patients [11,12].

The cause of the discrepancy of cTnT and cTnI in these patients remains unclear. Possible explanations are poor cardiосpecificity of the antibodies used in first generation assays of cTnT, re-expression of cTnT in damaged or regenerating skeletal muscle and degradation, oxidation or phosphorylation of cTnI [5].

In a previous study, we used serum-based immunoassays for cTnT and cTnI to measure troponins in urine samples of patients after MI or cardiac surgery [13]. In patients with normal renal function, no troponin excretion in urine was found. However, in patients with impaired renal function, cTnT and cTnI were detected in urine samples. Therefore, we were led to believe that the influence of renal function on troponin concentrations might be greater than it has been hypothesized up to now.

Later, Diris and others described cTnT fragments in the serum of ESRD patients and assumed an accumulation of these fragments due to impaired renal function [14]. However, in this study the investigations were conducted with antibodies which were not identical to those in the test kit from the reagent manufacturer (Roche Diagnostics). Fahie-Wilson and colleagues [15] found no evidence for cTnT fragments in ESRD patients.

A similar situation has been described for myoglobin (19.6 kDa), whose concentration in serum is commonly increased in patients with impaired renal function. This is again suggestive of renal elimination mechanisms [16]. α1-Microglobulin (31 kDa), for which glomerular filtration occurs, also is increased in patients with a reduced glomerular filtration rate (GFR) [17].

We, therefore, hypothesized a potential role of impaired renal function for the kinetics of cTnI and cTnT. To prove our hypothesis, we analysed the concentration time course in patients after cardiac surgery, using appropriate mathematical functions in a curve approximation in order to determine $t_{1/2}$ from the declining section of the curve.

### Patients and methods

**Study design**

In a prospective study, we analysed the concentrations of cTnT and cTnI over time after coronary artery bypass grafting (CABG) in 28 patients with or without impaired renal function. The study had been approved by the local Ethics Committee. Combined operations, such as heart valve replacement or reconstruction and resection of cardiac aneurysms, did not lead to exclusion of the respective patient, but their influences were analysed separately. AMI within the preceding 10 days before surgery led to exclusion of the patient. Diabetes mellitus (Dm) was an exclusion criterion only for the control group, since it is well established that Dm leads to proteinuria while GFR remains normal or even high (hyperfiltration) early in the course of diabetic nephropathy. Thereby proteinuria in Dm may influence the supposed renal clearance of troponins.

**Renal function**

Normal renal function was defined as creatinine clearance (Crea-Clear) of more than 60 ml/min/1.73 m². Crea-Clear of $\leq 60$ ml/min/1.73 m² has been defined as impaired renal function. For the classification of each patient, Crea-Clear was estimated according to the Cockcroft and Gault formula [18], using morning plasma samples for the measurement of Crea. In ESRD patients requiring cardiac surgery, Crea-Clear was set as 10 ml/min (with residual diuresis) or zero (anuria).

For comparison we also used the MDRD formula (four or six variables) to estimate GFR [19]. Albuminuria was measured using the urine albumin/creatinine ratio in spot urine. Post-operative plasma Crea follow-up data were used to define acute renal failure (50% increase and/or oliguria).

**Surgery**

Surgery was performed according to the standard institutional procedures. Aortic cross-clamp, heart–lung machine, surgical procedures, use of catecholamines and renal replacement therapies were documented. Overall characterizations for both patient groups are summarized in Table 1.

**Sampling and measurements**

Plasma samples were collected as part of pre-operative patient preparation and of the post-operative course check-ups as determined by the study protocol. Further sample preparation was carried out in accordance with laboratory standards. Aliquots from routine measurements were portioned and deep-frozen at $-78^\circ$C. The following laboratory parameters were determined in the plasma using standardized methods: cTnI with the Immulite-Turbo (chemiluminescent immunoassay) from Euro-DPC and cTnT with the Elecsys 2010 (electrochemiluminescent immunoassay) from Roche Diagnostics. Creatinine was determined through Jaffe reaction on a MODULAR Analytics (Roche Diagnostics). Albumin in spot urine was determined using a turbidimetric assay on Cobas Mira (Roche Diagnostics).

**Kinetics of cTnI and cTnT**

Based on the measured troponin values, the concentration courses were modulated with appropriate mathematical functions also known in pharmacokinetics (logarithmic normal distribution, Gauss function, sigmoidal function, asymmetric double sigmoidal function). The programs used were PeakFit 3.0 (Jandel Scientific, Germany) and SigmaPlot 7.0 (Jandel/Erkrath, Germany). From the modulated curves, the representative parameters $P_{max}$, $P_{pos}$, half-height breadth (HHB) and area under the curve (AUC) were derived.

Calculation of $t_{1/2}$ was achieved under the assumption that the curve decline shows an exponential course. Using an exponential function with two exponents for this curve range (60–120th h), it is possible to solve the exponential function $C(t) = C(0) * e^{kt}$ and to calculate $t_{1/2} = \ln(2)/k$. The program used was TableCurve 2D 5.0 (Jandel/Erkrath, Germany).
Statistics

Data analysis and descriptive statistics were performed using SPSS for Windows, version 11.0 (Jandel, Ekrath, Germany). Regression analysis was carried out according to the method of Passing and Bablok. Multiple regression analyses were performed for the determination of confounding factors such as age, Dm and renal replacement therapy. The Mann–Whitney U-test was used to evaluate the statistical significance of the differences in non-normally distributed metric variables, and the χ²-test or Fisher’s exact test were applied to evaluate categorical variables. P < 0.05 was considered to be statistically significant. The metric, non-normally distributed variables were shown as medians as well as 25th and 75th percentile, respectively, and the categorical variables were reported as absolute numbers and percentages.

Results

Crea-Clear and urine albumin/creatinine ratio

The assignment of patients to either the control or the study group was based on the calculated Crea-Clear of 60 ml/min as the cut-off to describe renal function. Crea-Clear for 13 patients with normal renal function was calculated at a median of 80.98 ml/min (67.75–101.85; 25th and 75th percentile, respectively), and for the group with impaired renal function (n = 15) the median was 37.15 ml/min (10.00–49.94; P < 0.001).

Albumin/creatinine ratio in spot urine in the group with normal renal function was 15.40 mg/g Crea (5.49–22.91) and in the group with impaired renal function 94.84 mg/g Crea (39.21–211.53; P < 0.001). The increased urine albumin in the latter group did not result predominantly from diabetic patients (P = 0.710 for the comparison of patients with impaired renal function with and without Dm).

Distribution of cofactors

Table 1 shows the distribution of cofactors among the groups. Patients in the control group were younger than patients in the study group. Dm was excluded from the control group (see ‘Study Design’ section).

Troponin time courses

For each patient, the individual curves for cTnI and cTnT were approximated as described. In each case, the functions with the lowest error sum of squares were selected. The complexity of most courses (e.g. biphasic for cTnT), almost invariably made it necessary to add several functions, in order to cover the overall course. The requisite number of measurements for a curve modulation with the given functions was available in each patient. The first point of the curves corresponds to the pre-operative value of the respective troponin. Zero on the time scale corresponds to the time of aorta cross-clamping, i.e. the beginning of ischaemia.

Figure 1 shows the time course of cTnI as well as the curve modulations resulting from the application of a logarithmic normal function for one patient with normal and one patient with impaired renal function. The lower section of the diagram lists the values for Crea-Clear.

cTnI curve parameters Pmax, Ppos, HHB and AUC were derived from the individual courses, and medians, 25th and 75th percentiles, respectively, were calculated (Table 2). Comparison of the patient groups
demonstrates that the curves for the patients with impaired renal function are characterized by significantly higher values for the cTnI concentration and position of their peak maxima, and that they generally show higher HHB and AUC than patients with no impairment of renal function. Figure 2 illustrates the cTnI concentration as an overall course of all patients. In spite of post-operative control measurements being limited to 5 days—only a few patients stayed longer in the hospital—we decided to include cTnT in curve analysis. Accordingly, a normalization of troponin T cannot be shown during the time of the hospitalization. Nevertheless, a biphasic concentration time course for cTnT becomes clear (Figure 3). As the comparison of curve parameters indicates, significant differences in the time course with respect to renal function are evident for cTnT too (Table 3).

As another characteristic quantity in the curves related to troponin clearance, we determined $t_{1/2}$ in the declining part of the cTnI time courses. A median half-life of 25.1 h (22.0–35.3; 25th and 75th percentile, respectively) was calculated for patients with normal renal function (Crea-Clear >60 ml/min). Patients with impaired renal function (Crea-Clear ≤60 ml/min) were found to have a significantly prolonged cTnI half-life of 38.4 h (35.9–51.9; $P = 0.001$).

For cTnT the calculation of $t_{1/2}$ could not be performed due to the limited time of the observation. TnI half-life after exclusion of patients with Dm ($n = 8$), patients with renal replacement therapy (four patients on maintenance haemodialysis, two patients requiring haemodialysis for acute post-operative renal failure) or very old patients (>75 years), respectively, remained significantly prolonged ($P = 0.003$, $P = 0.007$ and $P = 0.020$, respectively).

Figure 4 specifies cTnI half-life with respect to renal function and the presence or absence of Dm. We found no significant difference of cTnI $t_{1/2}$ between diabetic and non-diabetic patients with impaired renal function ($P = 0.152$).

In a multiple regression model, we analysed the influence of potential confounders on cTnI half-life.

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Table 2. Comparison of the curve parameters $P_{\text{max}}$, $P_{\text{pos}}$, HHB and AUC (median, 25th and 75th percentile, respectively) of cTnI in patients with and without impaired renal function after CABG

<table>
<thead>
<tr>
<th>Patients</th>
<th>Crea-Clear &gt; 60 ml/min</th>
<th>Crea-Clear &lt; 60 ml/min</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 28$</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>$P_{\text{max}}$ (µg/l)</td>
<td>1.25 (0.73–2.75)</td>
<td>9.13 (1.42–23.69)</td>
<td>0.037</td>
</tr>
<tr>
<td>$P_{\text{pos}}$ (h)</td>
<td>18.45 (14.95–25.18)</td>
<td>27.51 (20.71–34.56)</td>
<td>0.013</td>
</tr>
<tr>
<td>HHB (h)</td>
<td>47.44 (34.48–49.35)</td>
<td>56.73 (49.08–69.99)</td>
<td>0.004</td>
</tr>
<tr>
<td>AUC (µg h/l)</td>
<td>63.89 (37.99–165.21)</td>
<td>729.48 (93.2–1422.63)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

$P_{\text{max}}$: peak maximum; $P_{\text{pos}}$: peak position; HHB, half-height breadth; AUC, area under the curve.
The results of this model indicate that renal function is the only significant factor ($b = 0.748$, $P = 0.007$), whereas age ($b = -0.065$, $P = 0.709$), Dm ($b = -0.267$, $P = 0.205$) and requirement of haemodialysis ($b = 0.204$, $P = 0.260$) did not significantly influence cTnI$_{1/2}$.

**Discussion**

Several studies on the post-operative course of troponins after cardiac surgery have been published, mainly to investigate various operative techniques for myocardial protection [20], to investigate the diagnosis of a peri-operative MI [3,4], or for determination of long-term mortality [21].

For mainly clinical reasons we were interested in determining the correlation of troponin plasma concentrations with renal function.

For this purpose, we used patients undergoing CABG, because this is a common standardized intervention. Patients with renal disease have a high prevalence of cardiovascular disease, which may be partially explained by conventional cardiovascular risk factors such as Dm [22]. Since proteinuria is an early issue of diabetic nephropathy—while the patients show normal or even high GFR—and proteinuria may affect...
the supposed clearance of troponins, we decided to exclude Dm from the group of patients with Crea-Clear >60 ml/min (normal renal function), but allowed diabetic patients with impaired renal function (Crea-Clear ≤60 ml/min/1.73 m²) and performed a subgroup analysis in order to rule out bias resulting from the presence of advanced diabetic nephropathy.

The time period selected for our investigation (120 h) corresponds to those of other studies [3,4,20]. The concentration courses for cTnI and cTnT were similar to the troponin kinetics given in the literature for patients with cardiac surgery [3,4,20] or with AMI [1,2].

Based on our classification of patients according to renal function (Cockcroft and Gault estimation) the kinetics of cTnI and cTnT were analysed.

As expected, we found as main result of this study an impact of renal function on troponin kinetics. $P_{pos}$ differs significantly with respect to renal function, for both cTnI and cTnT. Further, $P_{max}$ and HHB of the curves also show higher values in patients with Crea-Clear ≤60 ml/min, so that, consequently, the AUC in patients with impaired renal function is greater as well.

Eventually, we analysed the declining part of the curve (60–120 h), in order to calculate $t_{1/2}$ for cTnI by curve approximation. It became apparent that the $t_{1/2}$ values estimated in the present study correspond to those of other studies [3,4,20]. Since the second peak were not possible.

Even after exclusion of patients over 75 years of age, patients suffering from Dm or patients requiring renal replacement therapy, respectively, the significantly prolonged half-life remained obvious.

In a multiple regression model, we were able to prove the dominant role of renal function compared with other confounders in the determination of troponin kinetics, namely cTnI half-life. In a subgroup analysis of patients with impaired renal function the presence of Dm did not result in a significant different cTnI half-life. Urine albumin/creatinine ratio also did not differ between patients with impaired renal function with and without Dm.

In order to prevent bias due to the estimation of GFR by use of the Cockcroft and Gault formula we re-evaluated cTnI half-life using MDRD formulae as well as pre-operative Crea values. Remarkably, we found no difference in the correlation between $t_{1/2}$ and renal function irrespective of the method used for the determination of renal function. Taken together, all these data strongly suggest a substantial renal clearance of troponins.

Ellis et al. [7] in a similar study did not find significant differences in cTnI half-life in patients without renal impairment compared with patients suffering from ESRD. Our main criticism is the short observation period of three days making it possible that the release of troponin rather than the elimination determined the course of troponin plasma concentrations in their study.

For the same reason, i.e. the limited time of observation, we did not calculate $t_{1/2}$ for troponin T. The stay in the hospital of most patients was limited to 5 days and measurements of cTnI plasma levels after the second peak were not possible.

The $t_{1/2}$ values estimated in the present study should not be regarded as absolute quantities for the elimination of cTnI, but as relative values determined by the individual rates of release and elimination. The clinical course after heart surgery is a complex process consisting of the biphasic troponin release through ischaemia and reperfusion or direct myocardial trauma and the elimination mechanisms of troponins.

We used the last declining part of the curve, under the assumption that active myocardial damage does no longer occur during this period. After reviewing operative reports and the documentation of the post-operative period of our patients, we concluded that there was no reason to assume a peri- or post-operative MI, respectively an early occlusion of a bypass graft in any of our cases. When evaluating declining curves the troponin transfer rate from the myocardium to the plasma should therefore be negligible.

A more pronounced myocardial damage and thereby increased release of cardiac markers to the plasma during CABG in patients suffering from renal failure cannot be ruled out absolutely. Indeed it is well known that chronic kidney disease of any degree portends a worsened prognosis for coronary artery
disease patients and long-term outlook in renal patients is closely related to cardiovascular events [23]. This leads to the logical and essential question about cardiac changes in uraemic patients. Schannwell describes left ventricular hypertrophy, interstitial myocardial fibrosis and alterations of myocardial microcirculation [24]. For our study it remains obscure whether a moderate renal insufficiency by itself (Crea-Clear 30–60 ml/min) was capable to produce damage to the myocardium thereby leading to altered kinetics of troponins. For the cardiac markers CK and CK-MB activity we found no convincing evidence of an increased release during heart surgery in our study population with impaired renal function.

Only little is known about the metabolism and the clearance of troponins [5,9]. Most large proteins appear to be catabolized in organs, such as liver, pancreas and the reticuloendothelial system. Smaller molecules, such as myoglobin and fatty acid-binding protein can be found in the glomerular filtrate [25]. Due to the fact that cTnI is a rather small molecule we hypothesized a substantial glomerular filtration and thus renal elimination of cTnI.

A comparison to other proteins, considering molecular weight (MG) and the glomerular sieving coefficient (θ) might be helpful [26,27]: albumin (MG: 66.5 kDa; θ: 7.7 × 10⁻⁵), α₂-microglobulin (MG: 31 kDa; θ: 0.09), myoglobin (MG: 19.6 kDa; θ: 0.75), heart-specific fatty acid-binding protein (14–16 kDa). Relevant information as to the renal elimination of these proteins may be found in the literature [10,16,17]. Hannemann-Pohl [16] has reported a 75% renal elimination for myoglobin and expected a proportion of 2–5% for cTnT. Therefore, it does not appear unjustified to assume an influence of the kidney on the concentration curve, although an underlying renal clearance of proteins (by filtration) is expected a proportion of 2–5% for cTnT. Therefore, it does not appear unjustified to assume an influence of the kidney on the concentration curve, although an underlying renal clearance of proteins (by filtration) is difficult to assess given the tubular re-absorption from the absence of the molecules in the urine.

In conclusion, the present study shows that kinetics of troponin T and I are different in patients with kidney disease compared with normal renal function after CABG. The cause may be either an impaired elimination or a more important and prolonged release or a combination of both. Troponin measurement after CABG in patients with kidney disease should therefore be interpreted with caution. Time-related changes of troponin together with other diagnostic tools are more helpful than an isolated measurement in assessing diagnosis of acute coronary syndrome and peri-operative myocardial ischaemia. In this context, it is still to be demonstrated whether the combination of cTnI and cTnT measurements and/or the definition of specific cut-off values for cardiac troponins will end the ‘decade of confusion’ [28] with respect to specificity and sensitivity of these markers for diagnosis of acute coronary diseases in renal failure.

Conflict of interest statement. None declared.

References


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