Autoantibodies to Cardiac Troponin Associate with Higher Initial Concentrations and Longer Release of Troponin I in Acute Coronary Syndrome Patients

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BACKGROUND: Cardiac troponin (cTn) is an established marker of myocardial infarction. Pronounced heterogeneity and the minute amounts released into the circulation constitute significant challenges for cTn detection. Recently, autoantibody formation to cTn was shown to be common and to interfere with immunoassay performance. In this study, we investigated cTn autoantibodies and cardiac troponin I (cTnI) in acute coronary syndrome (ACS) patients over a 1-year period after the index event.

METHODS: We used a second-generation cTnI assay designed to reduce the interference of cTn autoantibodies. The assay for cTn autoantibodies used 2 anti-cTnI antibodies to capture the ternary cTnI-complex, enabling unrestricted binding of the autoantibodies, which were detected with a labeled antihuman IgG antibody. We analyzed serum samples from 81 non–ST-elevation ACS patients taken at admission and after 1 week and 3 and 12 months.

RESULTS: We found 14 cTn autoantibody–positive patients (21%) among the 67 cTnI-positive and none among the 14 cTnI-negative patients. Nine were autoantibody-positive at admission, and 5 became positive at 1 week. Autoantibody signals significantly increased in the 1-week and 3-month samples. At all time points, cTnI was significantly increased in the autoantibody-positive group relative to the negative group. Persistent cTnI elevations at 3 and 12 months were seen in the patients already autoantibody positive at admission.

CONCLUSIONS: During ACS, patients with cTn autoantibodies have higher cTnI release and therefore larger myocardial damage than patients without autoantibodies. Their cTnI release also lasts longer, at least months. The possible prognostic impact of these observations must be evaluated in larger clinical cohorts.

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Concentrations of cardiac troponin (cTn), both cTnI and cTnT, are widely used in the early triage of chest pain patients. Because of excellent cardiac specificity, they constitute near-ideal biomarkers of myocyte injury in acute coronary syndrome (ACS) when combined with information about patient symptoms and electrocardiograms. Yet it is important to note that several other non–ischemia-related conditions can give rise to increased concentrations of cTn (1, 2). Because the amount of cTn released from necrotic cardiac tissue to circulation can be orders of magnitude smaller than creatine kinase MB (CK-MB) and myoglobin, achieving the full diagnostic potential of cTn demands tools of exquisite analytical sensitivity that are free from common sources of nonspecific interferences.

Despite considerable advances in designing highly sensitive immunoassays for cTn (3), the true concentrations of cTnI or cTnT in healthy control subjects have not been unequivocally established. An inherent difficulty with very sensitive immunological techniques is how to distinguish between the true target-related signal and any unspecific background noise, whether it is caused by specific artifacts of the reporter system, nonspecific binding, or a range of mechanisms potentially giving rise to falsely high or low signals, e.g., heterophilic antibody or complement factor interference. A further confounding factor in assays of cTn is its pronounced molecular heterogeneity, especially well documented for cTnI (4–6). Various complexes, fragmented forms, and posttranslational modifications make the selection of sandwiching antibodies for cTnI...
immunoassays very difficult if the intention is to measure all forms of the marker released from the necrotic tissue.

In previous communications, we have shown that autoantibodies to cTn (cTnAAbs) are commonly found in both healthy control subjects and hospitalized patients with or without a history of cardiac disease (7–9). Localization of the site in the cTn molecule prone to autoantibody interference has revealed that the stable midfragment of cTnI (aa 30–110), especially its C-terminal part, is the most commonly affected region (10). Despite the inhibiting influence of autoantibodies on the binding of cTnI-specific antibodies to the ternary cardiac troponin complex, it has not been ascertained whether the autoantibodies are specifically directed against epitopes on the cTnI molecule; recent unpublished observations suggest the autoantibody recognition to be conformation dependent rather than directed to the isolated I, T, or C proteins. Based on our observations of autoantibody interference with cTnI-specific antibodies, we designed a sensitive immunoassay for cTnI that largely circumvents this source of negative interference (11). This assay design deviates from the recently published recommendation of the IFCC (12).

The mechanisms for the appearance and maintenance of cTnAAbs are not known. An autoimmune reaction can conceivably be triggered by any release of cTn such as in myocardial infarction, inflammatory conditions of the heart, extreme physical endurance training, or cardiotoxic treatments. It was recently shown in mice that immunization with species-specific cTnI and cTnT gives rise to autoantibody formation (13). Interestingly, whereas autoantibodies to cTnI were associated with adverse cardiac effects and increased mortality, autoantibodies to cTnT did not induce similar effects. Injecting mice with monoclonal antibodies raised against human cTnI has also been shown to induce dilation and dysfunction of hearts, possibly by stimulating Ca2+ influx through the cardiomyocyte membrane (14). It has been suggested (15) that these observations in mouse models, together with the demonstration of the presence of antitroponin autoantibodies in people (8, 11), may indicate that formation of autoantibodies to cardiac troponins is a conceivable contributor to heart failure in humans as well.

The aim of this study was to determine the presence and relative quantities of circulating cTnAAbs in ACS patients at 4 time points: admission and 1 week (discharge) and 3 and 12 months after the index event. For this purpose, we used a previously described autoantibody test (9), in which 2 monoclonal antibodies are used to capture the added cTn ternary complex to which sample-derived cTn autoantibodies are bound. Moreover, the endogenous cTn concentrations were monitored from the same samples with a second-generation cTn assay specifically designed to circumvent the inhibiting action of endogenous cTnAAbs (11).

Materials and Methods

PATIENTS
We collected samples from patients with ACS (n = 148) between September 1998 and December 2000 from 9 different central hospitals in Finland, as described (16). ST-elevation myocardial infarction was an exclusion criterion. The inclusion criteria of the patients were as follows. Patients had to have clear symptoms of angina with electrocardiographic evidence of myocardial ischemia. Patients who met the anginal pain inclusion criteria but none of the electrocardiographic criteria were eligible to enter the study, if any of the cardiac biomarkers (cTnI, cTnT, CK-MB) were consistent with the occurrence of non–ST-elevation myocardial infarction. Patients with prolonged chest pain with ST-wave changes indicating either unstable angina (n = 43) or non–ST-elevation myocardial infarction (n = 105) were enrolled. The original study was a placebo-controlled study on clarithromycin treatment of patients with ACS (16). Blood samples from patients were taken at the time of hospitalization and 1 week, 3 months, and 1 year after hospital admission. For this study, we selected the 81 patients with serum samples from all 4 time points. Patients had no reperfusion therapy during the first week. Some of the patients later had a percutaneous coronary intervention or a bypass operation; neither of these therapies was done during an acute episode of coronary syndrome. Patients were followed for endpoints (death, myocardial infarction, unstable angina, or stroke) for an average (SD) of 436 (289) days. Baseline characteristics of the patients are shown in Table 1. All patients gave written informed consent, and the local ethics committee approved the study.

BIOCHEMICAL ANALYSES
The measurement of human cTnAAb was essentially performed as described (9). We diluted 150 ng of each of 2 biotinylated capture antibodies (mAb 4C2 and MF4; Hytest Ltd) in assay buffer (Innotrac buffer solution, red; Innotrac Diagnostics Oy) and immobilized them to streptavidin-coated microtiter wells (Innotrac Diagnostics Oy) in a total volume of 25 μL. After incubation for 1 h at room temperature, the wells were washed twice with a wash solution (5 mmol/L Tris-HCl, pH 7.75, 154 mmol/L NaCl, 1 g/L Germall II, and 0.05 g/L Tween 20). We diluted serum samples 5-fold with dilution buffer (37.5 mmol/L Tris-HCl, 120 mmol/L NaCl, 0.375 g/L NaN3, 0.6 g/L bovine gammaglobulin, 25 g/L BSA, 50 g/L D-trehalose, 0.8 g/L native...
mouse IgG, 0.05 g/L denatured mouse IgG, 2 g/L casein, 37 500 IU/L heparin). We added ternary troponin complex (Hytest Ltd) standard to a diluted serum sample aliquot to a final concentration of 30 g/L cTnI. To obtain the sample-specific background, we added the same volume of the standard diluent [75 g/L BSA in tris-saline-azide buffer (50 mmol/L Tris-HCl, pH 7.75, 150 mmol/L NaCl, 15 mmol/L NaN₃)] to another aliquot of the diluted sample. The samples were incubated for 1 h at 4 °C to allow binding of human auto-antibodies to the ternary troponin complex. We then transferred the samples (30 μL/well) to the wells containing immobilized capture antibodies and added 170 μL assay buffer per well. After incubation for 1 h at 36 °C, the wells were washed twice with wash solution. We added 50 ng europium-labeled antibody 3D3 (Hytest Ltd) in 200 μL assay buffer. After 6 washes, the wells were dried for 5 min under a stream of hot, dry air. After cooling, we measured the time-resolved fluorescence directly from the dry surface of the wells using a Victor 1420 Multilabel Counter (PerkinElmer Life and Analytical Sciences; Wallac Oy). We measured all samples in triplicate and calculated the mean signal. We calculated the specific signal by subtracting the signal of the background control aliquot from that of the other aliquot of the same sample to which troponin had been added. We regarded specific signals >100 counts per second (cps) as significantly different from the background control if Student’s t-test gave P ≤ 0.05 when the 3 replicates of the aliquots with or without added troponin were compared.

We measured cTnI concentrations using the second-generation Innotrac AioTM troponin I kit on the Innotrac Aio! immunoanalyzer according to the manufacturer’s instructions (Innotrac Diagnostics Oy). The antibodies used in this immunoassay are selected to enable detection of cTnI in the presence of cTnAAbs, in contrast to many conventional cTnI immunoassays using antibodies directed to the central region of cTnI (aa residues 30–110), which can be blocked by cTnAAbs (11). According to the manufacturer, the analytical detection limit of this assay is typically <0.01 μg/L. In this and a previous study (17), we found the analytical detection limit to be ≤0.005 μg/L.

Table 1. Baseline characteristics of patient groups.a

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Group A (cTnI+/cTnAAb−)</th>
<th>Group B (cTnI−/cTnAAb+)</th>
<th>Group B1 (first sample cTnAAb−)</th>
<th>Group B2 (first sample cTnAAb+)</th>
<th>Group C (cTnI−/cTnAAb+)</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>81</td>
<td>53</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.3 (9.7)</td>
<td>63.5 (9.9)</td>
<td>65.1 (8.9)</td>
<td>66.9 (8.9)</td>
<td>61.9 (8.9)</td>
<td>66.3 (10.2)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>22 (27.2)</td>
<td>13 (24.5)</td>
<td>6 (42.9)</td>
<td>6 (66.7)</td>
<td>0 (0)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8 (4.0)</td>
<td>27.2 (4.0)</td>
<td>26.4 (3.5)</td>
<td>26.8 (3.3)</td>
<td>25.8 (4.2)</td>
<td>25.8 (4.5)</td>
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<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>33 (40.7)</td>
<td>19 (35.8)</td>
<td>7 (50.0)</td>
<td>4 (44.4)</td>
<td>3 (60.0)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Former</td>
<td>27 (33.3)</td>
<td>17 (32.1)</td>
<td>6 (42.9)</td>
<td>5 (55.6)</td>
<td>1 (20.0)</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Current</td>
<td>21 (25.9)</td>
<td>17 (32.1)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
<td>1 (20.0)</td>
<td>3 (21.4)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>31 (38.3)</td>
<td>21 (39.6)</td>
<td>7 (50.0)</td>
<td>2 (22.2)</td>
<td>5 (100.0)</td>
<td>3 (21.4)</td>
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<tr>
<td>Diabetes, n (%)</td>
<td>18 (22.2)</td>
<td>12 (22.6)</td>
<td>5 (35.7)</td>
<td>3 (33.3)</td>
<td>2 (40.0)</td>
<td>1 (7.1)</td>
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<td>Hypercholesterolemia, n (%)</td>
<td>61 (75.3)</td>
<td>39 (73.9)</td>
<td>10 (71.4)</td>
<td>6 (66.7)</td>
<td>4 (80.0)</td>
<td>12 (85.7)</td>
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<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>19 (23.5)</td>
<td>11 (20.8)</td>
<td>5 (35.7)</td>
<td>4 (44.4)</td>
<td>1 (20.0)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acetylsalicylic acid</td>
<td>77 (95.1)</td>
<td>50 (94.3)</td>
<td>13 (92.9)</td>
<td>8 (88.9)</td>
<td>5 (100.0)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>68 (84.0)</td>
<td>43 (81.1)</td>
<td>12 (85.7)</td>
<td>8 (88.9)</td>
<td>4 (80.0)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>ACE-inhibitor/AT-blocker</td>
<td>15 (18.5)</td>
<td>9 (17.0)</td>
<td>6 (42.9)</td>
<td>2 (22.2)</td>
<td>3 (60.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Statin</td>
<td>35 (43.2)</td>
<td>22 (41.5)</td>
<td>5 (35.7)</td>
<td>3 (33.3)</td>
<td>2 (40.0)</td>
<td>8 (57.1)</td>
</tr>
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<td>hs-CRP, mg/L</td>
<td>5.7 (1.9–18.0)</td>
<td>5.8 (2.1–22.0)</td>
<td>10.9 (3.7–31.3)</td>
<td>11.0 (4.6–14.0)</td>
<td>10.0 (3.3–32.0)</td>
<td>1.7 (0.7–7.1)</td>
</tr>
</tbody>
</table>

a Data are mean (SD) or median (25th–75th percentile) unless noted otherwise.

A Significant difference (P < 0.05) vs group A.

B Significant difference (P < 0.05) vs group B.
when 20 replicates of Innotrac Aio! buffer were measured in a single run, and the cTnI concentration corresponding to a signal 3 SD greater than the mean of these measurements was calculated. The upper reference limit in serum samples, defined as the 99th percentile value in 167 apparently healthy individuals (66 women and 51 men age <50 years; 21 women and 29 men age >50 years), was reported to be 0.016 g/L by the manufacturer. The within-assay CV was <10% at 0.04 μg/L and 20% at 0.01 μg/L. All samples were analyzed in duplicate, and the mean concentration was calculated. Concentrations less than the analytical detection limit were given a value of 0.005 g/L. We considered patients to be cTnI positive when the concentration of cTnI was ≥0.02 μg/L in the first sample. The remaining patients were cTnI negative, with cTnI <0.02 μg/L in all 4 samples. We measured propeptide of B-type N-terminal natriuretic peptide (NTproBNP) (Roche Diagnostics GmbH), high-sensitivity C-reactive protein (CRP) (Orion Diagnostica), CK-MB mass (Roche Diagnostics GmbH), and cTnT (Roche Diagnostics GmbH) according to the laboratory standards of the Helsinki University Central Hospital.

**Statistical Methods**

We compared quantitative data using the t-test or Mann–Whitney test and analyzed categorical variables with the χ² or Fisher exact test to assess differences between the study groups. For all the statistical tests, a P value <0.05 was considered to indicate a statistically significant difference. Data were analyzed using SPSS 15.0 (SPSS Inc.).

**Results**

Of the 81 patients included in the study, 67 (83%) had a cTnI concentration ≥0.02 μg/L in the first sample. Of the cTnI-positive patients, 53 (79%) patients remained autoantibody negative (cTnAAb⁻) in all 4 samples (group A), whereas 14 (21%) patients were autoantibody positive (cTnAAb⁺) at any of the 4 time points (group B) (Fig. 1). None of the 14 cTnI-negative patients had detectable amounts of cTnAAbs at any time point (group C). Of the 14 cTnAAb⁺ patients, 9 who were initially cTnAAb⁺ remained so at the 3 follow-up time points (group B1). Five patients did not have detectable cTnAAbs in the admission sample but were positive at 1 week and at 3 months (group B2). At the 12-month time point, 2 of the 5 patients again had undetectable cTnAAbs. Thus 12 patients who were autoantibody positive at admission or 1 week remained so for 1 year, representing 18% of all cTnI-positive patients. The autoantibody signals at the 4 time points are

**Fig. 1.** Study patients grouped (positive/negative) according to cTn autoantibody signals (≥100 cps) and cTnI concentration (>0.02 μg/L).
shown in Fig. 2A. At every time point studied, the cTnAAb signals of the initially cTnAAb-negative group B2 remained significantly (Mann–Whitney $P < 0.05$) lower than those of group B1 with measurable cTnAAb signals at the first time point (Table 2). In the B1 group, the median signals at the second and third time points were equal, representing on average a 5.5-fold increase over the admission sample. At 12 months, the median signal still remained 3.5-fold higher than that of the admission sample.

Fig. 2. (A), Autoantibody signals of the 14 cTnAAb- and cTnI-positive patients (group B) at the 4 time points. Nine patients (group B1, ●) were already positive at admission, whereas 5 patients (group B2, ○) became positive at the 1-week sample. Fifty-three cTnI-positive patients (group A, □) were negative in the autoantibody test at all time points. (B), cTnI concentrations of group B1 (●) and group B2 (○). The gray area shows the 10th to 90th percentile range of the cTnI concentrations of group A patients.
The cTnI levels at the 4 time points of the 14 cTnAAb-positive patients in comparison with the 53 cTnAAb-negative, cTnI-positive patients are presented in Fig. 2B. Table 2 summarizes the comparisons of cTnI levels between the patient groups. At all 4 time points, the concentration of cTnI was significantly higher in group B than group A. In group B1 compared to group A, the cTnI concentrations did not significantly differ from each other at admission but did at the other time points. In contrast, significant differences between groups B2 and A were found for the 2 first time points but not at 3 and 12 months. In comparing group B1 and B2, cTnI concentration at admission was significantly higher in group B2. The highest cTnI concentration at 1 week occurred in a patient with a reinfarction at day 5. Removal of this sample from the analysis did not change the outcome of the statistical analysis.

Table 1 shows descriptive statistics of all patients and when divided into groups according to the cTnI and cTnAAb status. The groups did not significantly differ from each other with regard to age, sex, coronary artery risk factors, or medication. Concentrations of both CRP and NTproBNP [median (25th–75th percentile)] were significantly higher in the cTnI-positive patients (groups A and B) compared with the cTnI-negative patients (group C); 6.0 (2.3–23.0) vs 1.7 (0.67–7.1) mg/L, \( P = 0.012 \), and 861 (325–1740) vs 270 (108–870) ng/L, \( P = 0.023 \), respectively. There were 22 endpoints during the follow-up, but no significant differences were found in the numbers of endpoints between cTnAAb or cTnI groups. No significant differences were found between the cTnAAb/cTnI groups in relation to the original study drug, clarithromycin.

We calculated the ratios of cTnT/cTnI from the admission samples that had cTnI concentrations >0.04 \( \mu g/L \) and cTnT concentrations >0.06 \( \mu g/L \) (n = 47). The overall median (25th–75th percentile) ratio was 2.74 (1.93–4.85). After separation into 2 groups based on the cTnAAb test results, corresponding values were 2.28 (1.88–4.62) for the cTnAAb-negative samples (n = 42) and 5.51 (4.1–9.6) for the cTnAAb-positive samples (n = 5). This difference was highly significant (Mann–Whitney \( P = 0.009 \)).

**Discussion**

This investigation reports for the first time the levels of cTnAAb and temporal changes up to 1 year in 81 ACS patients. The methodology used was specifically developed for recognition and quantification of IgG-type cTn antibodies affecting epitopes located in the 30–110 midfragment of cTnI. In addition to the admission and discharge samples of the initial hospitalization period, 2 follow-up samples obtained at 3 and 12 months enabled long-term monitoring of cTnAAb and cTnI con-
centrations. Positive cTnAAb results were observed in 14 patients, representing 21% of the 67 patients positive for cTnI. Of these, 5 patients were initially cTnAAb negative, i.e., below the detection limit of the present assay, and turned positive from the discharge sample onwards. The median cTnAAb signal of this group was significantly lower than for the group already positive from the admission sample. This cTnAAb method is based on the measurement of IgG-type antibodies exclusively, which is a limitation of our study, as the antibody response in the case of these 5 patients possibly represents a primary immune response predominantly of IgM class antibodies.

Our previous investigations on cTnI recovery in clinically nondefined patient cohorts (7) as well as recent unpublished observations estimate the frequency of cTnAAb positive individuals to be 3%–6%, that is, substantially lower than what was seen in the present study (13%–20% of the patients being cTnAAb positive at any investigated time point). The present study cannot permit conclusions about the possible increased prevalence of cTnAAbs in ACS patients, however, since no age- and sex-matched control group was included. Further, 79% of the 67 ACS subjects who were positive for cTnI had no detectable amounts of cTnAAbs at any of the 4 time points. As in autoimmune diseases in general, it is conceivable that various genetic and nongenetic susceptibility factors are involved in determining why some individuals initiate autoantibody formation against the cTn released from the necrotic tissue and others do not. In comparison, autoimmune myocarditis is presently perceived as a multifactorial and genetically complex disease involving genes of the major histocompatibility complex as well as non-major histocompatibility complex genes (18). It is also conceivable that the pronounced and variable heterogeneity of circulating cTn may, in an apparently unpredictable way, introduce neoepitopes, possibly initiating an immune response.

Independent of the mechanisms for the appearance of cTnAAbs in these ACS patients, a major finding of this study is the significantly increased rate flux of cTnI in the cTnAAb− group at 3 and 12 months, well beyond the acute disease sequel. This was particularly pronounced in the group that already was positive for cTnAAb in the first sample. This continuous release of cTnI might have significant clinical impact by confusing the myocardial infarction diagnosis next time a patient needs medical attention. Persistent minor cTnI releases have recently been shown to predict cardiac mortality (19). The limited cohort of this study does not permit evaluation of this aspect.

cTnI concentrations were also significantly higher for the first two time points in the cTnAAb− groups compared with the cTnAAb+ group. An increase of up to 30-fold in cTnI concentrations at the 7-day discharge suggests that cTn antibodies may accelerate cTnI release and affect the size of the infarction. This is especially true in those patients turning cTnAAb-positive during the first week after ACS. There are 2 conceivable explanations for the high initial cTnI concentration in this group: the new antibodies produced may induce extra cTnI release, or the antibody production might be related to a large-sized infarction in addition to the patient’s predisposition to produce autoantibodies. The small sample size of the study does not allow us to draw more specific conclusions.

CRP was higher in cTnI-positive than in cTnI-negative patients, reflecting the known correlation between infarction size and the inflammatory reaction (19). In addition, patients who had cTnAAbs had higher CRP values than those without cTnAAbs; however, the difference was not significant within cTnI-positive patients. Antibodies might have some effect on the inflammatory reaction and therefore affect the size of the infarction.

From a methodological standpoint, it should also be acknowledged that the cTnI determinations were performed with an assay that was explicitly designed to enable detection of the target in the presence of high amounts of cTnAAbs. As reported earlier by us (11), some residual assay interference by cTnAAbs remains using this novel assay design and may be particularly notable in samples with very high concentrations of cTnAAbs, especially in combination with minor cTnI releases such as found at the 3- and 12-month time points. Of interest in this context is also the finding that the cTnT determination (results only available for the admission sample) is apparently also negatively affected by the presence of cTnAAbs. This result was obtained by calculating the cTnI/cTnT ratio. The ratio was significantly higher in patients with cTnAAbs, indicating that cTnAAbs interfere more with the cTnT measurement than with the cTnI methodology used in this study. Our result emphasizes the need for future generations of cTn assays not only to provide improved analytical sensitivity but also to achieve this in a manner that obviates the interfering/inhibiting effect of cTnAAbs.

Recently, Eggers et al. (20) reported on the occurrence of minor but persistent elevations of cTnI up to 6 months after the acute disease sequel in a large cohort of ACS patients. Interestingly, patients with persistent elevations of cTnI above a cutpoint of 0.01 µg/L, a concentration 4 times lower than the cutpoint recommended by the manufacturer, were independently predictive of total mortality. In a report by Miettinen et al. (17) using the same cTnI and cTnAAb methodologies as in this study, an increased cTnI efflux in patients with idiopathic dilated cardiomyopathy was associated...
with more prominent changes in the indices of left ventricular remodeling and function and poor clinical outcome. The increased cTnI efflux was highly correlated with presence of cTnAAbs.

In conclusion, these results suggest that ACS patients who have autoantibodies against troponin release more cTnI during the acute coronary event, and therefore may be predisposed to have larger myocardial infarctions. Furthermore, continued presence of cTnAAbs in serum is associated with sustained cTnI release. Larger studies of ACS patients with short- and long-term endpoints are clearly needed.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.