Short- and Long-term Individual Variation in Cardiac Troponin in Patients with Stable Coronary Artery Disease

Anna M. Nordenskjöld,1* Håkan Ahlström,2 Kai M. Eggers,3 Ole Fröbert,1 Allan S. Jaffe,4 Per Venge,5 and Bertil Lindahl3

BACKGROUND: A rise or fall of cardiac troponin is a prerequisite for the diagnosis of acute myocardial infarction. Defining significant changes requires knowledge of both biological and analytical variation. The short-term biological variation of cardiac troponin in healthy individuals is 3%–48%. However, healthy individuals may not be representative for patients in whom cardiac troponin measurement is often of clinical importance. Therefore, we studied the individual variation of cardiac troponin in patients with symptoms of stable coronary artery disease.

METHODS: Twenty-four patients scheduled for elective coronary angiography were included. Blood samples were drawn once at enrollment and serially at six 4-h intervals on the day before coronary angiography. Cardiac troponin was measured with hs-cTn assays from Abbott Laboratories (premarket cTnI assay) and Roche Diagnostics (Elecsys® cTnT assay with two different lots).

RESULTS: The short-term individual variation in cardiac troponin I (cTnI) was 14%, the reference change value (RCV) 49%, and RCV-log-normal (rise/fall) 54%–35%. The corresponding values for cTnT were 7%, 23%, and 26%–21%. The long-term variation for cTnI was 24%, RCV 69%, and RCV-log-normal (rise/fall) 97%–49%. The corresponding values for cTnT were 11%, 32%, and 37%–27%.

CONCLUSIONS: The short-term individual variation of cardiac troponin in patients with symptoms of stable coronary artery disease is similar to the biological variation previously demonstrated in healthy individuals. Our results suggest that a change in cardiac troponin concentrations of >50% can be used in attempting to diagnose acute myocardial injury. To detect significant long-term changes in cardiac troponin concentrations, larger changes will be required.

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Measurement of cardiac troponin is a prerequisite for the diagnosis or exclusion of acute myocardial infarction (AMI)1, and thus essential in the evaluation of patients with chest pain.2, 3 Guidelines advocate the use of a cardiac troponin cutoff concentration at the 99th percentile of a healthy control group, together with a rising and/or falling pattern.1, 4 The identification of dynamic changes is critical, because increased but relatively stable concentrations of cardiac troponin can be observed in chronic diseases, such as severe renal insufficiency and congestive heart failure.2, 5, 6 The ability to separate dynamic changes associated with acute myocardial infarction from fluctuations due to analytical imprecision and/or biological variation requires not only data in patients with AMI but also comparative data in healthy individuals and, where possible, those with cardiovascular disease. Because of inadequate data in many of these areas and the fact that these values are likely to be assay dependent, the degree of rise or fall necessary for the diagnosis of AMI has not been specified.1 A >20% rise from an already increased baseline value has been recommended as a criterion for the diagnosis of reinfarction based entirely on the analytical imprecision of the assays.1, 7 However, the 20% rise level assumes that the assay has a CV of \( \leq 7\% \). Recently, cardiac troponin assays fulfilling the criteria proposed by Apple8 for high-sensitivity cardiac troponin (hs-cTn) assays have been introduced9, 10, enabling a reliable measurement of cardiac tro-

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Nonstandard abbreviations: AMI, acute myocardial infarction; hs-cTn, high-sensitivity cardiac troponin; cTnT, cardiac troponin T; cTnI, cardiac troponin I; PUMI, Prevalence and Prognostic Value of Unrecognised Myocardial Injury in Stable Coronary Disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ECG, electrocardiogram; LoB, limit of blank; LoD, limit of detection; CVG, analytical CV; CVI, interindividual CV; CVT, total CV; RCV, reference change value; CVp, inter-individual CV; IL, index of individuality.
Cardiac troponin concentrations well below the 99th percentile among reference populations. This permits calculation of conjoint biological and analytical variation in healthy individuals (11). The few studies published so far have shown that the short-term biological variation of cardiac troponin is in the range of 3%–48%, whereas the long-term biological variation is in the range of 3%–114% (12–15). On the basis of the studies that used hs-cTnT assays, a change in cardiac troponin T (cTnT) concentration of >45%–90% is required to be sure that the change is not due to biological and analytical variation alone.

Measurements of biological variation by definition can be performed only in healthy individuals. However, healthy individuals are not representative of patients with acute chest pain in whom AMI ultimately needs to be ruled out. Moreover, recent data suggest that cardiac troponin concentrations can be increased in individuals with stable coronary artery disease (16). These issues emphasize the need to separately assess the variation in cardiac troponin concentrations even in diseased individuals, i.e., populations in which cardiac troponin measurements are of clinical interest. Patients with stable coronary artery disease, chest pain, and no AMI are among those who eventually are seen in emergency departments with chest pain necessitating evaluation for myocardial injury. We hypothesized that the individual variation in cardiac troponin concentrations might be higher in patients with coronary artery disease compared with healthy individuals. Therefore, the individual variation of cardiac troponin in these patients might be more appropriate for calculating the degree of rise or fall needed to separate changes caused by acute myocardial damage from “spontaneous” changes seen in patients without acute myocardial injury.

Accordingly, the aim of this study was to evaluate the short- and long-term individual variation of cTnI and cTnT, with two different troponin assays, in patients with verified or highly suspected but putatively stable coronary artery disease.

**Materials and Methods**

**STUDY POPULATION**

The present study is a substudy of the ongoing multicenter study PUMI (Prevalence and Prognostic Value of Unrecognised Myocardial Injury in Stable Coronary Artery Disease) (http://clinicaltrials.gov/ct2/show/NCT01257282). Patients with suspected stable coronary artery disease scheduled for coronary angiography were enrolled. Exclusion criteria were previous AMI, coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), heart failure, renal failure with an estimated glomerular filtration rate <30 mL/min/1.73m², or a contraindication to MRI. After study inclusion, blood samples were drawn, and an MRI investigation of the heart was performed before coronary angiography.

Twenty-four patients were enrolled in the present substudy at 2 centers between October 2009 and April 2010. There were no added inclusion criteria or exclusion criteria. The patients were admitted to the hospital the day before scheduled coronary angiography. At admission, an electrocardiogram (ECG) was obtained and continuous multilead ST monitoring was performed for 24 h. Blood samples and blood pressure measurements were taken serially every fourth hour, on 6 separate occasions, before coronary angiography. The first sample was taken between 0800 and 1000. The patients were in a nonfasting condition and had very low physical activity, but were not confined to bed, during the short-term study. On average, 23 days (4–58) passed between enrollment and admission to hospital. Figure 1 shows the flow chart for these patients.

![Timeline for long- and short-term collection of blood.](image-url)
the long-term study, blood samples from the time of initial enrollment and the first blood sample at the time of admission were used. In the short-term study, the 6 blood samples taken the day and night of admission were analyzed. All patients gave written informed consent. The study was approved by the local ethics committee (Uppsala 2007/214).

**BIOMARKER ASSAYS**

Blood was collected in EDTA-containing tubes and immediately centrifuged. The plasma was then stored at −70 °C until analysis. cTnI was analyzed on an Architect i2000SR platform by use of the precommercial Architect STAT hs-TnI assay (Abbott Laboratories). The limits of blank (LoB) and detection (LoD) of the assay are 0.5 and 1.2 ng/L, respectively; the 99th percentile among healthy subjects is 16 ng/L; and the 10% CV concentration is 3.9 ng/L according to the literature (17, 18). cTnT was analyzed twice by use of the Elecsys® hs-cTnT assay on a Cobas instrument (Roche Diagnostics). We remeasured samples using lot no. 167 345 with an expiration date of 2013–07 with the recently reformulated calibration curve given the previous problems with lot no. 160 197 (expiration date 2012–03) and the older calibration (19). All results presented for cTnT are analyzed with the new lot of reagents unless otherwise stated. The LoB for this assay is 3 ng/L, the LoD 5 ng/L, and the 99th percentile in apparently healthy individuals 14 ng/L (9). According to the manufacturer, the 10% CV concentration is 13 ng/L (9). A study has indicated significant differences in 99th percentile in healthy men and women (20).

The analyses were performed strictly according to the instructions of the manufacturers and using a single lot of reagents for cTnI and cTnT, respectively. Within-run analytical imprecision (CVa) was determined internally for cTnI on 230 duplicate samples and was found to be 8% at a concentration of 12 ng/L, corresponding to the mean value of cTnI in the present study. On the basis of 45 duplicate samples from the short-term study, with a mean concentration of 13 ng/L, the CVa for cTnT was 4%.

**ECG**

The resting 12-lead ECG and continuous multilead ST monitoring were analyzed by cardiologists blinded to the cardiac troponin results (A.M. Nordenskjöld, B. Lindahl). ECG changes were classified according to the Minnesota Code Classification System for Electrocardiographic Findings (21). An ST vector magnitude or ST change vector magnitude increase or decrease of ≥50 µV from the baseline for ≥1 min on multilead ST monitoring was considered indicative of an ischemic episode (22). A ventricular rate >120 bpm for 1 min or more was considered an episode of tachycardia for the purpose of this study.

**DATA ANALYSIS**

We calculated the intraindividual CV (CVi) from the coefficient of the total imprecision (CVt) of cardiac troponin at all time points. The CVt was determined from our internal validation of within-run CV at cardiac troponin concentrations corresponding to the mean values of cTnI and cTnT. The cardiac troponin values showed a positively (right) skewed distribution, and normality of the distribution was rejected by use of the Kolmogorov–Smirnov test. Therefore, in addition to the usual approach (23), we determined the reference change value (RCV) with the log-normal approach (24). For detailed equations, see Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol59/issue2.

Values of cTnT below the LoB were excluded from all analyses. Outliers were identified by the technique described by Horn et al. (25). Differences in mean CVt between different subgroups were calculated with a t-test for independent samples. All data analyses were performed by use of Predictive Analytics SoftWare (PASW statistics 17.03, SPSS).

**Results**

The baseline characteristics of the 24 patients are described in Table 1. In total, 23 patients had detectable concentrations of cTnI and 16 patients had detectable concentrations of cTnT. Coronary angiography was performed in all patients; 10 patients (42%) underwent...
PCI and 2 patients (8%) CABG due to significant coronary stenoses. The mean left ventricular ejection fraction measured with MRI was 68% (range 51%–78%). None of the patients had electrocardiographic Q-waves, ST-segment elevation, or ST-segment depression at study inclusion or the time of admission for blood sampling. Continuous multilead ST monitoring identified no patient with signs of acute ischemia or persistent tachycardia.

One patient had only the first 3 blood samples drawn and was therefore excluded from further analyses. In the remaining 23 patients, samples at all 6 time points were obtained. cTnI concentrations in all samples were above the LoD. cTnT concentrations in all samples but 2 were above the LoB, and cTnT concentrations in all samples (n = 16) were above the LoD.

At baseline (inclusion), cTnI concentrations ranged from 1.2 to 42.7 ng/L, mean (SD) 7.8 (10.5) ng/L. For cTnT, concentrations ranged from 5.5 to 32.1 ng/L, mean 12.7 (2.0) ng/L.

At admission (the short-term study), cTnI concentrations ranged from 1.2 to 104.6 ng/L, mean 11.7 (22.4) ng/L. Two patients had values above the 99th percentile concentration at inclusion, as did 2 additional patients at the time of admission for the short-term study. For cTnT, concentrations ranged from 6.0 to 32.7 ng/L, mean 12.5 (8.2) ng/L. Six patients had values above the 99th percentile concentration at inclusion, as did 5 patients when admitted for the short-term study.

SHORT-TERM VARIATION OF CARDIAC TROPONIN

The short-term concentration ranges of cTnI and cTnT are shown in Fig. 2. The mean CV\textsubscript{i}, CV\textsubscript{p}, CV\textsubscript{g}, and interindividual CV (CV\textsubscript{II}) RCV and index of individuality (II) of cTnI and cTnT in the total population are summarized in Table 2. The CV\textsubscript{i} for cTnI was 14%, RCV-normal was 49%, and RCV-log-normal (rise/fall) was 54%–35%. The corresponding values for cTnT were 7%, 23%, and 26%/–21%.

Figure 3 shows the distribution of the individual RCV-log-normal values for a rise in cTnI and cTnT. These values ranged from 13% to 160% for cTnI and from 7% to 58% for cTnT. From a statistical point of view (25), the cTnI values from 5 patients and the cTnT values from 2 patients were considered outliers. Excluding these patients, the CV\textsubscript{i} was 15% for cTnI and 7% for cTnT. When patients with chest pain ≥15 min and <72 h before admission were excluded, 19 patients remained for analysis of cTnI and 12 patients for cTnT. The CV\textsubscript{i} values in these patients were 15% and 8%, respectively.

For cTnI, the half of the patients receiving any kind of revascularization had a mean CV\textsubscript{i} of 15% compared to 16% in those not requiring revascularization (P = 0.80), and 8% compared to 9% for cTnT (P = 0.8).

LONG-TERM VARIATION OF CARDIAC TROPONIN

Long-term variation was calculated on the basis of the inclusion and admission samples, which were on average 23 (range 4–58) days apart. The CV\textsubscript{i} for cTnI was 24%, RCV-normal was 69%, and RCV-log-normal was 97%/–49%. The II determined in the long-term phase was 0.15. The CV\textsubscript{i} for cTnT was 11%, RCV-normal was 32%, and RCV-log-normal was 37%/–27%. The II was 0.18. The results are summarized in Table 2.

COMPARISON BETWEEN THE NEW AND OLD LOTS FOR cTnT

When cTnT was analyzed with the older lot or reagent and its calibrator, only 58 of the 161 values were above the LoB, 46 above the LoD (29%), and 20 above the 99th percentile concentration (12%). With the newer lot, 159 had values above the LoB, 119 (74%) above the LoD, and 33 (20%) above the 99th percentile (see online Supplemental Fig. 1). Thus, 65% more values were above the 99th percentile with the new lot compared to the old. Overall, the mean difference in cTnT concentration between the new and old lots was 4.2 ng/L (range −0.4 to 7.9 ng/L). For the values below the LoD with the old lot, the mean difference was 4.3 ng/L (range 0 to 7.1 ng/L). For the values above the 99th percentile concentration with the new lot, the mean difference was 4.1 ng/L (range −0.4 to 7.9 ng/L). The influence of the differences between the two lots on the calculated RCVs was minor. The short-term RCV for the new lot was 23% compared to 30% for the old lot. The log-normal RCVs for a rise/fall were 26%/–21 and 34%/–26, respectively.

Discussion

The present study is, to the best of our knowledge, the first to evaluate individual variation of cardiac troponin in patients with suspected stable coronary artery disease. These are the patients who are most apt to require careful evaluation for chest discomfort.

The short-term individual variation, CV\textsubscript{i}, in our group of patients with suspected stable coronary artery disease was 14% and 7% for cTnI and cTnT, respectively. To our surprise and contrary to our hypothesis, the individual variability of cardiac troponin concentrations in our patients was similar to or less than the biological variation described previously in healthy individuals (Table 3). Studies of healthy individuals so far have shown the short- and long-term biological variations of cardiac troponin to be in the range of 3%–48% and 3%–117%, respectively; the short-term RCV has ranged from 44% to 113% and the short-term log-
normal RCV for rising concentrations from 45% to 90% (12–15, 26, 27, 29). Similarly, in a recent study of patients presenting with chest pain in an emergency department, excluding patients with known stable angina, the individual variation was similar to that in healthy controls at 11% for cTnI and 18% for cTnT (28). In another recent study of patients with stable cardiovascular disease, the long-term CVi of cTnl was 28%, and log-normal RCV for rising and falling concentrations 98% and −50%, respectively, very similar to the long-term results in the present study (29).

Patients suspected of stable coronary artery disease represent a heterogeneous group. We therefore analyzed the individual variation of cardiac troponin both with and without the outliers. Furthermore, we probed for possible differences between patients with and without symptoms during the preceding 72 h and compared patients with hemodynamically significant coronary artery disease requiring revascularization to patients not requiring revascularization. Interestingly, there were only minor differences in CVi between these subgroups which are concordant with the data reported previously in healthy individuals. Thus, stable coronary arteriosclerosis per se does not seem to affect individual variability in cardiac troponin concentrations to a great extent.

Current guidelines recommend analytical precision to be ≤10% CV at the upper 99th percentile value of a healthy reference population (1, 2). In the present study, the CVa was well within this recommendation for both assays. When the individual variation of 14% and 7% for cTnI and cTnT, respectively, is added, the
change required to detect acute myocardial injury will obviously increase. On the basis of our results, a rising pattern of 54% or falling pattern of −35% for cTnI and 26% and −21% for cTnT would be necessary to define a significant change. All these figures are mean values.

From the distribution of individual RCV-log-normal for rising values (Fig. 3) it is obvious that the interindividual variation is large. Thus, in some individual patients a larger change than the mean RCV-log-normal for rising concentrations would be needed to diagnose an acute myocardial injury with certainty. In 22 of 23 patients (96%), the rising RCV-log-normal for cTnI was ≥100%, and in all 16 patients with measurable cTnT, the rising RCV-log-normal was ≥65%. Thus, applying a very conservative approach, the diagnostic cutoff for rising RCV-log-normal would be 100% for cTnI and 65% for cTnT. However, this would lead to a substantial number of patients in whom AMI would be falsely ruled out on the basis of a too-small observed increase in cardiac troponin. These data support the contention that the use of δ criteria will involve some tradeoffs between sensitivity and specificity.

After being informed about the calibration issue with the old lot of cTnT, we reanalyzed all samples using a new lot with the reformulated calibration curve. The proportion of patients with concentrations above the LoD with the new lot, in contrast to the old lot, was in line with what would be expected given the published results that used the precommercial hs-cTnT assay (6, 9, 16). The large differences in cTnT concentrations between the 2 lots raise several important issues. First, the higher cTnT concentrations

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<th>Variable</th>
<th>cTnI</th>
<th>cTnT</th>
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<td>46/23</td>
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<td>CVa, %</td>
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</tr>
<tr>
<td>II</td>
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<td>0.15</td>
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* After omitting values less than the LoD.

![Fig. 3. Histogram of log-transformed RCV values for rising cardiac troponin concentrations.](image)
(mean 4.2 ng/L) with the new lot in the critical range of values around the 99th percentile cutoff concentration led to 65% more values above that cutoff concentration. Thus a substantial number of patients in routine clinical practice with significant acute myocardial damage might have been falsely excluded when lots before the reformulation of the calibration curve were used. This negative effect on diagnosis might have been blunted by the use of serial samples and change criteria. These results also lead to questions concerning the validity of results in recently published studies of cTnT that used the old, incorrect lots. It would be desirable to list the specific lot numbers of cTnT used in all previously published studies and those going forward.

A recent study by Reichlin et al. (30) evaluated a diagnostic algorithm incorporating baseline cTnT values as well as absolute cTnT changes within the first hour of observation. A baseline cTnT concentration <12 ng/L and an absolute change within the first hour of <3 ng/L were used as rule-out criteria for AMI and had a negative predictive value of 100%. The suggested absolute change corresponds reasonably well with our

### Table 3. Short- and long-term biological and individual variation in cTnI and TnT.

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<th>CVᵣ</th>
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<td></td>
</tr>
<tr>
<td>cTnT</td>
<td>Roche E170</td>
<td>7.8</td>
<td>31</td>
<td>NA</td>
<td>NA</td>
<td>87</td>
<td>138</td>
<td>-58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elecsys 2010</td>
<td>9.7</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>86</td>
<td>135</td>
<td>-58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Modular E170</td>
<td>98</td>
<td>94</td>
<td>94</td>
<td>1.4</td>
<td>NA</td>
<td>315</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elecsys hs-TnT²</td>
<td>4</td>
<td>10.7</td>
<td>65</td>
<td>0.18</td>
<td>32</td>
<td>37</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* RCV⁺ and RCV⁻ increase and decrease percentages refer to nonparametric data and are log transformed.

b NA, not available.

² Patients with suspected coronary artery disease.
findings of a rising log-normal RCV of at least 34% (old lot) and 26% (new lot) over 4 h. At a cTnT concentration of 12 ng/L, an increase of 34% implies an absolute change of 4.1 ng/L, and an increase of 26% implies an absolute change of 3.1 ng/L. Unfortunately, it is not clear from the Reichlin et al. article which assay lot was used for analysis of cTnT. The sensitivity and specificity of the proposed diagnostic algorithm will be critically dependent on the assay version. It might be wise indeed to reconfirm those values with the new assay formulation.

The long-term individual variation, CVi, in our group of patients was almost twice as high as the short-term individual variation, 24% for cTnI and 11% for cTnT. The resulting rising/falling log-normal RCV for cTnI was 97%–49%. Thus, cardiac troponin must increase almost 100% to be able to detect a reliable change that exceeds fluctuations due to long-time variation alone when measurements are done weeks apart. Previous studies of long-term CVi in healthy individuals have shown a very large variation in results (Table 3) (12–15, 26, 27).

Cardiac troponin has a low within-person variation but a large between-person variation, which results in a low II (12). A II <0.6 indicates that a population-based reference interval with a fixed higher limit, i.e., for cardiac troponin the 99th percentile, is of limited value for diagnostic purposes. In the present study, the short-term II values for cTnI and cTnT of 0.08 and 0.12, respectively, were in the low end of what has been reported in comparable studies (12–14, 26, 27) and considerably lower than the 0.6 limit (Table 3). Only in 1 previous study has the II been >0.6 (13). Thus, these results indicate that serial testing showing rising or falling pattern is necessary for establishing a reliable diagnosis of acute myocardial injury by use of cardiac troponin.

A limitation of this study is that there were fewer values above the LoD for cTnT compared to cTnI. Therefore, comparison of the cTnT and cTnI results must be interpreted cautiously. Another limitation was that no designated phlebotomists were used, which may have introduced some preanalytic variation. However, troponin appears to be less sensitive to variation in handling compared with many other biomarkers.

In conclusion, this study of individual variation of cardiac troponin concentrations in patients with suspected and confirmed stable coronary artery disease shows that the individual variation in these patients seems to be quite similar to the biological variation seen in healthy individuals. Our results suggest that a short-term change in cardiac troponin concentrations of >50% is highly indicative of an acute myocardial injury. To detect significant long-term changes in cardiac troponin concentrations, a larger change is required. In addition, important differences were also noted in measured cTnT concentrations between the hs-cTnT assay lot with the recently reformulated calibration curve and the lot with the older calibration.

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References


