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Clinical Research

Variability in High-Sensitivity Cardiac Troponin T Testing in Stable Patients With and Without Coronary Artery Disease

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ABSTRACT

Background: High-sensitivity cardiac troponin T (hs-cTnT) is used to diagnosis acute myocardial infarction, often based on values exceeding the 99th percentile threshold (14 ng/L) of normal populations. The short- and long-term variability of hs-cTnT in stable patients with or without coronary artery disease (CAD) is unknown.

Methods: Prospective cohort study of 75 stable patients with CAD and 3 differing clinical profiles (stable angina [SA]; remote myocardial infarction [MI]; repetitive acute coronary syndrome [ACS]) and 25 controls without angiographic CAD, each with 15 hs-cTnT measurements over 1 year.

Results: Individual results (1491 measurements) did not vary over within-day, daily, weekly, monthly, seasonal, or yearly time windows.

RÉSUMÉ

Contexte : La troponine T cardiaque hautement sensible (TnTc-hs) est utilisée pour le diagnostic de l'infarctus aigu du myocarde, lorsque sa concentration est supérieure à la valeur seuil pour le 99e percentile (14 ng/l) dans la population normale. La variabilité à court et à long terme de la TnTc-hs chez les sujets dont l'état est stable, qu'ils soient ou non atteints de coronaropathie, n'est pas connue.

Méthodologie : Étude de cohorte prospective regroupant 75 patients atteints de coronaropathie dont l'état était stable, présentant 3 profils cliniques distincts (angine stable; infarctus du myocarde passé; événements coronariens aigus répétitifs) et 25 sujets témoins sans coronaropathie à l'angiographie, chacun ayant subi 15 mesures de la TnTc-hs sur une période de 1 an.

In patients presenting with suspected acute coronary syndromes (ACS), the high-sensitivity cardiac troponin I (hs-cTnI) or T (hs-cTnT) assay, with values exceeding the upper 99th percentile troponin level observed in apparently healthy individuals, has become the touchstone for the diagnosis of acute myocardial infarction (AMI).[1] However, troponin values above this cutoff are not specific for AMI and may indicate myocardial injury by other distinct mechanisms[1] or perhaps simply reflect some degree of spontaneous variability. Several prospective studies have also established that raised troponin values are associated with poorer clinical outcomes in a variety of clinical situations.[2-19] Consequently, cardiac troponin measurements are increasingly performed not only as part of the routine workup in patients presenting to emergency departments with suspected ACS but also for prognostication in a broad range of stable patients. This has led to the frequent finding of isolated raised troponin measurements of unclear clinical significance.

To interpret the significance of raised troponin values reliably, it is necessary to understand their spontaneously variability in clinically stable subjects. The natural variability of troponin values has not been rigorously examined over short or long periods, particularly in stable patients with coronary artery disease (CAD).[8,20] Test accuracy may vary in different clinical settings, including perhaps in different subsets of CAD subjects, a phenomenon known as the spectrum effect,[21,22] which has not been previously investigated in troponin testing.

This study addresses these knowledge gaps by prospectively examining the spontaneous variability of hs-cTnT measured serially at multiple and specific time intervals over a year in subsets of stable patients with and without distinct CAD histories and to investigate the determinants of this variability.

Methods

Patients

Details regarding the study population and the diagnostic criteria have been previously published.[23] In summary, a

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The overall median was 2.8 ng/L (interquartile range [IQR] 5.2 ng/L) with the highest median (6.3 ng/L) and variability (IQR 6. 9 ng/L) in the repetitive ACS group. Diabetes, impaired renal function, and raised C-reactive protein were independent predictors of higher hs-cTnT values (average increase by 8.5 ng/L [95% CI, 5.0-11.9], 5.0 ng/L [95% CI, 2.0-8.1] and 4.0 ng/L (95% CI, 1.0-7.0), respectively). The 99th percentile value of all hs-cTnT measurements in the combined stable patients with CAD was 39 ng/L compared with 14 ng/L in the non-CAD patients.

Conclusions: Individual hs-cTnT readings in both patients with and without CAD were stable over hours, days, weeks, and months. Diabetes, poor renal function, and elevated C-reactive protein were independent predictors of higher median and IQR hs-cTnT values, often exceeding conventional thresholds. These findings highlight the need for caution and clinical contextualization in the interpretation of hs-cTnT results.

Résultats : Les résultats individuels (1 491 mesures) n'ont pas varié selon le temps de la journée, les jours de la semaine, les semaines du mois, d'un mois à l'autre, d'une saison à l'autre ou à une intervalle d'une année. La concentration médiane dans l'ensemble était de 2,8 ng/l (intervalle interquartile [IIQ] de 5,2 ng/l), la concentration médiane la plus élevée (6,3 ng/l) et la variabilité la plus grande (IIQ de 6,9 ng/l) étant observées dans le groupe avec événements coronariens aigus répétitifs. Le diabète, l'insuffisance rénale et un taux élevé de protéine C réactive constituaient des facteurs prédictifs indépendants d'une concentration plus élevée de TnTc-hs (augmentation moyenne de 8,5 ng/l [intervalle de confiance (IC) à 95 %: de 5,0 à 11,9], 5,0 ng/l [IC à 95 % : de 2,0 à 8,1] et 4,0 ng/l [IC à 95 % : de 1,0 à 7,0], respectivement). La valeur correspondant au 99e percentile pour toutes les mesures de la TnTc-hs chez l'ensemble des patients atteints de coronaropathie dont l'état était stable était de 39 ng/l, comparativement à 14 ng/l chez les sujets non atteints de coronaropathie.

Conclusions : Les mesures individuelles de la TnTc-hs chez les sujets atteints ou non de coronaropathie étaient stables d'une heure, d'une journée, d'une semaine et d'un mois à l'autre. Le diabète, une mauvaise fonction rénale et un taux élevé de protéine C réactive constituaient des facteurs prédictifs indépendants d'une concentration médiane et d'un IIQ plus élevés pour la TnTc-hs, excédant souvent les valeurs seuils habituelles. Ces résultats démontrent la nécessité de faire preuve de prudence et de prendre en considération le contexte clinique au moment d'interpréter les résultats pour la TnTc-hs.

convenience sample of 3 distinct clinical groups of patients with stable CAD and a control group with no angiographic evidence of CAD were recruited for serial blood sampling to investigate spontaneous variability. Potentially eligible subjects were screened at a single large tertiary cardiac care hospital.

Group 1 had a history of repetitive ACS (AMI or unstable angina) with a minimum of 3 admissions, at least 2 of which were documented MIs. The last ACS had to have occurred within the previous 2 years but more than 3 months before initial blood sampling. There had to be at least 1 month between acute coronary events for both to be counted, and those occurring within 3 months of a revascularization procedure were not considered.

Group 2 had a history of stable angina of at least 7 years' duration and at no time any history of ACS. CAD had to be documented by angiography showing stenosis $\geq$70% of at least 1 major coronary artery or a myocardial imaging study showing an unequivocal reversible ischemic defect.

Group 3 had a single remote MI at least 7 years before study entry. These subjects could not have had angina (stable or unstable) either before or after their MI.

Group 4 had no CAD with unequivocally normal coronary angiograms, as assessed by 2 experienced observers, performed within 3 years of blood sampling. These subjects also had to have no clinical evidence of atherosclerotic disease in other vascular beds and were selected to be sex and age matched with subjects of the other groups.

Patients were excluded if they had known cancer within 5 years of the blood samples, any inflammatory/infectious disease within a month of the first sample, or surgery or angioplasty in the preceding 3 months. The hospital ethics committee approved the study and each participant gave written informed consent.

Study procedures

After recruitment, patients underwent physical examinations and fasting baseline blood tests after sitting at rest for at least 15 minutes. At each visit, patients underwent detailed structured questionnaires on their medical histories and medication to determine their clinical stability and to identify any events or factors that could have impact on health status. Also, for any patient with significant current inflammatory events—such as fever or hospitalization—blood sampling was to be delayed. Three blood samples for measuring hs-cTnT were collected during a single day at 6- to 8-hour intervals. In addition, there were 5 consecutive daily blood samples; 4 consecutive weekly samples; 3 consecutive monthly samples; 5 samples at trimonthly intervals to complete the year; 2 samples at a 1-year interval (baseline and 1-year follow-up). After the first day, blood samples were always drawn at the same time $\pm$ 1 hour. Blood samples taken at any single time could count more than once in these determinations of within-day, daily, weekly, monthly, seasonal, and yearly variability, so that the 22 time points were covered by 15 blood samples on 13 different days for each person.

All venipunctures were performed by the same 2 nurses, explicitly following the test manufacturer's (Troponin T hs, Roche Diagnostics, Florham Park, NJ) processing recommendations, using only heparinized samples. Blood samples were centrifuged upon collection and plasma was distributed in aliquots and frozen at minus 80° C (−112° F) until the analysis. All hs-cTnT measurements were performed

simultaneously on an automated platform modular analytics E170 using a highly sensitive immunoassay (Troponin T hs, Roche Diagnostics). According to the manufacturer, the limit of detection is 3.0 ng/L, and the 99th percentile value, which is considered the myocardial injury/necrosis threshold, is 14 ng/L. The laboratory technicians analyzing the biomarker were unaware of participant status. We evaluated analytical variability by remeasuring hs-cTnT in the 75 patients with CAD in the first blood sample they provided. We did this several months later in a single batch in the same laboratory.

Statistical methods

Undetectable values of hs-cTnT (< 3 ng/L) were treated as missing data and imputed, by random assignment, a value between 0 and 3 ng/L. In a sensitivity analysis, all undetectable values were assigned the constant value of 3 ng/L. Analytical variability was evaluated with the method of Bland and Altman.[24] We compiled descriptive statistics for all variables, including medians and interquartile ranges (IQR, the difference between the 75th and 25th percentile) of hs-cTnT, given their overall non-normal distribution, and percentages for baseline categorical variables across the 4 clinical groups. To predict the dependent hs-cTnT outcome with the recorded explanatory variables, we performed a generalized linear mixed effects analysis using a γ-link function, which acknowledges the nonindependence and non-normality of the observations. The potential covariates, selected initially for potential effects from a clinical perspective, included age, sex, clinical group, body mass index (BMI), smoking status (never, former, current), diabetes, arterial hypertension, history of heart failure, left ventricular ejection fraction (LVEF), serum creatinine, microalbuminuria, baseline C-reactive protein, and use of angiotensin-modulating drugs and β-blockers. Analyses were performed in R[25] using the lme4 package.[26]

Results

Description of clinical cohorts and hs-cTnT values

Characteristics of the 4 clinical groups recruited are presented in Table 1. The 3 groups with CAD were comparable in terms of age; sex; BMI; renal function; and use of aspirin, β-blockers, and lipid-lowering agents. The repetitive ACS group had a more frequent history of diabetes, arterial hypertension, smoking and heart failure, a lower LVEF, and greater use of angiotensin modulators and β-blockers. The group without CAD was slightly younger than the other 3 groups; had fewer men; less arterial hypertension and dyslipidemia; no diabetes; and higher serum cholesterol with lower use of lipid-lowering medications, aspirin, β-blockers, and angiotensin-modulating drugs. There were no differences in C-reactive protein values among the groups. During the study, there was 1 cardiovascular event, an ACS in a subject of the repetitive ACS group that occurred midway between month-6 and month-9 blood draws.

The 100 subjects underwent 15 serial hs-cTnT measurements on 13 different days over the ensuing year. All patients were clinically stable for all their blood draws. Of the 1500 potential blood samples, 9 were missing (3 from a person who was imprisoned, 2 from a patient hospitalized with cellulitis, 1 due to weather conditions, and 3 from a subject who underwent hip surgery). Of the available 1491 hs-cTnT values, 796 values (53.3%) were initially reported as undetectable (< 3 ng/L) and were given a randomly imputed value between 0 and 3 ng/L. A boxplot of all hs-cTnT values according to clinical group is displayed in Figure 1.

Analytical variability, assessed with 75 repeated measures, showed excellent technical reproducibility; the mean difference between 2 repeated hs-cTNT measurements was only 0.5 ng/L, with results almost uniformly within the expected 95% CI (Supplemental Fig. S1).

Temporal variability in individual hs-cTnT values

For each patient, we calculated individual median and IQR hs-cTnT values for within-day, daily, weekly, monthly, seasonal, and yearly time windows. The within-day values were based on morning, early afternoon, and early evening measurements recorded on the same day, whereas daily values were calculated from 5 consecutive days, weekly values from 4 consecutive weeks, monthly from 3 consecutive months, seasonal from 4 consecutive 3-month intervals, and yearly from baseline and 1 year. The median and IQR of all the individual results for each time interval are shown in Table 2, demonstrating that individual hs-cTnT values are invariant over within-day, daily, weekly, monthly, seasonal, and yearly time windows. Whereas individual values remain relatively constant over time (Fig. 2), between-individual variation was observed(Supplemental Fig. S2).

Determinants of between-individual hs-cTnT variation

A total of 103 of 1491 values (6.9%) exceeded the 99th percentile for normal individuals of 14 ng/L. The number of elevated hs-cTnT measurements varied according to clinical group (Table 2) and was not normally distributed (Fig. 1). Of the 375 troponin values observed in the group without CAD, only 2 values (0.5%) exceeded 14 ng/L. In contrast, among the 75 patients with CAD, 101 of 1116 measurements (9.1%) exceeded 14 ng/L: 66 of 370 (17.8%) in the repetitive ACS group, 17 of 375 (4.5%) in the single remote MI group, and 18 of 371 (4.9%) in the stable angina group. The 99th percentile of hs-cTnT in the combined group of 75 stable patients with CAD was 39 ng/L.

The overall median hs-cTnT value was 2.8 ng/L (IQR 5.4 ng/L). The repetitive ACS group had the highest hs-cTnT median value (6.3 ng/L) and the highest IQR (6.9 ng/L); the group without CAD had the lowest median hs-cTnT value (1.9 ng/L) and the lowest IQR (1.8 ng/L); intermediate values were found in the stable angina group (2.8 ng/L [median] and 5.4 ng/L [IQR]) and the single remote MI group (2.5 ng/L [median] and 4.4 ng/L [IQR]) (Table 2). Thus, among the clinical groups, the repetitive ACS group showed the greatest variability, the control group without CAD the least variability with the other groups being intermediate. This variability is shown graphically in Figure 1.

Fifteen of the 100 subjects had at least 1 hs-cTnT measurement above the normal threshold; the majority belonged to the repetitive ACS group 8 of 25 subjects (32%; 95% CI, 16-54) compared with 3 of 25 (12%; 95% CI, 3-32) subjects for each of the remote MI and stable angina groups and 1 of

Table 1. Baseline characteristics for the 4 clinical cohorts

	Control (n = 25)	Stable angina (n = 25)	Single MI (n = 25)	Repetitive ACS (n = 25)	*P* value
Sex					
Female	7 (28.0%)	3 (12.0%)	4 (16.0%)	3 (12.0%)	0.4
Male	18 (72.0%)	22 (88.0%)	21 (84.0%)	22 (88.0%)	
Age (years)					
Mean (SD)	61.2 (7.9)	66.3 (6.4)	64.6 (7.2)	65.6 (8.3)	0.09
Median (min, max)	63.0 [47.0, 77.0]	67.0 (54.0, 75.0)	65.0 (49.0, 76.0)	65.0 (49.0, 78.0)	
BMI (kg/m^2)					
Mean (SD)	29.4 (5.2)	28.4 (3.4)	28.6 (2.9)	29.9 (4.1)	0.5
Median (min, max)	28.7 (20.8, 39.4)	27.6 (23.6, 36.2)	28.2 (23.9, 35.4)	30.1 (22.9, 38.5)	
Missing	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
History of CHF					
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (32.0%)	< 0.001
No	25 (100.0%)	25 (100.0%)	25 (100.0%)	17 (68.0%)	
History of diabetes					
Yes	0 (0.0%)	7 (28.0%)	4 (16.0%)	8 (32.0%)	0.02
No	25 (100.0%)	18 (72.0%)	21 (84.0%)	17 (68.0%)	
History of HTA					
Yes	13 (52.0%)	18 (72.0%)	12 (48.0%)	20 (80.0%)	0.05
No	12 (48.0%)	7 (28.0%)	13 (52.0%)	5 (20.0%)	
History of smoking					
Yes	3 (12.0%)	4 (16.0%)	3 (12.0%)	7 (28.0%)	0.4
No	22 (88.0%)	21 (84.0%)	22 (88.0%)	18 (72.0%)	
C reactive protein (mg/L)					
Mean (SD)	3.11 (4.7)	1.67 (1.4)	1.94 (2.5)	3.00 (3.8)	0.3
Median (min, max)	1.5 (0.3, 21.1)	1.1 (0.2, 5.7)	1.1 (0.1, 12.4)	1.7 (0.2, 18.5)	
Serum creatinine (mmol/L)					
Mean (SD)	80.5 (11.7)	83.2 (16.8)	88.9 (24.7)	89.2 (24.6)	0.3
Median (min, max)	78.0 [59.0, 105]	80.0 [64.0, 124]	83.0 [66.0, 181]	87.0 [49.0, 176]	
eGFR ($mL/min/1.73\ m^2$)					
Mean (SD)	85.0 (14.5)	85.9 (17.8)	81.1 (20.5)	82.5 (22.4)	0.8
Median (min, max)	85.0 [57.1, 114]	85.6 (52.5, 118)	82.3 (34.0, 114)	80.4 (25.9, 120)	
Total cholesterol (mmol/L)					
Mean (SD)	4.8 (0.9)	4.0 (0.7)	3.9 (0.4)	3.8 (0.9)	< 0.001
Median (min, max)	4.6 (3.2, 6.5)	3.9 (2.9, 5.8)	4.1 (3.0, 4.6)	3.6 (2.5, 7.4)	
LDL cholesterol (mmol/L)					
Mean (SD)	2.8 (0.9)	2.2 (0.6)	2.1 (0.7)	2.1 (0.8)	0.002
Median (min, max)	2.8 (1.2, 5.0)	2.2 (1.2, 3.7)	2.1 (0.0, 3.6)	2.0 (0.6, 5.0)	
Missing	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Ejection fraction (%)					
Mean (SD)	62.0 (5.0)	63.6 (6.8)	54.1 (9.4)	46.2 (12.4)	< 0.001
Median (min, max)	60.0 (50.0, 73.0)	64.0 (45.0, 78.0)	52.0 (35.0, 70.0)	50.0 (20.0, 65.0)	
Missing	5 (20.0%)	2 (8.0%)	6 (24.0%)	0 (0.0%)	
Aspirin					
Yes	11 (44.0%)	24 (96.0%)	25 (100.0%)	24 (96.0%)	< 0.001
No	14 (56.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	
ACE inhibitors					
Yes	2 (8.0%)	9 (36.0%)	11 (44.0%)	18 (72.0%)	< 0.001
No	23 (92.0%)	16 (64.0%)	14 (56.0%)	7 (28.0%)	
β-Blockers					
Yes	7 (28.0%)	18 (72.0%)	17 (68.0%)	22 (88.0%)	< 0.001
No	18 (72.0%)	7 (28.0%)	8 (32.0%)	3 (12.0%)	
Lipid-lowering drugs					
Yes	10 (40.0%)	23 (92.0%)	24 (96.0%)	24 (96.0%)	< 0.001
No	15 (60.0%)	2 (8.0%)	1 (4.0%)	1 (4.0%)	

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; BMI, body mass index; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; MI, myocardial infarction: SD, standard deviation.

25 (4%; 95% CI, 1-22) subjects in the control group ($P = 0.023$) (Table 3).

Aside from clinical group, several other parameters were associated with both increased median and increased variability (IQR) of hs-cTnT values (Table 3): men vs women (median 3.7 ng/L vs 1.9 ng/L, IQR 5.5 ng/L vs 1.8 ng/L); diabetes vs no diabetes (median 8.3 ng/L vs 2.5 ng/L, IQR 12.2 ng/L vs 4.0 ng/L); and poorer renal function (serum creatinine above vs below the median: median 4.6 ng/L vs 2.4 ng/L, IQR 7.6 ng/L vs 3.3 ng/L). Older patients (> 65 years) had a small increase in median values (4.3 ng/L vs 2.4 ng/L) and IQR (6.5 ng/L vs 3.3 ng/L). Table 3 also shows the percentages of hs-cTnT values exceeding the 14 ng/L necrosis threshold in these same subsets: 30.3% in the presence of diabetes vs 1.5% without diabetes; 12.7% if C-reactive protein exceeded the median value vs 1.1 % if it was below the median; 13.3% in the presence of poorer renal function vs 0.5% with better function; 14.8% in those on angiotensin-modulating drugs vs 1.7% if not; and 11.4% in the presence of left ventricular ejection fraction below the median vs

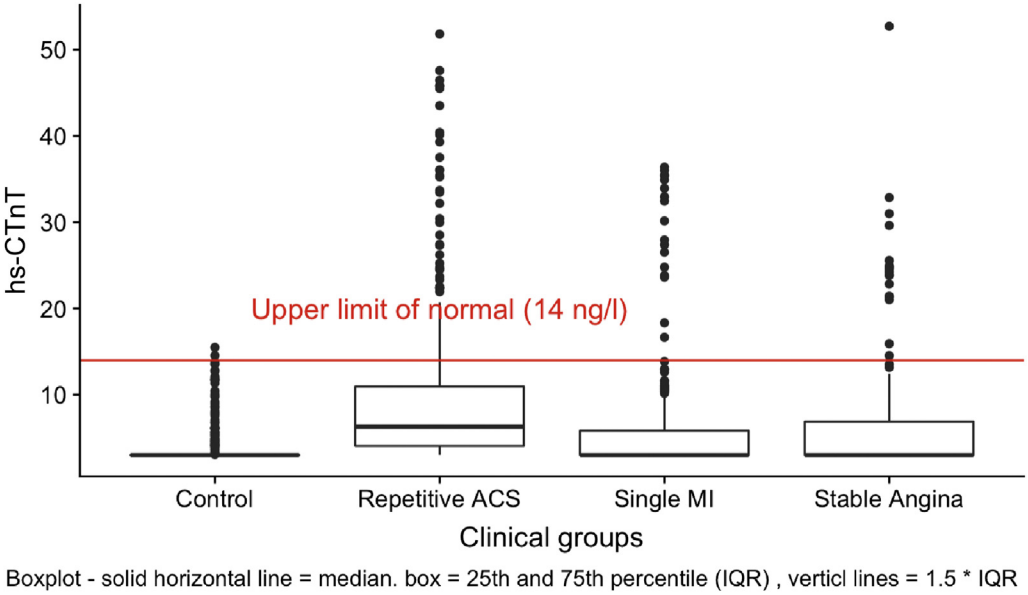

Figure 1. Boxplot of all high-sensitivity cardiac troponin T (hs-cTnT) measurements according to the clinical group.

0.2% if above the median. The variability of hs-cTnT as a function of these characteristics was not modified over time (Supplemental Fig. S3). Graphically, the variability of all hs-cTnT values according to these clinical characteristics is displayed in Supplemental Fig. S4.

A generalized linear mixed model that accounted for the correlated nature of the samples and the non-normality of the 1491 hs-cTnT values showed that only diabetes, poorer renal function and C-reactive protein were independent predictors of hs-cTnT. Although the overall median of the 1491 measurements was 2.8 ng/L (IQR 5.2 ng/L), the presence of diabetes increased the median value to 8.5 ng/L (95% CI, 5.0-11.9, $P < 0.0001$). Similarly, serum creatinine and C-reactive protein values above the median (81.5 μmol/L and 1.25 mg/L, respectively) were associated with median hs-cTnT increases of 5.0 ng/L (95% CI, 2.0-8.1, $P < 0.002$) and 4.0 ng/L (95% CI, 1.0-7.0, $P < 0.001$), respectively. The clinical CAD group, especially the repetitive ACS group, was associated with a median 3.2-ng/L increase, but this was not statistically significant (95% CI, −1.4-7.8, $P = 0.18$) in the multivariable model. No other explanatory variables were independently associated with hs-cTnT levels. Specifically, older age, sex, use of angiotensin-modulating drugs, and lower LVEF were not significant independent predictors in this model. The model results were insensitive to assigning hs-cTnT values < 3 to a single fixed constant value of 3 and to replacing median creatinine and history of diabetes in the generalized linear mixed model by median estimated glomerular filtration rate and median blood glucose, respectively.

Table 2. Median cardiac troponin T (cTnT) and interquartile range (IQR) of all 100 individuals at each different time windows

	Median (ng/L)	IQR (ng/L)	99th percentile
Hourly	5.3	1.1	6.6
Daily	5.5	1.6	7.3
Weekly	5.2	1.7	7.3
Monthly	5.2	1.7	7.2
Seasonal	5.2	1.9	8.2
Yearly	5.5	1.4	7.1

For each individual the average of their hourly (day 1, n = 3), daily (consecutive days, n = 5), weekly (consecutive weeks, n = 4), monthly (consecutive months, n = 3), seasonal (consecutive seasons, n = 4), yearly (baseline and at 1 year, n = 2), values were calculated. The median and IQR of these 100 average values for each time window are reported in this Table.

Discussion

Our study has 3 main findings. First, individual hs-cTnT values did not exhibit significant within-day, daily, weekly, monthly, seasonal, or 1-year variability. Second, there was a spectrum effect in the hs-cTnT values according to the clinical presentations of these stable patients with CAD. Patients with history of diabetes, mild to moderate renal dysfunction and higher C-reactive protein levels had higher hs-cTNT values, including levels above the currently reported 99th percentile threshold of 14 ng/L. Patients with CAD, especially those with repetitive ACS compared with the other CAD and non-CAD groups, also had a tendency to higher hs-cTnT values. Third, the greatest hs-cTnT variability was observed in these same clinical groups.

For the 375 troponin values in the non-CAD group, the 99th percentile was 14 ng/L, confirming previous observations about this threshold.[1] However, the 99th percentile value of the CAD group as a whole was markedly higher (39 ng/L). Specifically, of all 1491 hs-cTnT measurements, 4.5% of the values in the single remote AMI subset, 4.9% of the values in the stable angina subset, and 17.8% of the values in the repetitive ACS subset, exceeded the threshold of 14 ng/L. In terms of patients with at least 1 elevated value, this ranged from 4% in the control group to 32% in the repetitive ACS group. This spectrum effect between the stable patients with repetitive ACS compared with the other stable patients with CAD and compared with subjects with no CAD did not reach

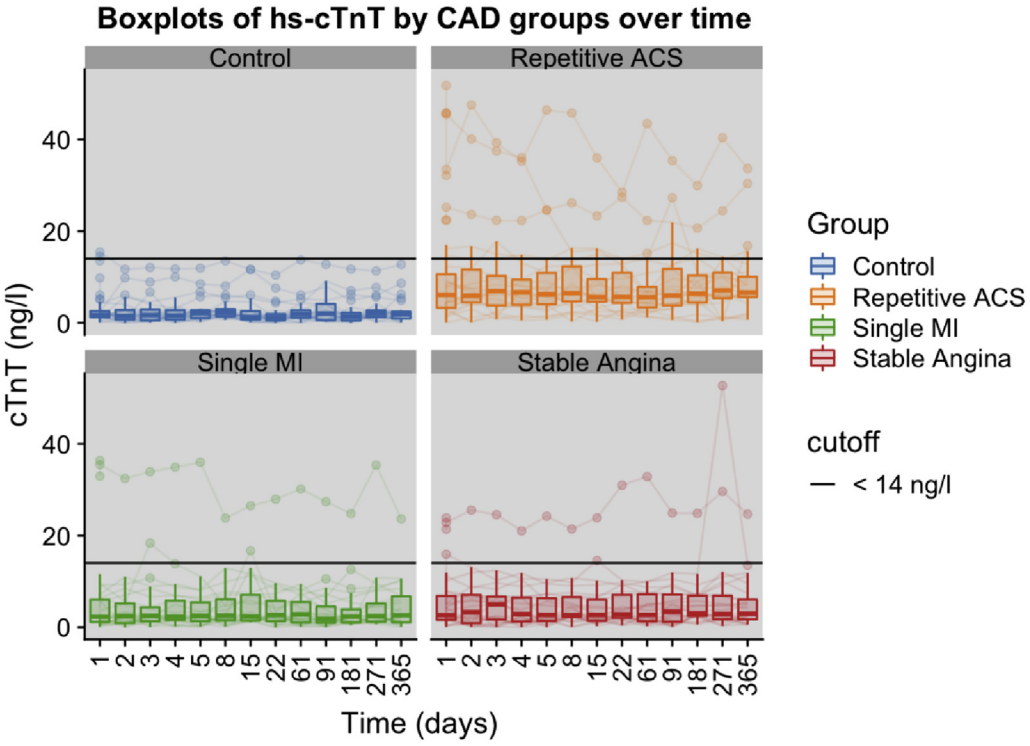

Figure 2. Boxplot of all high-sensitivity cardiac troponin T (hs-cTnT) values as a function of the clinical cohorts over time. The **horizontal lines** represent the serial values from the same individuals. ACS, acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction.

Table 3. High-sensitivity cardiac troponin T (cTnT) median values and variability (IQR) according to different clinical characteristics

					Tests > ULN		Pts > ULN	
	Pts (N)	Tests (N)	Median (cTnT)	IQR (cTnT)	N	%	N	%
Controls	25	375	1.9	1.8	2	1	1	4
Stable angina	25	371	2.8	5.4	18	5	3	12
Single MI	25	375	2.5	4.4	17	5	3	12
Repetitive ACS	25	370	6.3	6.9	66	18	0	0
Age < 65	45	672	2.4	3.3	28	4	5	11
Age ≥ 65	55	819	4.3	6.4	75	9	10	18
Women	17	254	1.8	1.8	11	4	1	6
Men	83	1237	3.6	5.5	92	7	14	17
BMI < median	50	749	2.6	4.5	40	5	7	14
BMI > median	49	727	3.8	6.1	63	9	8	16
DM −	81	1210	2.5	4	18	1	7	9
DM +	19	281	8.3	12.2	85	30	8	42
Creatinine < median	50	746	2.4	3.3	4	1	3	6
Creatinine > median	50	745	4.6	7.5	99	13	12	24
CRP < median	50	747	2.6	4.1	8	1	5	10
CRP > median	50	744	3.4	6.7	95	13	10	20
EF > median	28	419	2	2.9	1	0	1	4
EF < median	59	877	4.6	6.5	100	11	13	22
ACEI −	60	895	2.4	3.8	15	2	4	7
ACEI +	40	596	5	7.7	88	15	11	28
Lipid lowering −	19	285	1.7	1.5	0	0	0	0
Lipid lowering +	81	1206	4.1	5.8	103	9	15	19
Aspirin −	16	240	1.7	1.5	0	0	0	0
Aspirin +	84	1251	4	5.7	103	8	15	18
β-Blocker drugs −	36	537	2.2	3.3	15	3	4	11
β-Blockers +	64	954	4.2	5.8	88	9	11	17
TC < median	50	741	4.7	6.8	86	12	13	26
TC > median	50	750	2.3	3.2	17	2	2	4
LDL < median	50	744	4.4	6.4	83	11	11	22
LDL > median	49	732	2.5	3.7	20	3	4	8

Nine missing cTnT, 1 missing BMI, 13 missing EF values, 1 missing LDL.

ACEI, angiotensin converting-enzyme inhibitor; ACS, acute coronary syndrome; BMI, body mass index; CRP, C-reactive protein; DM, diabetes; EF, ejection fraction; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; Pts, patients; TC, total cholesterol; ULN, upper limit normal (14 ng/L).

statistical significance after adjusting for age, diabetes, and decreased renal function: factors known to contribute to increased troponin values.[10,27-29]

Previous studies have also found a higher prevalence of hs-cTnT values above the 14-ng/L threshold in patients with stable CAD, albeit measured at only 1[3,30-33] or 2 time points.[8] The causes of higher hs-cTnT values in these stable patients with CAD, particularly in those with CAD history punctuated by several ACS episodes, are unknown. Speculative mechanisms include continuous subclinical ischemic micro-injury, altered myocardial tissue metabolism, myocardial wall stress, inflammation, and reduced troponin clearance. It is plausible that such factors would be more strongly present in the subset of subjects with a history of repetitive ACS events.

To our knowledge, only 2 studies have reported hs-cTnT variability in patients with stable CAD. In 1 study, 24 patients were studied with a first measurement and, several days later, 6 measurements at 4-hour intervals; the variability documented was similar to the values reported in normal subjects.[20] In the second study, 1984 stable patients with CAD and diabetes had hs-cTnT measured twice at a 1-year interval.[8] The limited number of serial observations in these studies does not allow any comprehensive comparison with our findings. Although our study group was limited to 100 patients, the large number of values per patient at systematic time points lends weight to our observation that within-subject variability of troponin values is a direct function of the median value found in any subject; that is, the greater the median value, the greater the absolute variability.

It is pertinent for clinicians to be aware that patients with CAD, particularly patients with history of repeated ACS, may have values exceeding the 14 ng/L threshold in their stable state and that the presence of diabetes, raised C-reactive protein, and renal dysfunction may further contribute to higher troponin values in the absence of any apparent clinical instability. Our results also show that higher troponin values measured at 1 point in time increase the likelihood of greater variability on subsequent measurements, again in the absence of any apparent clinically evolving condition. Our findings reinforce the need for caution and clinical contextualization, pointing to the importance not only of the acute but also of the chronic medical history and clinical characteristics in the interpretation of raised troponin values.

Our study does have limitations. Subjects were not randomly selected, they were a convenience sample from a single tertiary centre, and the study group was relatively small. Our design and methods potentially lacked the power to rule out meaningful associations between hs-cTnT values and other clinical variables. Nevertheless, our study has strengths, including its compliance with standards proposed for the critical evaluation of biological variation by the European Federation of Clinical Chemistry and Laboratory Medicine Working Group.[34] It is also the first to have systematically examined hs-cTnT values at a large and comprehensive number of time intervals in well-defined subsets of stable subjects with distinct and homogeneous patterns of CAD history as well as a group without CAD totalling almost 1500 measurements. The use of repetitive sampling has allowed excellent control of non−time-dependent confounding factors, reasonable precision, and an enhanced understanding of the variability in these measurements. Moreover, the observation that the 99% percentile for the normal subjects in our study was the same as previously reported provides some reassurance regarding our sampling frame.

Conclusion

This study confirms the absence of meaningful spontaneous variability in individuals who are devoid of CAD. However, in patients with stable CAD, increased spontaneous hs-cTnT variability was observed with values not infrequently above the conventional 14 ng/L necrosis threshold, particularly in patients with repetitive ACS events, diabetes, mild-to-moderate renal dysfunction, and elevated C-reactive protein. These findings underscore the need to integrate the totality of the available evidence before arriving at a diagnosis of AMI in patients with CAD based uniquely on whether hs-cTnT values exceed the conventional necrosis threshold. Such hs-cTnT variability and its determinants should also be taken into account if this biomarker is to be used in risk prognostication in stable patients.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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