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Long-term biological variation of high-sensitivity cardiac troponin T using minimal important differences and reference change values in stable outpatients with cardiovascular disease

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ABSTRACT

Objective: To evaluate the long term biological variation of high-sensitivity cardiac troponin T (hs-cTnT) in stable outpatients with cardiovascular disease (CVD).

Methods: After applying 8 exclusion criteria to 965 patients, hs-cTnT was measured at index visit and at a 12-month interval in 169 stable outpatients presenting for routine follow-up visits for any CVD. Stability was defined as absence of any endpoint within the follow-up period. Reference change values (RCVs) and minimal important differences (MIDs) were determined to assess biological variation of hs-cTnT.

Results: MID and RCV for the 12 months interval in patients were 3.8 ng/L or 44.2%, respectively. MID and transformed MID values were lower than the corresponding RCV with a value of 5.1 ng/L for the transformed RCV and 28.1% for the transformed MID. Similar patterns were shown in different subgroups as sex, age, and renal function. We observed a baseline hs-cTnT value dependent change of MID and RCV with increasing values for MID and decreasing values for RCV which converge to stable values between a baseline hs-cTNT value of 11 to 25 ng/L.

Conclusions: Biological variation of hs-cTnT over 12 months in stable outpatients depends on the concentration at index visit, and is consistent among important prespecified subgroups. MID shows a low biovariability over 12 months.

Clinical Trials Identifier:NCT01954303

1. Introduction

Cardiac troponin (cTn) is the preferred biomarker for the detection of myocardial injury due to its high sensitivity and tissue specificity [1]. Therefore, it is clinically used in two different settings: First, it is the gold standard biomarker in acute cardiac pathologies, particularly in patients presenting with an acute coronary syndrome (ACS) where it allows the detection of non-ST-elevation MI [2]. In addition, cTn proved to be a reliable biomarker for risk stratification in chronic CVD including stable coronary artery disease (CAD) and chronic heart failure [3,4]. In the acute setting consideration of kinetic changes is clearly recommended by international guidelines since distinct cutoffs help to improve specificity of cTn for ACS [2]. Contrary, the value of kinetic changes in the long term setting remains unclear. A better understanding of cTn long term kinetic changes would particularly improve prognostication in CAD patients.

For the interpretation of biomarker changes both biovariability (biological variation) and disease related changes have to be considered. Biovariability is the random variation around a homeostatic set point resulting in different measurements of the biomarker without any kind of change. There are two main approaches to assess biovariabilty: anchor based and distribution based. While for the anchor based approach an indicator for change is necessary, the cohort needs to be clinically stable and free of any end-points for the distribution based approach. The latter is more widely applied. The reference change value (RCV) and the minimal important difference (MID) are the main statistical tools for distribution based calculations.

So far, RCVs for hs-cTn have been calculated for small entitys of healthy individuals [5], stable CAD [6], stable heart failure [7], and patients on hemodialysis [8,9] over a short period of time in cohorts with endpoints included. The aim of the present study was the evaluation of hs-cTnT biovariability using RCV and MID in a large cohort of

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outpatients reporting for routine evaluation of a stable disease ranging from known CAD with or without previous revascularization, chronic heart failure, hypertension, arrhythmias to healthy or near healthy individuals.

2. Methods

2.1. Study population

We investigated asymptomatic individuals or patients with chronic stable symptoms of miscellaneous cardiovascular diseases including angiographically confirmed coronary artery disease (CAD), a history of ACS, peripheral artery disease (PAD), hypertensive or valvular heart disease, chronic heart failure (CHF), venous thromboembolism, a history of a cerebrovascular event and arrhythmias including atrial fibrillation. The cohort was recruited at the department of cardiology at the University Hospital Heidelberg between June 2009 and June 2010. Patients were followed up for at least 6 months using medical history, questionnaire or telephon contact. The detailed characteristics of this population have been published previously [10]. The retrospective data analysis was approved by the local ethical committee.

2.2. Inclusion & exclusion criteria

Patients were included if they showed a stable clinical course and had a documented hs-cTnT value at index visit and at least one follow-up visit. Stability was defined as absence of acute cardiac decompensation, ACS or coronary intervention at either visit. Further to this, patients who experienced any relevant major adverse cardiovascular events (MACE) between visits or during follow-up were excluded. MACE were defined as all-cause mortality, AMI, rehospitalization due to ACS or decompensated heart failure, and stroke. To account for the time-dependence of biological variation, the interval between the two visits were set at 12 months (± 4 months). To account for reporting below the limit of detection we excluded all patients with a hs-cTnT value < 5 ng/L. Furthermore, patients with a hs-cTnT value > 52 ng/L were also excluded because the European Society of Cardiology (ESC) Guidelines define this cutoff as rule-in for non-STEMI [1]. Baseline characteristics were compared according to a hs-cTnT value on index visit according to the 99th percentile of a reference population (i.e. 14 ng/L) since this was reported to be a reliable cutoff for prognostication [11].

2.3. Diagnostic workup

Patients' workup included a 12-lead-ECG, echocardiography and carotid ultrasonography. At the discretion of the treating physician, stress testing (electrocardiogram [ECG], echocardiography or stress magnet resonance imaging), 256 slice CT coronary angiography, cardiac MRI, pulmonary function testing, Holter ECG, and 24 h blood pressure recording were performed. In addition, laboratory testing including hs-cTnT, blood count, clinical chemistry and coagulation was performed in every individual. Patients received regular follow-up visits with follow-up examination and medical tests.

2.4. Laboratory measurements

Troponin measurements were obtained during routine presentations. Cardiac troponin was measured in heparin plasma on a COBAS E411 using the hs-cTnT assay by Roche Diagnostics. The limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L [12]. The 10% covariant of variation (CV) was determined at 13 ng/L in 100 measurements in the authors' laboratory. The interassay CV was 8% at 10 ng/L and 2.5% at 100 ng/L. The intra-assay CV was 5% at 10 ng/L and 1% at 100 ng/L.

2.5. Statistical analysis

Variables were tested for normal distribution using the D'Agostino-Pearson test and were presented either as mean ± standard deviation, or as median with 25th and 75th percentiles. Categorial variables were compared using Chi^2. Continuous variables were compared using either Student *t*-test for parametric or Mann-Whitney *U* test for nonparametric variables. All tests were 2-tailed and a *p*-value < .05 was considered statistically significant. The biological variation of hs-cTnT was assessed via reference change values (RCV) and minimal important difference (MID) as detailed below. The potentially non-linear relation of both MID and RCV with the respective baseline-values were assessed using fractional polynomials. All analyses were performed using Stata 15 (StataCorp, Tx, USA).

2.5.1. Reference change value (RCV)

The combined effects of analytical (CVa) and biological (CVb) variation results in the total variation (CVt) of variances between repeat measurements. This relationship provides the basis for calculating values for within-individual variation (CVi), where $CVi = (CVt^2 - CVa^2, ^{1/2})$, CVa values for SD and mean were obtained from the respective assay descriptions [12].

The RCVs were calculated from median of the total variation values (CVt), according to the formula:

$$RCV = Z \times 2^{(1/2)} (CVa2/na + CVi2/ns)^{(1/2)},$$

where Z = 1.96 (i.e., the *Z*-score for 95% confidence with a 2-tailed $P < .05$); na is the number of replicate assays; and ns is the number of patient samples.

2.5.2. Minimal important difference (MID)

The MID was determined using the one-standard error of measurement-based approach developed by Wyrwich et al. [13] following the equation:

$$MID = SD \times SQRT(1 - r),$$

where SD is the population standard deviation and r is the reliability coefficient (i.e., the degree of absolute agreement among measurements). We selected the intra-class correlation coefficient as the reliability coefficient used in the above equation because it accounts for the proportion of variance in test values due to between-subject variation; it is simple to calculate; and, it provides an estimate of MID that is in good agreement with other methods [13,14].

To facilitate application, interpretation, and comparison of the RCV and MID values derived from our data, we transformed the individual values for RCV and MID into the corresponding relative or numerical values. Consequently, the numerical MID values were transformed into relative values by normalization to the respective group mean while the relative values for RCV were transformed into numerical values via multiplication with the respective group median.

3. Results

3.1. Patients

A total of 965 patients were screened for eligibility. The final study group consisted of 169 patients, with at least two consecutive hs-cTnT measurements in the detectable concentration range, free of any predefined endpoint within a pre-specified observation period of 365 days. (Fig. 1). Patients with a hs-cTnT value > 14 ng/L were older, more likely to be male and had more often a history of cardiomyopathy or chronic kidney disease. Furthermore, they had more often a medication for arterial hypertension or aspirin. Glomerular filtration rate (GFR) was lower in patients with hs-cTnT values < 14 ng/L whereas NT-pro brain natriuretic peptide (NT-proBNP) values were higher in this cohort. (See Table 1.)

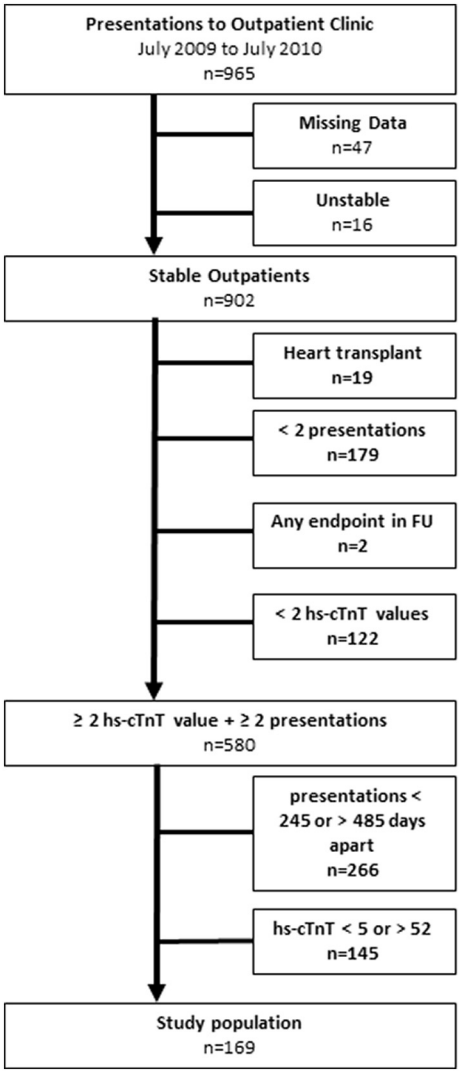

Fig. 1. Flow chart of included patients.

3.2. Biological Variation

Overall, MID was at 3.8 ng/L and RCV at 44.2%. Table 2 shows complete results including transformed absolute or relative values. In general, MID and transformed MID values were lower than the corresponding RCV values. For the MID compared to the RCV transformed there was about a 4 ng/L difference between both values. RCV and MID transformed started at similar values for low hs-cTnT concentrations. Consecutively, MID dropped to a steady level while the RCV was leveling out with higher hs-cTnT values with a difference of 5 to 10% between both values. RCV and MID transformed showed a drop from 50 to 60% for baseline hs-cTnT values of 5 ng/L after which they asymptotically converged against a value of below 20% for the MID and below 30% for the RCV. This lower limit was almost stable starting at baseline values of 11 ng/L hs-cTnT for the MID and about 25 ng/L hs-cTnT for the RCV. Conversely, RCV and MID transformed to absolute values showed a rise from about 0.5 ng/L for MID and about 3 ng/L for the RCV which converged against a value of about 3 ng/L for the MID and about 7 ng/L for the RCV. The upper limit was stable starting at baseline hs-cTnT 11 ng/L for MID and values of 24 ng/L for RCV. Throughout the entire concentration range beyond 25 ng/L hs-cTnT remained stable within the concentration range between 25 and 50 ng/L (Fig. 2).

3.3. Subgroups

While MID transformed and RCV reflect relative changes, RCV transformed and MID reflect absolute changes. Patients with hs-cTnT below 14 ng/L had a lower absolute change and a higher relative change. The same was observed for male patients compared to females. Patients with a reduced renal function or a higher age showed higher relative and absolute changes compared to the respective group (Table 2). The difference of higher absolute and relative changes was documented for all hs-cTnT levels for older and younger patients. Patients with a preserved renal function had a very low absolute change in low hs-cTnT values and a slightly higher absolute change in higher hs-cTnT values. Relative change followed a similar pattern with an overall smaller change for patients with a preserved renal function. Male Patients had a lower absolute change for lower hs-cTnT values but a higher absolute change for higher hs-cTnT values compared to females. In contrast relative changes were higher in males for low hs-cTnT

Table 1
Baseline characteristics according to troponin status.

		All			hs-cTnT ≤ 14 ng/L			hs-cTnT > 14 ng/L			p
n		169			105			64			
Age	Mean +/− SD	71		± 9.0	69	8,2	± 8.2	74		± 9.6	0.002
Gender	% Female	35		(21)	28		(27)	7		[11]	0.014
Hypertension	n (%)	148		(89)	92		(88)	56		(90)	0.709
Diabetes	n (%)	43		(26)	23		(22)	20		(31)	0.188
Dyslipidemia	n (%)	150		(90)	93		(90)	57		(89)	0.798
Smoking	Never/active/former	26	9	25	16	7	13	10	2	12	0.553
CAD	n (%)	115		(68)	68		(65)	47		(73)	0.241
Heart failure	n (%)	56		(33)	32		(30)	24		(38)	0.347
Cardiomyopathy	n (%)	30		(18)	14		[13]	16		(25)	0.054
Chronic kidney disease	n (%)	19		[11]	3		[3]	16		(25)	0.000
Hypertensive medication	n (%)	158		(93)	95		(90)	63		(98)	0.042
Diuretics	n (%)	81		(48)	48		(46)	33		(52)	0.460
Aspirin	n (%)	91		(54)	68		(65)	23		(36)	0.000
eGFR	Median (IQR)	77		(57–94)	80		(67–96)	64		(50–88)	0.003
NT-proBNP (ng/L)	Median (IQR)	310		(134–673)	279		(98–538)	414		(199–910)	0.002
1. hs-cTnT (ng/L)	Median (IQR)	12		(7–18)	8		[7–11]	19		(17–22)	0.000
2. hs-cTnT (ng/L)	Median (IQR)	11		(7–17)	8		[5–11]	18		(13–24)	0.000
Days between visits	Mean +/− SD	372		± 58.9	372		± 61	372		± 55	0.970
FU (days)	Mean +/− SD	795		± 208.9	776		± 216	827		± 193	0.130

CAD = Coronary artery disease, eGFR = estimated glomerular filtration rate, NT-proBNP = NT-pro brain natriuretic peptide, FU = follow-up, SD = standard deviation, IQR = inter quartile range, hs-cTnT = high sensitivity cardiac troponin T.

Table 2
MID and RCV values and their transformed values including the different subgroups, additionally within variation (CVi) and total variation (CVt) with IQR.

	RCVabs (ng/L hs-cTnT)	MID (ng/L hs-cTnT)	MIDrel (%)	RCV (%)			CVt			CVi		
Gesamt	**5.1**	**3.8**	**28.1%**	**44.2%**	17.6%	76.4%	**16.7%**	8.0%	28.0%	**15.9%**	6.2%	27.5%
≤14 ng/L	3.8	2.3	26.4%	47.0%	23.7%	87.1%	17.6%	9.8%	31.8%	16.9%	8.5%	31.4%
> 14 ng/L	5.5	3.3	15.9%	28.7%	4.1%	64.2%	11.4%	5.1%	23.7%	10.3%	1.0%	23.1%
Male	5.6	3.9	27.3%	44.2%	17.6%	76.4%	16.7%	8.0%	28.0%	15.9%	6.2%	27.5%
Female	3.8	3.2	30.1%	45.0%	16.5%	83.2%	17.0%	7.7%	30.4%	16.2%	5.8%	30.0%
eGFR ≥60	4.3	3.4	27.9%	41.6%	14.5%	86.5%	15.8%	7.1%	31.6%	15.0%	5.1%	31.2%
eGFR < 60	7.5	4.4	27.7%	47.0%	21.3%	74.4%	17.6%	9.1%	27.3%	16.9%	7.6%	26.8%
Age ≥ 70	6.3	4.1	28.5%	45.0%	10.8%	74.4%	17.0%	6.3%	27.3%	16.2%	3.7%	26.8%
Age < 70	4.2	3.4	27.3%	43.1%	21.1%	90.8%	16.3%	9.0%	33.1%	15.5%	7.5%	32.7%

RCVabs = absolute reference change value, MID = minimal important difference, RCV = reference change value, MIDrel = relative minimal importat difference, eGFR = estimated glomerular filtration rate.

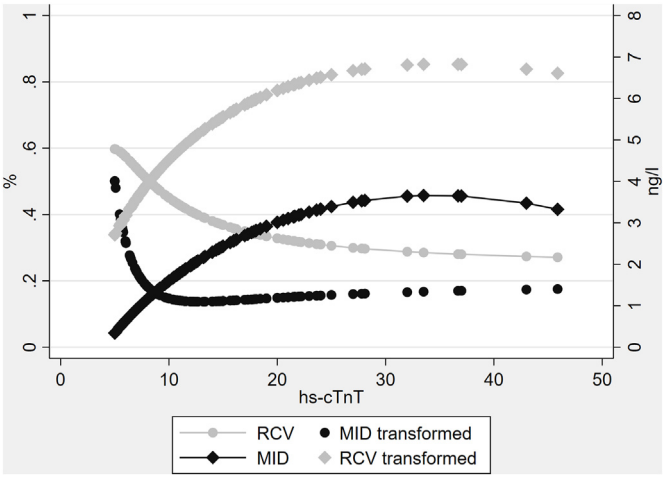

Fig. 2. MID and RCV and transformed values in relation to baseline hs-cTnT values.

values and similar for higher hs-cTnT values compared to females (**Supplemental Figs. 1–6**).

4. Discussion

Our study demonstrates four important and novel findings.

- Patients with stable CVD had low concentration changes of hs-cTnT even over a long sampling interval of one year
- Both MID and RCV values depend on the baseline hs-cTnT at the index event
- MID and RCV values were consistent and very similar among important subgroups such as renal impairment, older age and gender
- MID showed a lower biovariabiltiy than RCV irrespective of absolute or relative value and baseline hs-cTnT values

Cardiac troponins have proved to be valuable biomarkers not only in the diagnostic workup of ACS patients but also in the prognostication of acute and chronic CVD [3,4,10,15]. A better understanding of cTn long term variability would therefore improve prognostication of patients with stable CAD. To evaluate longitudinal changes within a biomarker it is mandatory to know its biological variation. Frequently used metrices for biovariabilty are RCV and MID. To the best of our knowledge MID in stable CVD has not been evaluated so far. Regarding RCV in CVD there is only little information available from few analyses [5–9]. These studies included CVD patients, unstable patients or patients with subsequent MACE. This contradicts the idea of a stable cohort and therefore biovariabilty of hs-TnT should not be calculated based on such populations. This may be an explanation for the huge variation of calculated RCV values between 8 and 80% in these analyes [5–9]. Additionally, since RCV and MID are time dependent and testing intervals of these studies did not exceed 3 months at the most, a more detailed comparison is not possible. In the present study, we evaluated the biological variation at a very common time interval for routine check-ups in stable patients with chronic disease i.e. 12 months.

The increasing use of hs-cTnT for risk stratification in non-acute conditions including monitoring of novel heart failure drugs, cancer toxicity, and risk stratification in primary care and the general population nessecitates novel metrices that allow monitoring of relevant concentration changes taking into account physiological changes (biological variation).

MID and RCV are established metrices of biological variation. While RCV relates closely to the idea of random variation around a homeostatic set point, MID addresses the idea of stability in the light of repeatability.

Although results of this pilot study are promising, independent external validation is required before the use can be recommended for daily clinical practice. Nevertheless, MID values were stable at around 3 ng/L in this analysis, a value that is very similar to the small amount of cTn concentration change that allows to rule-out MI in suspected ACS using a 0/1 h protocol [16]. Therefore it seems that even over a time span of one year absolute concentrations do not change much beyond 3 ng/L.

To the best of our knowledge no data have been published on baseline value dependend MID and RCV values. In this study, RCV and MID values changed depending on the magnitude of baseline hs-cTnT. RCV decreased as baseline concentrations increased until a stable plateau was reached at a baseline hs-cTnT concentration of about 25 ng/L or higher. Contrary, MID demonstrated a reverse relationship with increasing values as baseline hs-cTnT inclined. At intermediate baseline concentrations beyond 25 ng/L MID was also stable irrespective of the baseline hs-cTnT concentration. This pattern was also observed for transformed MID and RCV values, while MID values were lower than the respective RCV values. Additionally, the transformed MID reached the plateau for baseline hs-cTnT values below the 99th percentile.

MID and RCV values were consistent and very similar among important subgroups such as renal impairment, older age and gender. To the best of our knowledge, subgroup analyses on MID and RCV for hs-cTnT in stable CVD patients have not been reported so far.

In this analysis we used two different metrices to calculate biovariability. The MID and its transformed relative value was always lower than the respecitive RCV. This rises the question of their clinical relevance. Further analyses should be made to evaluate if values above the MID represent disease related changes or whether a value above the RCV should be considered.

In conclusion, our study indicates that biological variation of hs-cTnT over 12 months in stable outpatients depends on the concentration at index visit, and is consistent among important subgroups at low concentration changes.

5. Limitations

Since we depend to a certain degree on referral to our tertiary centre we cannot completely exclude a pre-selction bias of our patients. The measurement of biological variation via MID and RCV is context dependent and therefore the results may not be transferred to other settings. Nevertheless, we used a timing interval of 12 months representing a typical routine follow-up of stable patients with cardiovascular disease. Having used distribution based approaches it is mandatory to perform the analyses in a stable cohort. Given the retrospective character of this analysis we cannot rule out hidden changes in the patients. All patients with clinical endpoints were excluded in this analyses.

In addition, we did not have access to a second, similar outpatient cohort and were therefore not able to perform an external validation. However, our data provide a promising new concept that may be incorporated into ongoing studies testing the cardioprotective effects of novel heart failure drugs or aim to prevent cardiotoxicity in cancer patients. At last we know that these results are time-dependent and therefore a different values might be true for longer or shorter time intervals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2019.03.003.

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