Short- and long-term biological variation for cardiac troponin I using a high sensitivity assay: implications for clinical practice

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Abstract

Background: New generation assays for cardiac troponin have improved analytical sensitivity and precision, thereby lowering the 99th percentile cutoff value, resulting in higher frequencies of positive results. We determined the short (within-day, wd) and long-term (day-to-day) biological variability and calculation of the reference change values (RCV) for use in serial troponin testing. Such studies were not possible before the development of these new assays.

Methods: For the assessment of short-term variation, blood was collected on every hour for 4 hours (5 samples each) on 12 healthy subjects. For the assessment of long-term variation, blood was collected every other week for 8 weeks (4 samples each) on 17 healthy subjects. The analytical coefficient of variation (CVa), intra-individual (CVi) variation, total (CVt) variation, index of individuality (II), and lognormal RCV were computed according to the approach by Bruins et al. (Clin Chem 2004;50:2052-58) and Fokkema et al. (Clin Chem 2006;52:1602-3).

Results: Using this approach, values for various parameters related to the biological variability of cardiac troponin I are shown in the table below.

Conclusions: We observed a non-parametric (left skewed) distribution of the data from both sets, justifying the need log-normal transformation. This distribution produces an RCV for increasing troponin results that are higher than the RCV for decreasing results.

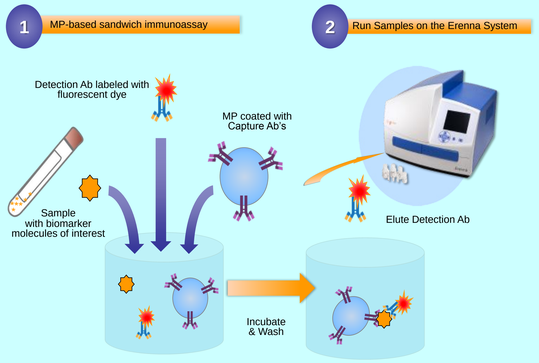
The RCV establishes statistical criteria for the interpretation of serial change values. For patients who present with chest pain to an emergency department, serial testing and use of the short-term RCV enables differentiation between those who have acute coronary syndrome (ACS, increasing troponin), resolving ACS (decreasing troponin), or chronic cardiac disease (e.g., heart failure, stable troponin). For patients taking cardiac toxic drugs, the long-term RCV enables detection of myocardial involvement. As such, high-sensitivity troponin may become a routine “heart function test” for therapeutics.

Parameter	Short-term	Long-term
CVa, %	8.3	14.9
CVi, %	9.7	14.1
CVt, %	56.8	63.0
Index of individuality	0.21	0.39
Precision goals, %	4.8	7.0
Inaccuracy goals, %	14.4	16.1
Reference change values:		
Up	+46	+81
Down	-32	-45

Introduction

- Cardiac troponin is the mainstay for diagnosis of acute coronary syndromes.
- The ESC/ACC recommends use of the 99th percentile as the cutoff concentration.
- Most commercial cTnI assays cannot measure troponin in blood of health subjects. Therefore, biological variability studies could not previously be conducted.
- The Singulex Erenna assay has a detection limit of sensitivity of 0.2 ng/L, 10% CV at 1.8 ng/L and 99th percentile at 10 ng/L.
- This assay was used to determine the biological variability for cTnI.

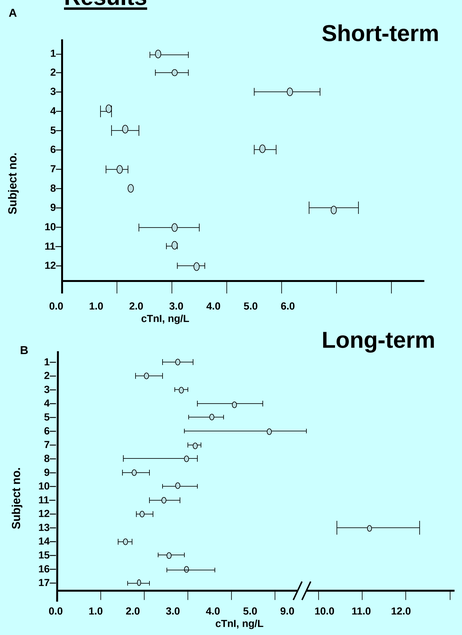
Singulex Erenna single-photon assay for cTnI



Methods

- Short-term BV: blood was collected from 12 healthy subjects (6 M, 6F) hourly for 4 h through a heparin lock.
- Long-term BV: blood was collected from 17 healthy subjects (9 M, 10 F) biweekly for 8 weeks.
- All samples were centrifuged and serum stored frozen at -70°C prior to analysis on the Erenna analyzer.
- The analytical (CV_A), intra-individual (CV_I) and inter-individual (CV_G) variances were computed.
- The index of individuality and goals for precision and accuracy were determined using formula established by Fraser et al.
- As the distribution of results was non-parametric, an asymmetric log-normal was used to determine the reference change values (RCV).

Results



Comparison to other biomarkers

Marker	CV_A	CV_I	CV_G	II	RCV	Duration	Ref
CK	14.0	22.0	42.2	0.52	72.2	daily	Ross et al.
CK-MB, activity	29.1	4.9	14.1	0.35	81.8	daily	Ross et al.
CK-MB, mass	6.8	18.4	61.2	0.30	54.4	daily	Ross et al.
Myoglobin	13.4	17.6	46.6	0.38	61.2	daily	Ross et al.
Troponin I	8.3	9.7	56.8	0.21	+46, -32	hourly	This study

Marker	CV_A	CV_I	CV_G	II	RCV	Duration	Ref
Myoglobin	6.0	11.1	13.8	0.80	35.0	weekly	Panteghini et al.
hsCRP	5.2	42.2	92.5	0.46	11	8 weekly	Macy et al.
S-myloid A	4.0	25.0	61.0	0.40	70.1	weekly	Melzi d’Eril et al.
MPO	4.0	36.0	30.0	1.20	100	weekly	Dednam et al.
BNP	8.4	40.0	41.0	0.98	113	weekly	Wu et al.
NT-BNP	3.0	35.0	35.0	1.00	98	weekly	Bruins et al.
Troponin I	14.9	14.1	63.0	0.39	81,-45	weekly	This study

Examples

- Two patients who present with chest pain and non-diagnostic ECGs:

Time	Case #1 (% change)	Case #2
Presentation	0.07	0.72
4 h	0.12 (+50%)	
8 h	0.57 (+375%)	0.89 (17%)
12 h	1.69 (+200%)	
16 h	5.10 (+200%)	1.27 (43%)

Discharge diagnosis and interpretation:

- **Case #1. Early AMI. Presentation sample and 4 h sample show significant increase for diagnosis.**
- **Case #2. Dilated cardiomyopathy.; increasing troponin values below RCV.**

Conclusions

- Myocardial “event markers” such as CK, CK-MB, myoglobin, and short-term cTnI have low index of individual and low RCV values.
- Myocardial “disease” markers such as CRP, SAA, MPO, BNP, NT-proBNP and long-term cTnI have higher index of individuality and higher RCV values.
- Short-term BV is useful for interpreting serial change values in patients who present to the ED with chest pain.
- Long-term BV is useful for interpreting serial change values in patients who may have cardiotoxic drugs.