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Absolute *versus* relative changes in cardiac troponin T: corresponding cut-offs based on quantile generalized additive models (qgam)

Running title: Absolute *vs.* relative cardiac troponin T changes

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Abstract

Background: The diagnosis of myocardial injury/infarction (MI) mainly relies on relative changes in cardiac troponin. However, absolute change cut-offs provide greater diagnostic sensitivity. We determined the absolute changes in high-sensitive cardiac troponin T concentrations (absΔhs-cTnT) corresponding to the main relative cut-offs (relΔhs-cTnT), using a quantile generalized additive model (qgam).

Methods: Plasma Δhs-cTnT from patients selected with a time variation of 1 to 6 hours were collected over a 6-year period. The absΔhs-cTnT-to-relΔhs-cTnT relationship was fitted using qgam, after ordered quantile-based normalization (OQN) to reduce the influence of extreme values.

Results: The qgam regression curve was nonlinear. Classifying patients (n=9753) above the recommended relΔhs-cTnT and predicted absΔhs-cTnT cut-offs as positive, the MI diagnosis rates were similar, and more reliable using the OQN-transformed data-based qgam, as compared to the untransformed data-based one.

Conclusions: Through an optimized qgam-based approach accounting for heavy-tailed distributions, absolute Δhs-cTnT are provided for the corresponding relative Δhs-cTnT cut-offs.

Keywords: high-sensitivity cardiac troponin, variations, myocardial infarction.

Introduction

Cardiac troponin change (ΔcTn) is the cornerstone of myocardial infarction/injury (MI) diagnoses. When cTn values are >99th percentile URL (99PURL), a >20% rise and/or fall directs the diagnosis towards acute MI, whereas a ≤20% change suggests chronic myocardial injury [1]. When the initial baseline cTn value is ≤99PURL, a relative change >50% is in favor of MI, this relative cut-off taking into account both analytical and biological variations. The 4th Universal Definition of MI (4UDMI) mainly considers relative ΔcTn, but it also presents the advantage of absolute ΔcTn. The extent to which absolute or relative change is preferable for MI diagnosis is an old debate. Ten years ago, Reichlin et al showed a 2-hour absolute change in high-sensitive cardiac troponin T (absΔhs-cTnT) of higher diagnostic accuracy for acute MI than the relative change (relΔhs-cTnT), regardless of whether the baseline cTn levels were low or high [2]. Similarly, Mueller et al demonstrated that absΔhs-cTnT performs better than relΔhs-cTnT for the diagnosis of acute coronary syndrome (ACS) and acute non-ACS-related troponin increases [3]. Indeed, given that the rise and/or fall of cTn often exceeds 20% in both these contexts, and does so systematically in acute cardiac diseases, the "diagnostic overlap" explains why relΔhs-cTnT fails to rule-in non–ST-segment elevation MI (NSTEMI). In accordance, and based on these two main publications, the 4UDMI underlines that "*absolute cTn changes appear superior to relative percent changes with hs-cTn assays (…) especially when the initial value is increased*", and claims that "*the use of a fixed absolute value change criteria (…) provides greater sensitivity*" [1]. For greater changes, recommendations rely on absΔhs-cTnT-based diagnostic criteria, notably 5 times the 99PURL with normal baseline value for MI associated with percutaneous coronary intervention (PCI-related type 4a MI), or 10 times for MI associated with coronary artery bypass grafting (CABG-related type 5 MI) [1]. Furthermore, the recent 2020 ESC Guidelines for the management of ACS reminds that cTn elevations beyond 5-fold the URL have high (>90%) positive predictive values for acute type 1 MI [4]. Many MI-related studies provided relevant absΔhs-cTnT results, for various specific contexts; therefore, the question that arises is to what relative variations these results correspond. To answer this, we modeled the absΔhs-cTnT-to-relΔhs-cTnT relationship using a quantile nonparametric additive regression model (qgam) [5], in order to provide different corresponding Δhs-cTnT cut-offs.

Materials and Methods

A total of 218,063 hs-cTnT tests were assayed at our laboratory (Pitié Salpêtrière-Charles Foix University Hospital, AP-HP, Paris, France) over a 5.8-year period (April 2012 to January 2018), and extracted from the laboratory information system (GLIMS® software, MIPS-CliniSys, Chertsey-Surrey, UK). Of these, 9,753 were serial tests from patients aged 18-100 years and selected with serial time variations of 1 to 6 hours (Figure 1). Plasma hs-cTnT was assayed using

an electrochemiluminescent immunoassay on two Modular®E170 (Roche, Mannheim, Germany) [6]. Outliers were not removed, but ties were excluded (n=94 repeated pairs of absΔhs-cTnT and relΔhs-cTnT). Nevertheless, given the extremely tail-heavy distributions of absΔhs-cTnT and relΔhs-cTnT, which would make the qgam regression less reliable, both these datasets were transformed using an ordered quantile normalization (OQN), using the 'orderNorm' function from the 'bestNormalize' R package. This transformation is a rank-based procedure by which the values are mapped to their percentile, which is then mapped to the same percentile of the normal distribution. After the qgam regression, the transformed predicted values were inverted via the 'predict' function from the same R package.

The median quantile of the absΔhs-cTnT-to-relΔhs-cTnT regression was fitted using the 'qgamV' function of the 'mgcViz' R-package, which allows a graphical visualization of qgam models ('qgam' R-package) [7, 8]. The 'qgamV' function was programmed with cubic regression spline smooths ('cr'), and base dimensions chosen high enough (k=30) to allow sufficient degrees of freedom. The 'cqcheck' function from the 'qgam' R package was used to visually check what proportion of absΔhs-cTnT falls below the fitted median quantile, named $\widehat{P}(\text{absΔhs-cTnT}<\hat{\mu})$.

The predicted absΔhs-cTnT were first determined for different relΔhs-cTnT cut-offs, using the 'predict.gam' function of the 'mgcv' R-package. Secondly, following recommendations [1], the relΔhs-cTnT values were categorized as suggestive of MI if greater than ±50% (rise and/or fall) with one hs-cTnT value above the 99PURL, or ±20% with two hs-cTnT values above the 99PURL, considering the well-known Roche 99PURL cut-off of 14 ng/L. Then, in order to test whether absΔhs-cTnT may lead to MI proportions similar to relΔhs-cTnT, we reassessed the categorization by substituting the ±50% and ±20% cut-offs by the corresponding fitted absΔhs-cTnT values, for untransformed and OQN-transformed data-based models. A McNemar's Chi-squared test was used for comparisons of paired proportions, considering a *P*-value <0.05 as significant. All the statistics and qgam plots were computed in R (version 4.0.3, R Foundation, Vienna, Austria).

Results

Of the 9,753 Δhs-cTnT (men 70.1%; women 29.9%), the proportions of negative ("*fall*") and positive ("*rise*") changes were 42.9 and 57.1%, respectively. A focus of qgam regression curves is depicted on Figure 2, for untransformed (2A) and OQN-transformed data (2B), both displaying a nonlinear profile. Table 1 provides the main corresponding values between the two types of variation with, notably, absΔhs-cTnT values of –90.0, –43.8, +19.9, +52.0 ng/L for relΔhs-cTnT cut-offs of –50, –20, +20, +50%, respectively. The qgam checking plot from untransformed data (Figure 2C) shows that the higher the relΔhs-cTnT, the more the $\widehat{P}(\text{Δhs-cTnT(ng/L)}<\hat{\mu}$ deviates from 0.5, especially above 200% where $\widehat{P}(\text{Δhs-cTnT(ng/L)}<\hat{\mu}$ is <0.4 or >0.6. This is not the case for the OQN-based qgam checking plot (Figure 2D), which shows $\widehat{P}(\text{Δhs-cTnT(ng/L)}<\hat{\mu}$ closer to

0.5 from –50 to 500% relΔhs-cTnT, thus demonstrating OQN as an effective way to optimize the qgam regression. Considering the OQN-based qgam, replacing the –50, –20, +20, +50% relΔhs-cTnT cut-offs from recommendations by the corresponding predicted absΔhs-cTnT (i.e., –90.0, –43.8, +19.9, 52.0 ng/L, Table 1) resulted in similar rates of MI, with only 0.06% diagnostic discrepancies (P =0.68), which demonstrates the quality of the qgam regression. Conversely, still according to the OQN-based qgam, a 70 ng/L absΔhs-cTnT cut-off (i.e., 5-fold the 99PURL, known to have >90% positive predictive value for acute type 1 MI [4]) would correspond to a 70.9% relΔhs-cTnT cut-off. In the same way, a 140 ng/L absΔhs-cTnT (e.g., 10 times the 99PURL cut-off used for CABG-related type 5 MI diagnosis [1]), would correspond to a 132.0% relΔhs-cTnT cut-off. Considering now the untransformed data-based qgam, the same 70 and 140 ng/L cut-offs correspond to 74.8 and 151.2% relΔTnT cut-offs respectively. Classifying patients above these corresponding relΔhs-cTnT cut-offs as positive, the theorical proportions of MI were significantly different between the untransformed and OQN-transformed data based qgams (+0.53 and +1.07%, respectively; P <0.0001). Given the most reliable checking profile (Figure 2D compared to 2C), these minor -but significant- differences in theoretical MI proportions suggest the OQN-based qgam as most efficient for the prediction of high absΔhs-cTnT cut-offs.

Discussion

Few studies have compared the absolute *vs*. relative changes in hs-cTnT from the standpoint of diagnostic cut-offs. Among these, Reichlin et al. found an area under receiver operating characteristic curve (AUROC) of 0.95 (absΔhs-cTnT) *vs.* 0.76 (relΔhs-cTnT) for the diagnosis of AMI, with an AUROC-derived cut-off for a 2-hour absΔhs-cTnT of 7 ng/L [2]. Mueller et al. found an AUROC of 0.90 (absΔhs-cTnT) *vs*. 0.75 with a ROC-optimized rise or fall of 9.2 ng/L to rule out NSTEMI in patients admitted at the emergency room (ER), and of 6.9 ng/L to rule out NSTEMI in ACS patients [3]. Irfan et al. also confirmed the higher accuracy of absΔhs-cTnT over relΔhs-cTnT for AMI diagnosis, either 1 hour (AUROC 0.93 *vs*. 0.67) or 2 hours after being admitted in the ER (AUROC 0.95 *vs*. 0.75), with ROC-optimized absolute cut-offs of 5 and 7 ng/L, respectively [9]. Furthermore, Biener et al. calculated a sensitivity of 95.6% and specificity of 57.4% for NSTEMI diagnosis for a rising absΔhs-cTnT ROC-optimized cut-off of 8.8 ng/L, but a lower sensitivity (82.2%) and specificity (56.8%) for a 20% relΔhs-cTnT. They therefore recommended to consider absolute rather than relative hs-cTnT changes -and rising rather than falling- to diagnose NSTEMI [10]. All these studies highlight the higher accuracy of absΔhs-cTnT, as specified in the 4UDMI [1]. One must, however, remember the main drawback of using the absolute change: the fact that it is assay dependent. This makes our study of interest since, to the best of our knowledge, the correspondence between absolute and relative change has never been specifically assessed for the Roche hs-cTnT. This work provides a new approach, the qgam

regression, optimized through an ordered-quantile transformation to take account for tail-heavy distributions so that the spline basis functions are evenly distributed across relΔhs-cTnT (i.e., to concentrate the spline basis functions where there was more data). This method could serve for further studies aiming at modelling relationships between biomarkers with highly skewed distributions, and/or for which outlier removal should be avoided.

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Table 1. Corresponding cut-offs between absolute and relative Δhs-cTnT

No transformation			Ordered-quantile normalization		
Relative Δhs-cTnT (%)	Absolute Δhs-cTnT (ng/L)	(–ACL ; + ACL)	Relative Δhs-cTnT (%)	Absolute Δhs-cTnT (ng/L)	(–ACL ; + ACL)
–50	–93.7	(–100 ; –87.4)	–50	–90.0	(–96.3 ; –83.7)
–20	–36.8	(–42.6 ; –31.0)	–20	–43.8	(–49.6 ; –38.0)
–10	–17.9	(–23.0 ; –12.9)	–10	–14.0	(–19.1 ; –8.9)
–5	–9.0	(–13.7 ; –4.3)	–5	–8.1	(–13.0 ; –3.1)
0	–0.7	(–5.1 ; 3.8)	0	0	(–4.5 ; 4.5)
5	6.8	(2.6 ; 11.0)	5	6.1	(2.1 ; 10.1)
10	13.2	(9.1 ; 17.3)	10	10.6	(6.6 ; 14.6)
20	23.3	(19.2 ; 27.3)	20	19.9	(15.9 ; 23.9)
50	47.9	(43.5 ; 52.2)	50	52.0	(47.6 ; 56.5)
100	95.8	(90.2 ; 102)	100	105	(99.7 ; 111)
200	167	(160 ; 174)	200	179	(172 ; 185)
500	235	(227 ; 243)	500	271	(262 ; 280)
1,000	361	(351 ; 371)	1,000	450	(437 ; 463)
10,000	2,323	(2,269 ; 2,377)	10,000	2,050	(2,001 ; 2,098)

Legends

Figure 1.

Flowchart of the data selection process. Abbreviations: Δhs-cTnT: high-sensitive cardiac troponin T variation; LIS: laboratory information system.

Figure 2.

Qgam plots of the absolute Δhs-cTnT =*f* (relative Δhs-cTnT) regression determined using untransformed data (A) and ordered-quantile-normalized data (B) (n=9,753). The solid black curve and its gray area represent the predicted values and its two-standard deviations. The dashed black curves represent the predicted analytical change limit. The concentric gray contour lines represent the ten-by-ten percentiles of the nonparametric kernel density estimation. The qgam checking plots represent the proportion of absolute Δhs-cTnT that falls below the fitted quantile ($\widehat{P}$(Δhs-cTnT(ng/L)<$\hat{\mu}$)) for untransformed data (C) and ordered-quantile-normalized data (D), knowing that roughly 50% of absolute Δhs-cTnT values would be expected to fall below the fitted median quantile. The horizontal black dashed line represents the median quantile, the dots are the $\widehat{P}$(Δhs-cTnT(%)<$\hat{\mu}$ for each bin of relative Δhs-cTnT, and the black crosses are the 95% confidence intervals for median quantile. If the dots fall outside the confidence intervals, then $\widehat{P}$(Δhs-cTnT(%)<$\hat{\mu}$ might be deviating too much from the median quantile. Overall, the deviations from the theoretical median quantile are more reduced for normalized data-based qgam than for untransformed data-based ones. Abbreviations: $\widehat{P}$(Δhs-cTnT(ng/L)<$\hat{\mu}$): proportion of absolute Δhs-cTnT that falls below the fitted median quantile; Δhs-cTnT: high-sensitive cardiac troponin T variation; qgam: quantile generalized additive model.