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Diagnosis of acute myocardial infarction in hemodialysis patients may be feasible by comparing variation of cardiac troponins during acute presentation to baseline variation.

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ABSTRACT

Acute myocardial infarction (AMI) is defined as a dynamic change in cardiac troponin (cTn) with at least one cTn value exceeding the 99th percentile of a reference population in combination with typical clinical symptoms. In hemodialysis (HD) patients, a broad range of cTn concentrations is found, partially due to patient-specific comorbidities. Therefore, the 99th percentile cannot be used in HD patients and decision algorithms to diagnose AMI should be based on temporal variations of troponin.

In this study, relative and absolute variations of cTn in a large population of asymptomatic hemodialysis patients were established during a period of 15 months. Patients were stratified according to their history of coronary artery disease (CAD). An intra-individual long term variation of 23% for cTroponin I (cTnI) and 12% for cTroponin T (cTnT) was found for patients without a history of CAD. The corresponding reference change values (RCVs) were 69% and 39% respectively. For patients with a history of CAD this variation was 29% for cTnI and 10% for cTnT, with RCVs of 86% and 35% respectively.

During follow up, 27 HD patients developed an acute myocardial infarction (AMI). During these events, irrespective of CAD history, cTnI increased > 172% and cTnT increased > 97% above baseline cTn as measured during clinically stable periods three months separate to the event.

Therefore, if a HD patient has symptoms of an acute event and a cTn increase that exceeds the RCVs described here, AMI may be suspected. If the troponin increase exceeds 172% for cTnI or 97% for cTnT, AMI is likely.

1. Introduction

Acute myocardial infarction (AMI) is defined as a change in cardiac troponin (cTn) with concordant clinical symptoms and at least one cTn result exceeding the 99th percentile of a reference population [1]. For healthy people, the 99th percentiles have been thoroughly investigated using sensitive cTn assays and vary between different assays and populations [3–7]. Recent reports use the relative or absolute changes in cTn levels as a diagnostic tool for ischemic myocardial damage [8–12]. A change in cTn concentration that exceeds the reference change value (RCV) is considered clinically significant and may suggest acute myocardial necrosis.

In hemodialysis (HD) patients the dynamics in cTn concentration is more complicated. Patients with end stage renal disease (ESRD) have higher mean cTn levels and 99th percentiles compared to healthy individuals and large intra-individual variation exists [14–20]. Moreover, many patients have a history of coronary artery disease (CAD), a predisposition of increased cTn concentration [17,21]. Due to a higher baseline cTn concentration and a higher intra-individual variation in cTn, the relative change in cTn levels during an acute event in hemodialysis patients differs from the normal population [16,18].

Despite these reports, a description of 'normal' baseline variation within a population of chronic stable HD patients has, to the best of our knowledge, not yet been published. Importantly, roughly 50% of patients on dialysis suffer from CAD which might impact the concentration and variation of cTn during stable baseline period. This makes analysis of cTn variation stratified into patients with or without a history of CAD essential.

The first goal of this study was to establish the baseline variation of cTn in a large population of clinically stable HD patients stratified according to history of CAD. The second goal was to establish a threshold

Abbreviations: hs-cTnT, high-sensitivity cardiac troponinT; NSTEMI, non–ST-elevation myocardial infarction; RCVs, reference change values; II, index of individuality; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; UAP, unstable angina pectoris; CVi, within-individual biological imprecision; CVt, coefficient of the total imprecision; CAD, coronary artery disease; CDK, chronic kidney disease; ESRD, end stage renal disease.

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of 'excess' variation compared to patient specific baseline variation that may be used in the diagnostic work-up of suspected AMI.

2. Material and methods

2.1. Patient cohort

In this longitudinal cohort study, all chronic HD patients of the Catharina Hospital Eindhoven, The Netherlands were included. Patients were eligible for inclusion if they were ≥ 18 years of age and were on hemodialysis treatment for at least two months. Patients were included between May 1, 2007 and May 31, 2012 and were followed for a maximum period of 35 months. During this study, a switch in measurement methods from cTnI to hs-cTnT has occurred, leading to inclusion in either the cTnI -or hs-cTnT cohort, or both. Censoring events were transferred to other dialysis clinics, transplantation, death or end of dialysis. Patients were treated according to national quality guidelines, with a minimum hemodialysis frequency of three times per week for at least 4 h with a target eKt/V > 1.2 per dialysis session. Patient characteristics (gender, age and dialysis vintage) and the history of CAD (documented as coronary artery syndrome, myocardial infarction, coronary artery stenosis seen on coronary angiography or the performance of acute cardiac endovascular procedure) were collected from the medical patients' charts. During the study period the occurrence of AMI was scored. This study was conducted according to the declaration of Helsinki and approved by the Medical Ethical commission of Catharina Hospital according to Dutch law.

2.2. Sample collection

During the course of our study every 3-monthly routine laboratory control included either cTnI or cTnT or both for a total period of 15 months for each patient. Within the study period, cTnI was measured from May 1st, 2007 until January 31, 2011 and hs-cTnT was measured from January 1st, 2011 until May 31, 2012. Samples obtained within a three month period after cardiac surgery, or directly after percutaneous coronary intervention (PCI) were excluded from analysis.

The procedure of blood collection was in accordance with national legal requirements and approved by the medical ethical commission of our institution. Blood samples were collected in heparinized tubes (Vacutainer ref. 368861, Becton Dickinson BV, Breda, The Netherlands) and were taken prior to dialysis. Laboratory analysis was performed within 4 h after collection of the samples.

2.3. Laboratory technique

cTnI was measured with the cTnI ultra assay on an Advia Centaur immunochemistry analyzer (Siemens Medical Solutions Diagnostics, the Hague, the Netherlands) and cTnT was measured with the hs-cTnT assay on a Cobas e601 immunochemistry analyzer (Roche Diagnostics, Almere, the Netherlands) using the manufacturer's assay kits. The TnI-Ultra troponin kit is a second-generation, high-sensitivity test with an analytical CV of 10.7% at a concentration of 27 ng/L [3]. The hs-cTnT troponin kit is a fourth generation, high-sensitivity test with an analytical CV of 7.8% [9]. In our laboratory, the CVs obtained for the lowest level of QC material were 9.1% for cTnI (at 58 ng/L) and 4.9% for hs-cTnT (at 24 ng/L).

2.4. Absolute percentiles of cTn

The cTnI and hs-cTnT concentration percentiles were calculated for patients with and without a history of CAD separately. Data from one to five consecutive measurements in this period were used for the analysis of the absolute percentiles of cTn, and at least two consecutive measurements for the analysis of absolute cTn variation. To obtain absolute intra-individual variation in cTn, the greatest difference between cTn measurements was calculated per patient, either with or without a history of CAD, by subtracting the lowest from the highest concentration. cTn concentrations < 3 ng/L (hs-cTnT) and < 10 ng/L (cTnI), which represent values less than the limits of detection, were set to 3 ng/L and 10 ng/L.

2.5. Baseline cTn variation

Only patients with at least two cTn measurements were included in this analysis. To calculate the 95th percentile of intra-individual change in concentration, absolute changes between two cTn results with an interval of 3, 6, 9, 12 or 15 months were used.

For calculation of RCVs, hs-cTnT and cTnI values below the limit of detection (3 ng/L and 10 ng/L respectively) were excluded from analysis. All remaining patients with 2 or more cTnI or hs-cTnT results were analyzed. RCVs were evaluated with both normal and log-normal approaches as described [9]. Using a normal approach, we calculated within-individual biological imprecision (CV_i) from the coefficient of the total imprecision (CV_t) of cTn at all time points, as follows: $CV_i = \sqrt{CV_t^2 - CV_a^2}$. Herein CV_a is analytical variation found to be 7.8% with the Cobas e601 hs-cTnT assay [9] and 10.7% with the Siemens Advia Centaur cTnI [8]. The inter-individual variation (CV_g) is calculated as follows: $CV_g = \sqrt{(CV_t^2 - CV_i^2 - CV_a^2)}$. The limits of the symmetrical RCV were determined as: $RCV = Z \times \sqrt{2 \times \sqrt{CV_a^2 + CV_i^2}}$, where $z = 1.96$ (z score for 95% confidence). The median normal deviation of the log-normal distribution (σ) was calculated from the median CV_t (as a decimal value), as: $\sigma = \sqrt{1n(CV_t^2 + 1)}$. The asymmetrical limits for the upward (positive) value for the log-normal RCV (RCV^+) and for the downward (negative) value for the log-normal RCV (RCV^-), were calculated as follows: $RCV+ = {}^{(z \times \sqrt{2 \times \sigma})-1}_{e} \times 100$, $RCV^- = {}^{(-z \times \sqrt{2 \times \sigma})-1}_{e} \times 100$, where $z = 1.96$ (z-score for 95% confidence). The index of individuality (II) was calculated with the simplified equation: $II = CV_i/CV_g$, where CV_g is the inter-individual CV. We could use the simplified equation because for cTnI and hs-cTnT, CV_a was much smaller than CV_i.

2.6. Delta cTn during AMI

All cTn measured in patients after the onset of symptoms of AMI (prolonged acute chest pain, dyspnoea or nausea), up to a maximum of 24 h, were collected and compared to patients own 'baseline' cTn measured in a stable period. cTn in patients was measured after onset of symptoms at first presentation in hospital and at least once every after 3, 6 and/or 9 h thereafter up to 24 h after presentation. Patients with clear changes in ECG, indicating STEMI, and patients with unstable angina pectoris were excluded from analyses. A total of 27 patients experienced AMI; 19 patients during follow up with cTnI and 8 patients during follow up with hs-cTnT. Absolute and relative delta cTns were calculated by subtracting the cTn concentration during clinically stable periods three months separate to the event, from the cTn concentration during AMI. For the calculation of sensitivity and specificity, these delta cTns were compared to baseline variation in HD patients irrespective of their history of CAD.

2.7. Statistical analysis

Outliers were identified by the technique described by Reed et al. [20]. Statistical analyses were performed using chi-square test for binary patient characteristics and Mann–Whitney-U-test for continuous data analysis. Correction for parameters was performed with binary logistic regression analysis. Sensitivity and specificity of absolute and relative delta cTn during AMI were analyzed with ROC curves. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).