Automated Analysis of the 12-lead ECG in the Emergency Department: Association Between High-sensitivity Cardiac Troponin I and the Cardiac Electrical Biomarker

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Abstract: Timely detection of myocardial injury is essential for appropriate management of patients in emergency department (ED) evaluated for acute myocardial infarction. A novel electrocardiogram (ECG) metric, the Cardiac Electrical Biomarker (CEB), uses eigenvalue modeling of the 12-lead ECG and quantifies dipolar vs. multipolar forces. The goal of this project was to study association between the CEB and high-sensitivity troponin I (HsTnI). We conducted a retrospective study of patients, evaluated in the ED for acute myocardial infarction [n = 411; 57.6 ± 13.2 years; 186 (45%) men; 266 (64%) African-Americans]. Resting 12-lead ECG and HsTnI were measured at presentation and at 3, 6, and 9 hours after the initial measurement. The CEB was measured by the VectraplexECG System (VectraCor, Totowa, NJ). Patient-specific longitudinal analysis was performed to study association between the CEB with HsTnI changes over time. The CEB indicated myocardial injury in 116 (28.2%) study participants. HsTnI was significantly elevated during ED observation period in patients with myocardial injury, diagnosed by the CEB [median (interquartile range), 10.3 (5.2–31.4) vs. 6.3 (3.5–16.5) ng/L; $P = 0.002$]. In a mixed-effects linear regression adjusted for age, race, and sex, increasing HsTnI was associated with the CEB elevation [β-coefficient, 0.071 (95% confidence interval, 0.008–0.134); $P = 0.027$]. In conclusion, in patients in ED evaluated for acute myocardial injury, increasing values of HsTnI were associated with increasing values of the CEB, suggesting that myocardial injury is the mechanism that underlines acute changes in the CEB.

Key Words: electrocardiogram, emergency medicine, acute coronary syndrome, cardiac electrical biomarker

Each year, a large number of patients are evaluated in emergency departments (EDs) for acute myocardial infarction (AMI). AMI is diagnosed based on the history of present illness, 12-lead electrocardiogram (ECG), and cardiac biomarkers. Failure to identify patients in the early stages of AMI can result in failure to provide beneficial therapies. The third universal definition of AMI[1] requires a rise and/or a fall in cardiac troponin, with at least 1 troponin value above the 99th percentile. It is recommended that blood samples for troponin measurement are drawn at presentation and repeated 3–6 hours later to optimize clinical sensitivity for ruling in AMI. Traditional 12-lead ECG is less informative very early in the course of ST-elevation myocardial infarction (STEMI) and especially in non-STEMI.

Recently, new ECG technology was proposed to detect myocardial injury. Development of the novel VectraplexECG System with

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Cardiac Electrical Biomarker (CEB) or VectraplexAMI was based on factor analysis[2] with simplex optimization. Acute myocardial injury may result in heterogeneous electrical field.[3,4] VectraplexAMI index was developed by Schreck,[5] who postulated that CEB measures the degree of the multipolarity of the cardiac electrical field.

We conducted a retrospective study of adult patients in ED with available serial digital 12-lead ECGs and high-sensitivity troponin I (HsTnI) results, with the goal of determining whether myocardial injury is the mechanism that underlines acute changes in CEB. We hypothesized that the CEB correlates with HsTnI in patients admitted to ED with suspected AMI.

METHODS

Study Population

We retrospectively analyzed data from an ongoing prospective observational cohort study of patients in ED evaluated for AMI. Since January 2012, the original cohort enrolled consecutive patients who presented with symptoms suggestive of acute coronary syndrome (ACS) such as acute chest pain, shortness of breath, or other sensations presumably caused by myocardial ischemia. Patients 25 years or older were eligible for enrollment if treating clinicians suspected AMI and ordered an ECG and troponin measurement for further evaluation. Serial ECG and troponin measurements were performed at presentation and at 3, 6, and 9 hours after presentation at the discretion of treating clinicians. Each time, blood samples were drawn to measure troponin with the clinical assay (Access II AccuTnI assay; Beckman Coulter, Chaska, MN), an additional 5 ml of blood was obtained, processed, and stored in a −80°C freezer. HsTnI was measured in batches, at least 1 month after the index presentation, using the Abbott Laboratories' (Abbott Park, IL) research-use ARCHITECT *STAT* HsTnI assay. The study was approved by the Johns Hopkins Institutional Review Board, and all study participants signed a written informed consent form.

For this retrospective ancillary study, participants were included if the following inclusion criteria were fulfilled: (1) patients were presented to the Johns Hopkins Hospital ED from January 16, 2012 to June 26, 2012; (2) serial digital 12-lead ECGs were recorded at presentation and at 3, 6, and 9 hours after presentation; (3) serial HsTnI results were available at presentation and at 3, 6, and 9 hours after presentation. Participants were excluded if recorded 12-lead ECGs (1) had missing leads or leads placement error; (2) had frequent premature ventricular contractions; and (3) had large visible baseline wandering or noise. Patients with ventricular pacing or atrial fibrillation/flutter with rate for ventricles above 90 bpm were excluded as well. Of note, patients with typical STEMI on ECG were excluded from the original cohort, given that there is no diagnostic dilemma with the diagnosis and management of STEMI. The exclusion of patients with STEMI also allows us to evaluate the CEB in patients in whom standard ECG is nondiagnostic.

High-sensitivity Troponin Assay

HsTnI was measured using the Abbott Laboratories research-use ARCHITECT *STAT* hsTnI assay. The 99th percentile URL of this

assay is 34.2 ng/L for males, 15.6 ng/L for females, and 26.2 ng/L overall. The limit of detection is 1.2 ng/L.[6] HsTnI data were used for research purposes only.

ECG Analysis

Serial digital ECGs of the study participants were extracted from the JHH ECG MUSE database (GE Healthcare, Wauwatosa, WI) for subsequent analysis. All 12-lead ECGs used in the study were recorded using the GE-Marquette MAC 5000 ECG system (GE Medical Systems, Milwaukee, WI) at the JHH ED in the time period from January 16, 2012 to June 22, 2012. Each 12-lead ECG was reviewed and clinically evaluated by 2 investigators (D.G. and L.G.T.), blinded to all other clinical data. For each ECG, investigators evaluated cardiac rhythm and determined the presence or absence of left bundle branch block, right bundle branch block, pathological Q wave, ST segment elevation or depression, and nonspecific ST-T changes. The first ECG, recorded at the JHH ED, was compared with the previously recorded ECG (if available), and observed ECG abnormalities were categorized as "new," or "old." Each ECG was adjudicated and included into 1 of 5 categories: new STEMI, new non-STEMI, new nonspecific ST-T changes, unchanged abnormal ECG, and normal ECG. Inter-reader agreement was evaluated, and in case of disagreement, the final ECG diagnosis was based on the third ECG reader (JHH attending cardiologist) assessment.

The CEB for each ECG was calculated automatically by VectraplexECG System, as previously described[5] and provided by Vectracor, Inc. (Totowa, NJ). A predefined threshold was used. We considered that values of the CEB greater than 94 units indicated myocardial injury, as recommended by the manufacturer.

Outcomes

All clinical, laboratory, and ECG data were reviewed by an independent endpoints adjudication committee, blinded to the results of the VectraplexECG analysis. AMI was defined according to the guidelines,[1] where there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Statistical Analysis

All statistics were computed using STATA 13 (StataCorp LP, College Station, TX). Results are presented as mean ± SD for normally distributed variables and as median and interquartile range for skewed continuous variables. Normally distributed continuous variables were compared using the Student t test. The Wilcoxon rank-sum test was applied to skewed continuous variables—HsTnI and the CEB. Dichotomized variables were compared by Pearson χ^2 test. Spearman rank correlation coefficient r_s was calculated to quantify relations between HsTnI and the CEB. Then HsTnI and the CEB variables were log-10-transformed to normalize distribution, for subsequent regression analysis.

To determine whether the patient-specific changes in the CEB are associated with the HsTnI changes during observation in the ED, we ran the generalized least squares random-effects linear regression analysis. We accounted for correlation of the repeated troponin and ECG observations by including a random intercept for each patient and control for the patient's CEB (centered). Adequate fitting of the model was checked to ensure that the specified quadrature has adequately approximated the likelihood. The model was adjusted by age, sex, and race.

RESULTS

Study Population

The study population consisted of middle-aged adults (57.6 ± 13.2 years), 65% were African-Americans (n = 266), and 55% were women (n = 225). Among the African-Americans, there were more women than men [159 (60%) vs. 107 (40%);

$P = 0.006$], whereas an opposite sex composition was observed in non-African-Americans [66 (45.5%) women vs. 79 (54.5%) men; $P = 0.006$]. Risk factors of coronary heart disease were frequently observed: 263 patients (64%) had hypertension, 131 patients (32%) had diabetes mellitus, and 263 patients (64%) were current or former smokers. Approximately a quarter of study participants (n = 106; 25.8%) were current or former cocaine users.

ECG Analysis: The VectraplexAMI Index

The CEB indicated myocardial injury in 116 (28.2%) study participants. Clinical characteristics of patients with and without myocardial injury are shown in Table 1. Patients with myocardial injury as detected by the CEB were older, more likely to have hypertension, hypercholesterolemia, and heart failure. HsTnI was significantly elevated during ED observation period in patients with myocardial injury, diagnosed by the CEB (Table 1).

There were no patients with typical STEMI ECG presentation among study participants. Pathological Q wave and right bundle branch block were more frequently observed, whereas a normal 12-lead ECG was less frequent in the myocardial injury group (Table 1).

Association Between High-sensitivity Cardiac Troponin I and the Cardiac Electrical Biomarker

During the first 3 hours of observation at the ED, HsTnI and the CEB did not correlate. However, statistically significant correlation was found and strengthened during the next 6 hours of observation ($r = 0.163$; $P = 0.036$ and $r_s = 0.179$; $P = 0.018$), and further at the fourth 3-hour period ($r = 0.227$; $P = 0.026$ and $r_s = 0.217$; $P = 0.034$). Figure 1 illustrates correlation between HsTnI and the CEB. Longitudinal changes in HsTnI and CEB are presented on Figure 2.

In the univariate generalized least squares random-effects linear regression model, changes in HsTnI were associated with the changes in the CEB: β-coefficient, 0.083 (95% confidence interval, 0.022–0.144); $P = 0.008$. Thus, increasing HsTnI by an order of magnitude (10-fold increase) was associated with 8.3% increase of the CEB value. After adjustment for age, race, and sex, association between HsTnI and the CEB remained significant: β-coefficient, 0.071 (95% confidence interval, 0.008–0.134); $P = 0.027$.

DISCUSSION

This study showed that in patients evaluated for AMI in the ED, increasing by an order of magnitude HsTnI is associated with simultaneously increasing value of the CEB. Therefore, an underlying myocardial injury is an important mechanism of acute changes in the CEB in this study population.

Multipolar vs. Dipolar Forces in the Cardiac Electrical Field

The cardiac electrical field of a healthy subject is primarily dipolar.[7] At the same time, it is known that occurrence of local myocardial injury results in the development of the voltage gradient between the ischemic and nonischemic myocardium.[8] The vector of myocardial injury current differs from the heart vector. Thus, occurrence of myocardial injury leads to the appearance of multipolar cardiac electrical field.[9] The CEB quantifies the quality of the cardiac electrical field, and in particular, whether the cardiac field is predominantly dipolar, or whether multipolar forces in the cardiac electrical field are present, and how much. VectraplexAMI is provided for the end-user as a single number. In this study, we used the CEB threshold of 94 units, as recommended by the Vectracor, Inc., for detection of myocardial injury.[5] Additional studies are needed to define optimal threshold for discriminating between no AMI and AMI cases.

Simplex optimization (nonlinear optimization technique) was applied to the ECG signal to obtain and reconstruct the ECG

TABLE 1. Clinical and ECG Characteristics of Patients with and Without Myocardial Injury as Determined by VectraplexAMI Index

|	VectraplexAMI ≤94 (N = 295)	VectraplexAMI >94 (N = 116)	*P*
Age (SD), yr	**56.7 (12.5)**	**59.9 (14.7)**	**0.039**
Men, n (%)	136 (46.1)	50 (43.1)	0.583
African-Americans, n (%)	186 (63.1)	80 (69.0)	0.259
Hypertension, n (%)	**180 (61.0)**	**83 (71.6)**	**0.045**
Diabetes Hx, n (%)	95 (32.2)	36 (31.0)	0.819
Heart failure, n (%)	**66 (22.4)**	**38 (33.8)**	**0.029**
Current or former smokers, n (%)	186 (63.1)	77 (66.4)	0.527
Current or former cocaine users, n (%)	72 (24.4)	34 (29.3)	0.306
Hypercholesterolemia, n (%)	**126 (42.7)**	**64 (55.2)**	**0.023**
Family Hx CHD, n (%)	105 (35.6)	44 (37.9)	0.657
HsTnI #1, median (IQR)	**6.3 (3.5–16.5)**	**10.3 (5.2–31.4)**	**0.002**
HsTnI #2, median (IQR)	**6.2 (3.2–14.8)**	**9.2 (4.6–28.6)**	**0.021**
HsTnI #3, median (IQR)	**6.55 (3.5–16.0)**	**12 (4.8–30.4)**	**0.018**
HsTnI #4, median (IQR)	6.55 (3.55–13.9)	12.45 (4.7–32.7)	0.076
Pathological Q wave on ECG, n (%)	**38 (12.9)**	**40 (34.5)**	**<0.0001**
Normal ECG, n (%)	**122 (41.4)**	**15 (12.9)**	**<0.0001**
Right bundle brunch block, n (%)	**5 (1.7)**	**15 (12.9)**	**<0.0001**
Left Bundle branch block, n (%)	6 (2.0)	3 (2.6)	0.731

CHD, coronary heart disease; Hx, history; IQR, interquartile range.
Bold indicates statistical findings.

signal,[2,10–13] and to calculate a proprietary CEB. This is the first study to examine whether myocardial injury (as determined by changes in hsTnI) is associated with acute changes in the CEB. Our findings suggest that in patients with high pretest probability of AMI, an underlying myocardial injury, as detected by an increasing HsTnI, is associated with elevation of the CEB.

Clinical Implications of Association Between HsTnI and the CEB

Surface ECG is traditionally used for the diagnosis of an acute myocardial injury.[1,14] Historically, typical ECG presentation of AMI [acute ST segment elevation with Q (QS) wave formation] was a major diagnostic criterion, equally important for AMI diagnosis, along with clinical presentation, and elevation of cardiac biomarkers.[14] However, with the advent of cardiac troponins, it has been demonstrated that the sensitivity and specificity of the acute changes in the ST segments on an ECG are modest, with sensitivity ranging from 50% to 100%, and specificity ranging from 71% to 91%,[15,16] and inconsistent among individual readers. Besides differences in the accuracy of myocardial injury detection between cardiac troponin and ECG, other dissimilarity is apparent. Traditional ECG interpretation not only suggests the presence or absence of myocardial injury but at the same time determines localization and extent of the myocardial injury, predicting the possible culprit vessel and
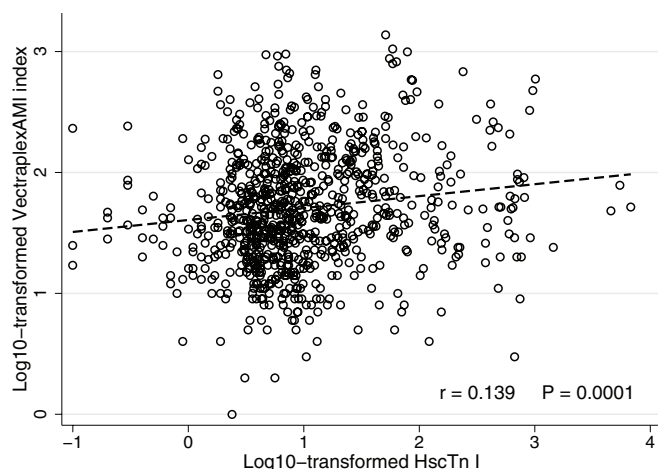
FIGURE 1. Correlation between high-sensitivity cardiac troponin I and CEB in patients in emergency department.
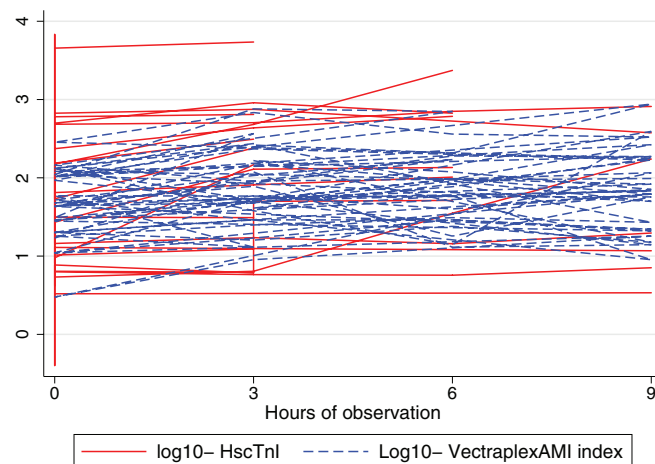
FIGURE 2. Spaghetti plot of longitudinal changes in high-sensitivity cardiac troponin I and CEB in patients, observed at the Johns Hopkins Hospital Emergency Department.

complications. This was especially important in the era of conservative AMI management. However, it does not make any difference for current therapeutic strategies.[17] In addition, it is worth noting that while cardiac troponin quantifies myocardial injury by a single number, ECG AMI diagnosis is dichotomized (yes or no), and requires complex knowledge of pattern recognition. The Silvester score[18–22] is a successful example of ECG quantification of the MI size, but its accuracy is limited in the case of multiple MIs. Furthermore, to our knowledge, no prior methods have quantified acute myocardial injury on ECG. Quantification of the J-point amplitude dynamic changes is not sufficient for such a purpose.

Thus, in the current realm of clinical practice, the CEB offers a simple 1-number quantification of the myocardial injury on the surface ECG. Ease of use, low cost, wide availability, and a possibility of the continuous monitoring of the surface ECG in the ED make the CEB promising for future use, especially in the areas with limited resources.[23] Future validation of the CEB in the prospective study is needed.

Limitations

We have to acknowledge several limitations that have to be taken into account. First, these observations are derived from a retrospective analysis from a single tertiary cardiac center, and need to be replicated in prospective studies. Second, we excluded obvious STEMI cases with clear ECG presentation and therefore, possibly created bias for assessment of the CEB. In the case of STEMI cases, association between the CEB and HsTnI could be even more prominent. However, we thought to test the CEB in the most clinically challenging scenario: in cases when traditional ECG assessment is not informative.

CONCLUSIONS

In conclusion, in patients in ED evaluated for acute myocardial injury, increasing values of HsTnI were associated with increasing values of the CEB, suggesting that myocardial injury is associated with acute changes in the CEB in the population of patients with high pretest probability of acute myocardial injury.

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DISCLOSURES

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