

## Consensus

# Diagnostic Utility of Cardiac Biomarkers in Discriminating Takotsubo Cardiomyopathy From Acute Myocardial Infarction

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## ABSTRACT

**Background:** Takotsubo cardiomyopathy (TC) mimics acute myocardial infarction (AMI). We postulated that ventricular dysfunction in TC in the absence of significant myocardial necrosis would produce higher B-type natriuretic peptide (BNP)/troponin T (TnT) and BNP/creatinine kinase MB fraction (CKMB) ratios than in AMI.

**Methods and Results:** We studied 58 consecutive TC (age  $65.8 \pm 82.9$ ) and 97 AMI patients (age  $59.8 \pm 83.4$ ). The ratios of BNP/TnT and BNP/CKMB were calculated with the use of first simultaneously drawn laboratory values. Receiver operating characteristic curves were used to distinguish TC from AMI with 95% specificity based on cardiac biomarker ratios. Median BNP/TnT and BNP/CKMB ratios were, respectively, 1,292 [interquartile range 443.4–2,657.9] and 28.44 [13.7–94.8] in the TC group and 226.9 [69.91–426.32] and 3.63 [1.07–10.02] in the AMI group ( $P < .001$ ). TC can be distinguished from AMI with 95% specificity with the use of BNP/TnT ratio  $\geq 1,272$  (sensitivity 52%) and BNP/CKMB ratio  $\geq 29.9$  (sensitivity 50%).

**Conclusions:** The value of BNP is significantly higher in TC than in AMI. Early BNP/TnT and BNP/CKMB ratios help to differentiate TC from AMI with greater accuracy than BNP alone. (*J Cardiac Fail* 2014;20:2–8)

**Key Words:** Takotsubo cardiomyopathy, cardiac biomarkers, electrocardiogram and acute myocardial infarction.

Takotsubo cardiomyopathy (TC) is a disorder of transient ventricular systolic dysfunction thought to be precipitated by severe emotional or physical stress.<sup>1–4</sup> Echocardiography and/or ventriculogram typically shows left ventricular apical ballooning.<sup>1,5</sup> Patients usually present with chest

pain with electrocardiographic (ECG) changes mimicking an acute myocardial infarction (AMI). Approximately 1%–2% of patients presenting with acute coronary syndrome (ACS) are ultimately diagnosed with TC.<sup>6,7</sup>

An elevated plasma concentration of B-type natriuretic peptide (BNP) is an established marker of left ventricular dysfunction.<sup>8</sup> Both troponin T (TnT) and creatinine kinase MB fraction (CKMB) are elevated in the setting of membrane leak caused by acute myocardial necrosis, whereas the production and release of BNP is related to ventricular distention with or without myocyte necrosis.<sup>8–10</sup> It is known that BNP and TnT are increased in both TC and AMI.<sup>10,11</sup> However, because TC is a disease primarily causing distention of the ventricles and characterized by reversible myocardial dysfunction without necrosis, a greater increase in plasma BNP compared with TnT or CKMB has been demonstrated, compared with AMI.<sup>10,12–15</sup> TC has also been associated with significant QTc interval prolongation on ECG.<sup>16,17</sup>

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Manuscript received August 10, 2013; revised manuscript received December 8, 2013; revised manuscript accepted December 9, 2013.

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See page 8 for disclosure information.

1071-9164/\$ - see front matter

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<http://dx.doi.org/10.1016/j.cardfail.2013.12.004>

Currently, TC is a diagnosis of exclusion according to the modified Mayo Clinic Criteria, which involve performing coronary angiography to confirm the absence of obstructive coronary artery disease (CAD).<sup>18</sup> In the present study, we sought to determine if we could improve our noninvasive ability to distinguish between TC and AMI with the use of cardiac biomarker ratios obtained early during presentation.

## Methods

This was a retrospective cohort analysis (matching for cases and respective control subjects) done at a single tertiary care center (Cleveland Clinic Foundation, Cleveland, Ohio), after appropriate Institutional Review Board approval. We studied 225 consecutive TC patients from the period of January 2006 to February 2012 based on the following criteria of diagnosis: acute presentation with ACS-like symptoms, with acute ST-segment and T-wave changes on the ECG and rise in the cardiac enzymes (CKMB and TnT), typical echocardiographic and angiographic findings (ballooning of the left ventricle), complete reversibility of ejection fraction (EF) based on repeated transthoracic echocardiography, and absence of significant (>50%) CAD and acute plaque rupture based on angiography.

To be included in the study, a patient had to have had biomarkers determined at the time of admission. We excluded the following patients: <18 years old, known chronic kidney disease (CKD) stage III–V with estimated glomerular filtration rate <60 mL/min according to the Modification of Diet in Renal Disease equation,<sup>19</sup> acute kidney injury (AKI) at time of admission according to the criteria proposed by the Acute Dialysis Quality Initiative group,<sup>20</sup> history of congestive heart failure (CHF) with a history of left ventricular ejection fraction (LVEF) <45% on the last available echocardiogram, known nonischemic cardiomyopathy, microbial and toxic myocarditis, septic shock, acute pulmonary embolism, and severe aortic stenosis on the last available echocardiogram.

A total of 225 consecutive patients with TC were studied. 118 patients were excluded because of unavailability of simultaneously drawn first available BNP, CKMB, and TnT. Of the others, 22 patients did not meet our diagnostic criteria for TC. Sixteen patients had preexisting CKD. Eight patients were excluded because of AKI. Two patients were excluded because of preexisting CHF. One patient was excluded because of concurrent chemotherapy that was potentially cardiotoxic. After applying the exclusion criteria, 58 patients (case subjects) were selected, and their baseline clinical characteristics were recorded by manually reviewing their electronic medical records.

Subsequently, a control group of patients that met the criteria of AMI based on the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction were assembled.<sup>21</sup> Ninety-seven such AMI patients were selected to keep the study power >90% to show a significant difference in the 2 groups of TC and AMI. The QTc interval duration was recorded and initial ECG was analyzed for acute ST-segment and T-wave changes, and both, case and control subjects were divided into ST-segment elevation and non-ST-segment elevation groups. QTc was deemed to be prolonged if it was >470 ms.<sup>22,23</sup> These variables were followed for 72 hours after admission. All case and control subjects underwent coronary angiography during hospitalization in a standard

fashion. The degree of coronary obstruction was deemed to be significant in the setting of >50% stenosis in a major epicardial vessel.

Although it is true that atypical variants of TC are less clinically confusing with coronary artery disease, our focus was to correlate the first available cardiac biomarkers regardless of echocardiographic findings. We did not study echocardiographic data for global versus segmental dysfunction. The study was done to retrospectively compare initial cardiac biomarker profiles in TC and AMI.

## Laboratory Measurements

We recorded first simultaneously available levels of TnT, CKMB, and BNP after presentation. All measurements for TnT and CKMB were done by electrochemiluminescence immunoassay technique with the use of the Roche Cobas 6000e analyzer (Roche Diagnostics). All determinations of BNP were done by chemiluminescence immunoassay technique with the use of the Advia Centaur analyzer (Siemens Medical Solutions Diagnostics). As such, we standardized the laboratory analysis for all study subjects.

## Statistical Methods

Continuous measures were described with the use of mean and standard deviation or median and interquartile range (IQR) and were compared between groups with the use of standard *t* testing or Wilcoxon rank sum test. Categorical measures were summarized as frequency and percentages and were compared between groups with the use of chi-square test. Receiver operating characteristic (ROC) analyses of absolute values of BNP, TnT, and CKMB, and 2 ratios (BNP/TnT and BNP/CKMB) were performed to assess their ability in differentiating TC case subjects from AMI control subjects. We wanted to assess whether the ratio of BNP/TnT or BNP/CKMB would be better in distinguishing TC from AMI compared with individual cardiac biomarker values alone. Therefore, paired comparison was performed on the area under the ROC curve (AUC) of BNP, TnT, CKMB, and the ratios BNP/TnT and BNP/CKMB. In addition, analysis of ECG findings revealed that presence of QTc interval prolongation was more common in TC case subjects than in AMI control subjects. Logistic regression model was used to compare the distinguishing ability of combination of BNP/CKMB and presence of QTc interval prolongation compared with the BNP/CKMB ratio alone. All analyses were performed with the use of SAS 9.2 and R 2.12.1 software.

## Results

A total of 155 patients were studied from January 2006 to February 2012. Of these, 58 were diagnosed with TC (case subjects) and 97 had angiographically proven AMI (control subjects). Of the case subjects, 22/58 (38%) were found to have ST-segment elevation (STE-TC) and 36/58 (62%) had no ST-segment elevation (NSTE-TC) in their initial ECGs. In the control group, 38/97 (39%) had ST-segment-elevation MI (STEMI) and 59/97 (61%) had non-ST-segment-elevation MI (NSTEMI). Within the NSTEMI subgroup of the control subjects, most patients had significant multivessel disease. There were 7 patients with significant left main disease, 26 with significant

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