High Cardiac Troponin I Is Associated With Transesophageal Echocardiographic Risk of Thromboembolism and Ischemic Stroke Events in Non-Valvular Atrial Fibrillation Patients

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Background: Abnormalities in the left atrium (LA) detected on transesophageal echocardiography (TEE) are reliable predictors of thromboembolism in patients with atrial fibrillation (AF). Cardiac troponin I, a marker of subclinical myocardial damage, may also be a predictor of thromboembolic events in patients with AF. The relationship between cardiac troponin I and thromboembolic risk on TEE, however, remains unclear.

Methods and Results: TEE and laboratory data, including high sensitivity cardiac troponin I (hs-cTnI) and CHA2DS2-VASc score, were analyzed in 199 patients with non-valvular AF (NVAF). Patients were stratified into those with or without LA abnormality, defined as LA appendage flow velocity <20 cm/s or dense spontaneous echo contrast. On multiple logistic analysis of the clinical variables, hs-cTnI was associated with LA abnormality (95% CI: 1.0003–1.020, P=0.034). The area under the curve for LA abnormality increased on addition of hs-cTnI to CHA2DS2-VASc score. The incidence rate of ischemic stroke was higher in the high hs-cTnI group than in the low-hs-cTnI group (log-rank test, P<0.05).

Conclusions: Elevated hs-cTnI was independently associated with LA abnormality in NVAF patients. hs-cTnI level may be a useful biomarker for risk stratification of thromboembolism in NVAF patients.

Key Words: High-sensitivity cardiac troponin I; Non-valvular atrial fibrillation; Transesophageal echocardiography

Atrial fibrillation (AF) is a major risk factor for cardiogenic embolism, and CHADS2 and CHA2DS2-VASc scores have been used as risk stratification indices for evaluation of embolic risk in patients with non-valvular AF (NVAF). Cardiac troponin I, a sensitive marker of myocardial tissue injury,4 including acute coronary syndrome (ACS).5,6 Recent clinical studies have demonstrated that the release of high-sensitivity cardiac troponin I (hs-cTnI) is associated with thromboembolism in patients with AF.7,8 but the relationship between TEE parameters and hs-cTnI remains unclear. B-type natriuretic peptide (BNP) is also associated with LA thrombus and cardioembolic stroke.9,10 Therefore, the aim of the present study was to examine the relationship between cardiac biomarkers, including hs-cTnI, clinical risk factors for thromboembolism, TEE parameters and clinical events, including cerebral infarction, in patients with NVAF.

Methods

Subjects
We retrospectively evaluated 199 consecutive patients with NVAF (159 men; mean age, 64±10 years) who underwent TEE to determine potential embolic risk at Toyama University Hospital from December 2004 to February 2017. We excluded patients with infectious disease, acute cardiovascular disease, valvular heart disease or sinus rhythm on TEE. ACS was also excluded on electrocardiography. None of the patients was in the postoperative phase in this study. Baseline characteristics, including CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; 2 points)11 and CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years; 2 points, diabetes mellitus, stroke/transient ischemic attack; 2 points, vascular disease, age 65–74 years, sex category: female),12 were obtained for each patient from medical records. Blood samples were taken in the fasting
state immediately before TEE. Hs-cTnI was measured using chemiluminescent immunoassay on the ARCHITECT i2000SR (Abbott Diagnostics; analytical range, 0.0–50,000 ng/L). The lowest concentration measurable with a coefficient of variation of <20% is 1.3 ng/L, and lowest concentration measurable with a coefficient of variation of <10% is 4.7 ng/L; the 99th percentile upper reference limit for healthy subjects is 26.2 ng/L. In addition to routine biochemistry, BNP and D-dimer were also measured. The study was approved by the institutional ethics committee at Toyama University Hospital, and informed consent was obtained from each patient.

### Echocardiography

Transthoracic echocardiography was performed with a 3-MHz transducer connected to an ultrasound machine (SSA770A, Toshiba, Tokyo, Japan) and a broadband 3.5-MHz phased-array transducer connected to an ultrasound system (Vivid E9, GE Healthcare, Bucks, UK). Left atrial dimension (LAD), left ventricular end-diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF) were determined from M-mode images.

TEE was performed with a 5-MHz multiplanar transducer. Patients were studied in the fasting state, with premedication including topical anesthesia of the hypopharynx with lidocaine spray and i.v. diazepam. Multiple standard tomographic planes were imaged. Subsequently, severity of blood stagnation in the left atrium (LA) and LAA was assessed using spontaneous echo contrast (SEC) and LAA peak flow velocity. The severity of SEC in the LA was defined as reported previously: 0, none (absence of echogenicity); 1+, mild (minimal echogenicity detectable only transiently during the cardiac cycle with optimal gain settings); 2+, mild–moderate (transient SEC without increased gain settings and denser pattern than 1+); 3+, moderate (dense swirling pattern during the entire cardiac cycle); and 4+, severe (intense echodensity and very slow swirling patterns in LAA, usually similar in the main LA cavity). Dense SEC was defined as SEC 3+ or 4+.

LAA peak flow velocity was determined on pulse wave Doppler echocardiographic interrogation at the LAA orifice. Peak outflow velocity signals within each R-R interval were averaged over a minimum of 6 cardiac cycles. LA abnormality was defined as dense SEC or LAA peak flow velocity <20 cm/s.

The severity of SEC was determined by 2 independent observers. Any difference was resolved by a third independent observer.

### Statistical Analysis

Data are expressed as mean±SD. Patients were divided into 2 groups with or without LA abnormality. Between-group means and proportions were compared with Student’s t-test and chi-squared test, respectively. Multiple logistic regression analysis was used to clarify independent predictors of LA abnormality. Explanatory variables were selected...
Hs-cTnI and LA Abnormality Correlation

were older, had significantly higher CHADS2 and CHA2DS2-VASc scores and had a higher prevalence of several comorbidities than those without LA abnormality (Table 1).

There was no significant difference in the proportion of medications, including anticoagulant drugs, between the 2 groups. LogBNP, high-sensitivity C reactive protein (hs-CRP) and hs-cTnI were higher in patients with LA abnormality than in those without. Of the echocardiographic variables, LAD differed significantly between the 2 groups, but LVDd and LVEF did not (Table 2). On multiple logistic regression analysis, CHA2DS2-VASc score, logBNP, and hs-cTnI were independently associated with LA abnormality (Table 3); LAD on echocardiography, however, was not associated with LA abnormality.

The AUC for LA abnormality was 0.688 for CHA2DS2-VASc score, 0.713 for logBNP and 0.743 for logBNP plus hs-cTnI. The addition of hs-cTnI significantly improved the predictive ability for LA abnormality when compared with logBNP alone (P=0.007). On univariate analysis, the cut-off for hs-cTnI on the ROC curve was 11.4ng/L, and from clinical variables that had P<0.1 on univariate analysis. Given that plasma BNP was log-normal distributed, logBNP was used for comparison of BNP. The increased discriminative value of BNP and hs-cTnI to predict LA abnormality was analyzed by estimating the difference in the area under the receiver operating characteristic (ROC) curve (AUC). The composite endpoints of all-cause death and ischemic stroke were determined from medical records from September 2017. The outcomes were plotted using a Kaplan-Meier survival curve and compared on log-rank test. P<0.05 was considered significant. All analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and medication are listed in Table 1. One hundred and twenty-two patients (61.3%) underwent TEE before catheter ablation for AF. The prevalence of LA abnormality was 45.7%. Patients with LA abnormality were older, had significantly higher CHADS2 and CHA2DS2-VASc scores and had a higher prevalence of several comorbidities than those without LA abnormality (Table 1). There was no significant difference in the proportion of medications, including anticoagulant drugs, between the 2 groups. LogBNP, high-sensitivity C reactive protein (hs-CRP) and hs-cTnI were higher in patients with LA abnormality than in those without. Of the echocardiographic variables, LAD differed significantly between the 2 groups, but LVDd and LVEF did not (Table 2). On multiple logistic regression analysis, CHA2DS2-VASc score, logBNP, and hs-cTnI were independently associated with LA abnormality (Table 3); LAD on echocardiography, however, was not associated with LA abnormality.

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### Table 2. Laboratory Data and TTE Results vs. LA Abnormality Status

<table>
<thead>
<tr>
<th>n</th>
<th>Total</th>
<th>LA abnormality</th>
<th>P-value(-) vs. (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>108</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Dimer (μg/mL)</td>
<td>0.66±0.45</td>
<td>0.63±0.41</td>
<td>0.71±0.49</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>185.5±35.1</td>
<td>187.9±34.8</td>
<td>182.5±35.4</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>146.6±107.6</td>
<td>164.8±126.7</td>
<td>125.0±74.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.3±1.8</td>
<td>14.6±1.5</td>
<td>14.0±2.0</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>0.91±0.27</td>
<td>0.89±0.25</td>
<td>0.93±0.29</td>
</tr>
<tr>
<td>LogBNP</td>
<td>4.8±1.0</td>
<td>4.5±1.0</td>
<td>5.2±0.8</td>
</tr>
<tr>
<td>Hs-CRP (mg/dL)</td>
<td>0.09±0.11</td>
<td>0.08±0.11</td>
<td>0.11±0.12</td>
</tr>
<tr>
<td>Hs-cTnI (ng/L)</td>
<td>34.3±136.2</td>
<td>10.1±16.0</td>
<td>63.1±197.4</td>
</tr>
<tr>
<td>TTE</td>
<td></td>
<td></td>
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<tr>
<td>LAD (mm)</td>
<td>44.7±7.0</td>
<td>43.1±6.7</td>
<td>46.6±7.0</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>49.9±8.1</td>
<td>50.0±8.1</td>
<td>49.7±8.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.7±13.4</td>
<td>56.2±13.8</td>
<td>57.3±13.0</td>
</tr>
</tbody>
</table>

Data given as mean±SD. BNP, B-type natriuretic peptide; Hs-CRP, high-sensitivity C-reactive protein; Hs-cTnI, high-sensitivity cardiac troponin I; LAD, left atrial dimension; LVDd, left ventricular end-diastole dimension; LVEF, left ventricular ejection fraction; sCr, serum creatinine; TTE, transthoracic echocardiography. Other abbreviations as in Table 1.

### Table 3. Indicators of LA Abnormality

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
<td>OR</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>1.544</td>
<td>1.297–1.866</td>
<td>&lt;0.001</td>
<td>1.343</td>
</tr>
<tr>
<td>D-Dimer (μg/mL)</td>
<td>1.483</td>
<td>0.783–3.095</td>
<td>0.230</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>0.996</td>
<td>0.987–1.004</td>
<td>0.282</td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>0.996</td>
<td>0.992–0.999</td>
<td>0.006</td>
<td>0.997</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.825</td>
<td>0.695–0.971</td>
<td>0.020</td>
<td>1.134</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td>1.659</td>
<td>0.582–4.886</td>
<td>0.343</td>
<td></td>
</tr>
<tr>
<td>LogBNP</td>
<td>2.404</td>
<td>1.718–3.478</td>
<td>&lt;0.001</td>
<td>1.764</td>
</tr>
<tr>
<td>Hs-CRP (mg/dL)</td>
<td>13.441</td>
<td>1.044–231.986</td>
<td>&lt;0.001</td>
<td>1.765</td>
</tr>
<tr>
<td>Hs-cTnI (ng/L)</td>
<td>1.019</td>
<td>1.005–1.037</td>
<td>&lt;0.001</td>
<td>1.006</td>
</tr>
<tr>
<td>TTE LAD (mm)</td>
<td>1.077</td>
<td>1.033–1.127</td>
<td>&lt;0.001</td>
<td>1.043</td>
</tr>
</tbody>
</table>

LA abnormality, left atrial flow velocity <20cm/s and/or left atrial spontaneous echo contrast ≥3+. Other abbreviations as in Tables 1,2.
The prevalence of LA thrombi was similar between the 2 groups (6.3% in the high hs-cTnI group vs. 3.7% in the low hs-cTnI group, P=0.422).

Patients were followed for 3.8±3.2 years after baseline determination. Of 199 patients, 16 (8.0%) died (cardiac, n=6; non-cardiac, n=10), and 9 (4.5%) had ischemic stroke including 6 cardioembolic events. Using the ROC cut-off calculated on univariate analysis, CHA2DS2-VASc score and logBNP were not associated with subsequent ischemic stroke (Figure A, B). In contrast, the incidence of ischemic stroke was higher in the high-hs-cTnI group than in the low-hs-cTnI group (Figure C).

**Discussion**

The major findings of the present study are as follows: higher hs-cTnI was associated with higher CHADS2 and CHA2DS2-VASc scores; and elevated hs-cTnI was associated with LA abnormality and subsequent ischemic stroke in patients with NVAF.

**TEE and Clinical Thromboembolic Risk**

To the best of our knowledge, the present study is the first to report the relationship between hs-cTnI and TEE parameters for prediction of subsequent thromboembolism in patients with NVAF. Thromboembolic risks on TEE included dense SEC, low LAA flow velocity, and LA thrombus in the present study. LA abnormality is a well-known risk factor for thromboembolism in patients with NVAF.15-17 SEC and reduced LAA flow velocity are associated with LA thrombus formation as well as with thromboembolic events.13-14 Of note, severity of SEC was not altered with anticoagulant therapy, and the presence of SEC may indicate thromboembolic risk under the current anticoagulation therapy for AF patients.19 Indeed, patients with dense SEC in the present study had several comorbidities including heart failure, previous stroke and vascular disease.

**Troponin Complex**

Troponin forms a complex of troponin I, C and T proteins in skeletal muscles and cardiomyocytes, and is scattered along actin filaments. Of the troponin complexes, troponin T and I have myocardial specificity but not troponin C. Troponin I or T are therefore elevated by necrosis of cardiomyocytes caused by myocardial ischemia, and measurement of troponin I or T is useful for diagnosing ACS and predicting outcome.5,6 Troponin T, however, is known to be released from skeletal muscles in certain diseases such as chronic renal failure and Duchenne-type muscular atrophy.4,20 Therefore, we considered troponin I to be the most specific cardiac biomarker and selected it in the present study.

**Cardiac Biomarkers and Thromboembolic Risk**

Recently, several cardiac biomarkers have been proposed to predict cardioembolic stroke in AF patients. Of these, plasma BNP is a useful predictor of cardioembolic stroke as well as LA abnormality, including LA thrombi, in NVAF patients.9,10,21 Given that atrial emptying is likely to diminish with impaired diastolic relaxation, diastolic impairment or elevated LV filling pressure may cause not only elevation of BNP but atrial blood stagnation and thrombus formation. In the present study, logBNP was independently associated with LA abnormality (Table 3),
but not with subsequent ischemic stroke (Figure B).

Similar to BNP, an association has also been reported between elevated cardiac troponin I and cardiovascular events, including thromboembolic events, in patients with AF. In a sub-study of the ARISTOTLE trial, elevation of hs-cTnI as well as of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was independently correlated with increased risk of embolic stroke, major bleeding and mortality.7 Adding troponin I to CHADS2-VASc score improved predictability for stroke and cardiac death.8 In the present study increased hs-cTnI was closely associated with LA abnormality (Table 3) and subsequent ischemic stroke in patients with NVAF (Figure C).

Hs-cTnI, TEE and Thromboembolism in NVAF Patients
In the present study, patients with LA abnormality had significantly higher hs-cTnI. Although the mechanisms for the release of troponin in AF patients have not been elucidated, several possible mechanisms have been proposed. First, rapid ventricular responses may cause relative ischemic change in the myocardium even if there is no coronary artery disease (CAD). Rapid atrial pacing has been shown to increase troponin in patients with and without CAD, suggesting that excessive myocardial fiber stretching could cause the release of troponin from the cytosolic pool into the bloodstream. Second, in patients with AF, myocardial blood flow may be decreasing via irregular rhythm. Indeed, following cardioversion, myocardial blood flow was found to be partly restored. Reduced ventricular perfusion during AF may cause angiotensin II-induced oxidative stress and injury. Taken together, troponin I may be elevated in patients with AF. Particularly, as compared with none or transient elevation, persistent elevation of this biomarker could confer a greater risk of stroke and vascular death in patients with AF. Finally, in AF, inflammation, fibrosis, endothelial dysfunction and poor contractile atrium perpetuate the AF rhythm. These factors may cause a hypercoagulable state, resulting in thrombus formation. Troponin I has been reported to be elevated in inflammatory status. The suggested mechanism is speculated to be the mediation by tumor necrosis factor-α and activated young granulocytes, leading to the leakage of troponin without myocardial injury due to hyperpermeability of cardiomyocyte membrane. In this study, the proportion of persistent/permanent AF and prevalence of heart failure were significantly higher in the group with LA abnormality than in the group without. Although the mechanisms of hs-cTnI elevation in patients with AF were not clarified in the present study, the addition of hs-cTnI level to the conventional risks for thromboembolic events may be useful for risk stratification of NVAF patients.

Study Limitations
Several limitations of the present study should be addressed. First, the relatively small sample size from a single institution may have affected the statistical analysis. Second, follow-up data on hs-cTnI were not available, and hs-cTnI level at the time of events was unknown, which may have weakened the present results. The use of a single examination point in each patient could not lead to concrete, direct evidence of the significance of troponin elevation in AF. Third, the duration of AF was not measured in this study. The duration of AF is associated with LA stagnation, and therefore may serve as a confounding factor. Finally, CHADS2 and CHADS2-VASc scores were lower in the present study than in large-scale clinical trials reported thus far. The mean CHADS2 score was 1.6 in the present study, but was 2.2, 3.5 and 2.0 in the RE-LY, ROCKET-AF, and ARISTOTLE trials, respectively. Sixty-one percent of the patients underwent TEE before catheter ablation of AF, and therefore had low CHADS2 score. Additionally, >90% of the patients received oral anticoagulation therapy at baseline. These patient characteristics may explain the reduced thromboembolic events and mortality during the follow-up period in the present study.

Conclusions
Although limited for the aforementioned reasons, the present study suggests that elevated hs-cTnI is independently associated with LA abnormality on TEE in NVAF patients with low thromboembolic risk. Further large-scale, prospective studies are needed to clarify the link between thromboembolic risk and events and hs-cTnI in these patients.

Disclosures
The authors declare no conflicts of interest.

References


