The Usefulness and Limitations of Point-of-care Cardiac Troponin Measurement in the Emergency Department

Kenichiro Suzuki¹, Kimiaki Komukai¹, Kotaro Nakata¹, Ryeonshi Kang¹, Yuhei Oi¹, Eri Muto¹, Yusuke Kashiwagi¹, Mitsutoshi Tominaga¹, Satoru Miyanaga¹, Tetsuya Ishikawa¹, Kenji Okuno², Masahiko Uzura² and Michihiro Yoshimura³

Abstract:

Objective  This study was carried out to examine the usefulness of point-of-care (POC) cardiac troponin in diagnosing acute coronary syndrome (ACS) and to understand the limitations of a POC cardiac troponin I/T-based diagnoses.

Methods  Patients whose cardiac troponin levels were measured in the emergency department using a POC system (AQT System; Radiometer, Tokyo, Japan) between January and December 2016 were retrospectively examined (N=1,449). Patients who were <20 years of age or who were admitted with cardiopulmonary arrest were excluded. The sensitivity and specificity of the POC cardiac troponin levels for the diagnosis of ACS were determined.

Result  One hundred and twenty of 1,449 total patients had ACS (acute myocardial infarction, n=88; unstable angina n=32). On comparing the receiver operating characteristic (ROC) curves, the area under the curve (AUC) values for POC cardiac troponin I and cardiac troponin T were 0.833 and 0.786, respectively. The sensitivity and specificity of POC cardiac troponin I when using the 99th percentile (0.023 ng/mL) as the diagnostic cut-off value were 69.0% and 88.1%, respectively. The sensitivity of POC cardiac troponin I (99th percentile) was higher in the patients sampled >3 hours after symptom onset (83.3%) than in those sampled ≤3 hours after symptom onset (58.8%, p < 0.01).

Conclusion  When sampled >3 hours after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. However, when sampled ≤3 hours after the onset of symptoms, careful interpretation of POC cardiac troponins is therefore required to rule out ACS.

Key words: point of care, cardiac biomarkers, acute coronary syndrome

(Intern Med 57: 1673-1680, 2018)

(DOI: 10.2169/internalmedicine.0098-17)

Introduction

Rapid diagnostic techniques are needed in the emergency department, especially for acute coronary syndrome (ACS), as early coronary reperfusion can improve the prognosis of ACS (1, 2).

ACS should be diagnosed based on the symptoms and the results of electrocardiography (ECG), and ultrasound cardiology (UCG), and blood sampling. Many ACS patients present with chest pain, but some do not (3-5). Care should therefore also be taken to correctly diagnose patients who do not present with chest pain. Furthermore, some patients do not show ECG changes and lack segmental asynergy on UCG. The recent development of biomarkers of cardiac injury can help in the diagnosis.

Troponin complex is a contractile element consisting of troponin C, I, and T (6). Each has skeletal and cardiac isoforms. When the membrane of cardiac muscle cells is injured, cardiac troponins flow from the cardiac muscle cells...
The patients were divided into two groups: patients with and without ACS. The diagnosis was determined retrospectively after discharge by one of the investigators. The following data (if appreciable) were taken into consideration in the diagnosis: the symptoms, physical findings, electrocardiogram findings, ultrasound echocardiography findings, chest X-ray findings, computed tomography findings, laboratory findings other than cardiac troponin levels, their response to the specific treatment and the follow-up in an outpatient clinic. ACS was confirmed by coronary angiography (CAG). In three cases of clinically suspected ACS, the patients did not undergo CAG. Two of these three cases were hospitalized, and the ACS diagnosis was confirmed during the course of hospitalization. However, in one case, the family refused hospitalization, so this case was excluded from the study. ACS was also categorized as ST-elevating myocardial infarction (STEMI), non-ST-elevating myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Myocardial infarction was defined when a rapid increase or decrease in cardiac injury markers other than the cardiac troponins (creatinine kinase, creatine kinase MB isoenzyme) was confirmed. Myocardial injury due to coronary artery spasm was categorized as myocardial infarction. Fig. 1 shows a schematic illustration of the patients included in the present study.

The age, sex and other laboratory findings of the two groups (ACS and non ACS) were compared. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (10) coefficient modified for Japanese patients (11): eGFR = 194 × \( \frac{Cr^{-1.094 \times age^{-0.203}}}{7.42} \) (×0.739 for female subjects for correction) (mL/min/1.73 m²). Continuous variables were expressed as the median [interquartile range (IQR)] and were compared using the Mann-Whitney test. Categorical variables were expressed as the number (percentage) and compared using the chi-squared test. A receiver-operating characteristic (ROC) curve analysis was performed to examine the sensitivity and specificity of the POC cardiac troponins in the diagnosis of ACS. The cut-off points where the sum of the sensitivity and specificity was highest were also shown.

It takes time for the biomarker levels to increase. Early admission can therefore lead to an increase in false-negative results. Thus, a histogram of the various cut-off values for ACS, based on the time between onset and the sampling, was created.

Renal failure is considered to be one of the reasons for false-positive results when cardiac troponins are used for the diagnosis of ACS. Thus, the false positive rate in non-ACS patients is shown in relation to the eGFR. The 99th percentile values of normal population supplied by the Radiometer were used as cut-off values (troponin T, > 0.017 ng/mL; troponin I, > 0.023 ng/mL). The false positive rate was compared between POC cardiac troponin I and T using the McNemar test for each renal function level. For this analysis, the non-ACS patients with available data for both POC cardiac troponin T and I were included. Multiplicity in sta-
The final diagnoses of the patients are shown in Table 1. One hundred and twenty of a total 1,449 patients were diagnosed with ACS. The clinical characteristics of both groups are shown in Table 2. The eGFR values were higher in the ACS group, as were the serum creatinine kinase (CK) and creatine kinase MB isoenzyme (CKMB) levels and the NT-pro brain natriuretic peptide (BNP) and POC cardiac troponin I/T levels. The frequency of chest pain was also higher in the ACS group; however, 32.5% of the ACS patients did not present with chest pain. The symptoms of the ACS patients without chest pain are shown in Table 3.

We performed an ROC curve analysis to examine the sensitivity and specificity of various POC cardiac troponin cut-off values in the diagnosis of ACS (Fig. 2). The area under the curve (AUC) for cardiac troponin I was 0.833, while that for cardiac troponin T was 0.786. POC cardiac troponin I was superior to troponin T, especially with regard to the specificity (Fig. 2). We drew an ROC curve for patients who were sampled at ≤ 3 hours after the onset of symptoms and those who were sampled at > 3 hours after the onset of symptoms (Fig. 3). The AUC was higher when patients were sampled > 3 hours after the onset of symptoms.

We next examined the sampling time-dependence of the sensitivity. Early sampling led to false-negative results; however, even when patients were sampled at > 6 hours after the onset of symptoms, few cases were POC cardiac troponin I-negative (Fig. 4). All of these cases were diagnosed with UAP. We calculated the sensitivity and specificity of POC cardiac troponin I using several cut-off values for patients sampled at ≤ 3 hours or > 3 hours after the onset of symptoms (in addition to the cut-off values for all patients). The sensitivity (using the 99th percentile as the cut-off value) was higher in patients sampled > 3 hours after symptom onset (83.3%) than those sampled ≤ 3 hours after symptom onset (58.8%, p<0.01) (Table 4).

The dependence of false-positive results on the renal function is shown in Table 5. When the eGFR was low, the false-positive rate increased in both POC cardiac troponin I and T. However, the false positive rate was much higher when POC cardiac troponin T was used, especially in patients with lower eGFR values.

The present study showed the following: 1) some patients with ACS do not experience chest pain; 2) POC cardiac troponin I was superior to POC cardiac troponin T for diagnosing ACS; and 3) POC cardiac troponin I was suitable for the diagnosis of ACS in the emergency department setting when sampling was performed at > 3 hours after the onset of symptoms.

### Discussion

The diagnosis of acute coronary syndrome

In the present study, ACS was diagnosed retrospectively based on clinical findings. Acute myocardial infarction (MI) was defined by rapid increases and decreases in biomarkers of cardiac injury. Under the third definition of MI, the use of cardiac troponins and the 99th percentile of a normal reference popula-
Figure 2. The receiver-operating characteristic curves for the detection of ACS by POC troponins.

Table 2. The Characteristics of the Patients with and without ACS.

|                  | All          | ACS          | Non-ACS       | p   |
|------------------|--------------|--------------|---------------|-----|
| N                | [1,449]      | [120]        | [1,329]       |     |
| Gender Male n (%)| [871 (60.1)] | [93 (77.5)]  | [778 (58.5)]  | <0.001 |
| Age (years)      | [70 (55.79)] | [71 (61.78)] | [70 (54.80)]  | NS  |
| Chest pain n (%) | [279 (19.3)] | [81 (67.5)]  | [198 (14.9)]  | <0.001 |
| WBC (μL)         | [7,600 (5,900-10,225)] | [8,200 (6,830-10,500)] | [7,500 (5,800-10,200)] | <0.05 |
| CK (U/L)         | [110 (69-186)] | [159 (100-365)] | [107 (66-180)] | <0.001 |
| CKMB (U/L)       | [10 (7-15)]  | [15 (10-34)] | [10 (7-15)]   | <0.001 |
| eGFR (mL/min/1.73m²) | [63.8 (43.1-80.9)] | [60.3 (36.6-75.7)] | [64.5 (43.5-81.3)] | <0.05 |
| NT-proBNP (pg/mL) | [223 (64-1,333)] | [714 (149-4,000)] | [204 (62-1,250)] | <0.001 |
| Cardiac troponin I (μg/L) | <0.010 (0.010-0.012) | 0.084 (0.014-0.963) | <0.010 (0.010-0.010) | <0.001 |
| Cardiac troponin T (μg/L) | <0.010 (0.010-0.017) | 0.059 (0.011-0.510) | <0.010 (0.010-0.015) | <0.001 |

Continuous variables were expressed as the median (IQR). Categorical variables were expressed as the number (percentage). The number sampled was shown in [], as some cases were missed.

| ACS without chest pain 39 |
|---------------------------|
| Chest discomfort           | 16 (41.0)   |
| Dyspnea                   | 18 (46.2)   |
| Chest discomfort and/or dyspnea | 30 (76.9) |
| Disturbance of consciousness | 5 (12.8)   |
| Drop                      | 1 (2.6)     |
| General fatigue           | 1 (2.6)     |
| Palpitation               | 1 (2.6)     |
| Neck pain                 | 1 (2.6)     |

Number in the parenthesis indicates percentage.

Schneider et al. (7) reported that reducing the POC cardiac troponin cut-off value from the 99th percentile by half can increased the sensitivity. In the present study, the reduced cut-off value led to an increase in sensitivity (Table 4). In UAP, the diagnostic performance of high-sensitive cardiac troponins is not sufficient (12). Furthermore, in the present study, when measurements were performed at > 6 hours, a small number of false negatives for UAP occurred. In cases involving very small amounts of myocardial damage, UAP is difficult to diagnose based solely on biomarkers of myo-
In the present study, all of the patients who presented to the ED and in whom the POC cardiac troponin level was measured were included, as ACS without chest pain is not rare. Indeed, 24% of ACS patients do not experience chest pain (4). Myocardial infarction is not recognized in approximately 30% of cases (13). Silent myocardial infarction is related to hypertension, age, diabetes, sex (13), and renal dysfunction (5). Thus, care should be taken to detect ACS in patients who do not present with chest pain. The symptoms of the ACS patients without chest pain are listed in Table 3.

ACS without chest pain

In the present study, all of the patients who presented to the ED and in whom the POC cardiac troponin level was measured were included, as ACS without chest pain is not rare. Indeed, 24% of ACS patients do not experience chest pain (4). Myocardial infarction is not recognized in approximately 30% of cases (13). Silent myocardial infarction is related to hypertension, age, diabetes, sex (13), and renal dysfunction (5). Thus, care should be taken to detect ACS in patients who do not present with chest pain. The symptoms of the ACS patients without chest pain are listed in Table 3.

Cardiac troponin T and I

The sensitivity of POC cardiac troponin I and T were similar. However, the specificity of POC cardiac troponin I was far superior to that of troponin T (Fig. 2). Cardiac troponin T mRNA is expressed in the skeletal muscle of patients with end-stage renal failure or Duchene muscle dystrophy but not in healthy skeletal muscle. In contrast, cardiac troponin I mRNA is not expressed in normal or diseased skeletal muscle (14). The plasma cardiac troponin T level is also increased in Pompe disease patients with skeletal damage (15). In the present study, the false-positive rate for POC cardiac troponin T was much higher than that for

Figure 3. The receiver-operating characteristic curves for the detection of ACS by POC cardiac troponins in patients sampled at ≤3 hours or >3 hours after the onset of symptoms.

Figure 4. A histogram of the various cut-off values of POC cardiac troponin I for the diagnosis of ACS, according to the time between the onset of symptoms and sampling.
troponin I, especially in patients with a low renal function (Table 5). This result is consistent with the fact that the expression of cardiac troponin T, but not troponin I, is increased in the skeletal muscle of patients with end-stage renal failure.

**The time-dependence of the sensitivity of cardiac troponins**

It takes a several hours for the biomarker levels to rise; thus, the concentration of POC cardiac troponin I was plotted against the time between the onset and the sample time (Fig. 4). In our hospital, some ACS patients were admitted very quickly, due to the efficiency of the ambulance service. In these cases, POC cardiac troponins were less sensitive than high-sensitive troponins. However, at > 3 hours from the onset of symptoms, the sensitivity increased to reasonable levels. The repeated measurement of POC cardiac troponin can increase the accuracy, especially for patients who are admitted soon after the onset of symptoms.

**Japanese STEMI guideline**

In the guideline for the management of patients with STEMI (JCS 2013) (16), the qualitative measurement of cardiac troponin or heart-type fatty acid-binding protein (H-FABP) with whole blood at bedside is recommended (Class I indication). The whole blood test at bedside takes only 15 minutes (17). Troponin T (qualitative measurement) increases > 4 hours after the onset of symptoms. H-FABP is a

---

### Table 4. The Sensitivity, Specificity, PPV, and NPV for Various Cut-off Values of POC Cardiac Troponin I.

| Cut off | Sensitivity | Specificity | PPV | NPV |
|---------|-------------|-------------|-----|-----|
| ≥0.010 (μg/L) | Limit of detection | 79.3 | 75.2 | 22.4 | 97.6 |
| ≥0.012 (μg/L) | Half 99th percentile | 77.6 | 78.5 | 24.6 | 97.5 |
| ≥0.022 (μg/L) | Calculated from ROC | 70.7 | 87.7 | 34.2 | 97.1 |
| >0.023 (μg/L) | 99th percentile | 69.0 | 88.1 | 34.3 | 96.9 |

| Patients sampled ≤3 hours after the onset (n=816) |
| Cut off | Sensitivity | Specificity | PPV | NPV |
|---------|-------------|-------------|-----|-----|
| ≥0.010 (μg/L) | Limit of detection | 72.1 | 79.9 | 24.6 | 96.9 |
| ≥0.012 (μg/L) | Half 99th percentile | 70.6 | 82.6 | 27.0 | 96.9 |
| ≥0.017 (μg/L) | Calculated from ROC | 66.2 | 87.2 | 31.9 | 96.6 |
| >0.023 (μg/L) | 99th percentile | 58.8 | 90.4 | 35.7 | 96.0 |

| Patients sampled >3 hours after the onset (n=513) |
| Cut off | Sensitivity | Specificity | PPV | NPV |
|---------|-------------|-------------|-----|-----|
| ≥0.010 (μg/L) | Limit of detection | 89.6 | 67.5 | 22.2 | 98.4 |
| ≥0.012 (μg/L) | Half 99th percentile | 87.5 | 72.0 | 24.4 | 98.2 |
| ≥0.017 (μg/L) | Calculated from ROC | 83.3 | 84.5 | 35.7 | 98.0 |
| ≥0.063 (μg/L) | Calculated from ROC | 79.2 | 92.3 | 51.4 | 97.7 |

PPV: positive predictive value, NPV: negative predictive value

### Table 5. The False-positive Rates for POC Cardiac Troponin I and T in Relation to eGFR Values in Non-ACS Patients.

| eGFR (mL/min/1.73m²) | Troponin I | Troponin T | Troponin I | Troponin T |
|----------------------|------------|------------|------------|------------|
|                      | False positive n/N (%) | False positive n/N (%) | False positive n/N (%) | False positive n/N (%) |
| <15                  | 27/91 (29.6) | 69/76 (90.7) | 21/72 (29.2) | 65/72 (90.3) |
| 15–30                | 23/91 (25.3) | 44/76 (57.9) | 19/74 (25.7) | 43/74 (58.1) |
| 30–45                | 31/154 (20.1) | 44/134 (32.8) | 25/127 (19.7) | 42/127 (33.1) |
| 45–60                | 31/229 (13.5) | 43/202 (21.3) | 24/195 (12.3) | 43/195 (22.1) |
| 60–75                | 15/279 (5.4) | 16/244 (6.6) | 7/233 (3.0) | 16/233 (6.9) |
| 75–90                | 20/239 (8.4) | 20/219 (9.1) | 17/209 (8.1) | 20/209 (9.6) |
| >90                  | 6/200 (3.0) | 7/187 (3.7) | 6/182 (3.3) | 7/182 (3.8) |

*: statistical test was not performed due to hierarchical procedure.
low-molecular-weight protein that exists in the cytosol; it therefore increases earlier than cardiac troponin (16, 17). POC cardiac troponins in the present study showed a lower sensitivity than H-FABP, especially ≤ 3 hours after the onset. However, the specificity of H-FABP for myocardial infarction is around 50% (17). Therefore, when patients are admitted very quickly after symptom onset, the use of H-FABP is recommended.

**Serum cardiac troponin levels in non-ACS patients**

In some patients without ACS, the levels of POC cardiac troponins exceeded the normal range. Several factors are involved in the increase in the serum concentration of cardiac troponins. Cardiac troponin is a heart-specific structural protein. However, when the cardiac muscle cells are injured, the proteins inside the cell flow into the systemic circulation. Thus, it is reasonable for the concentration of a biomarker of cardiac muscle injury to increase under certain conditions aside from acute myocardial infarction, including other cardiac diseases as well as non-cardiac diseases, such as myocarditis, arrhythmias, exposure to cardiotoxic agents, heart failure, Takotsubo cardiomyopathy, sepsis, renal failure, severe acute neurological diseases, and critical illness (3, 6, 18, 19).

**Study limitations**

The present study is associated with several potential limitations. First, the sample size was small. Second, our hospital is a tertiary emergency medical facility. In addition to patients with chest pain, patients with traumatic injuries due to traffic accidents, whose POC cardiac troponin levels were measured frequently, were included in the analysis. The sensitivity and specificity were affected by the study population. Third, we only used the AQT system to measure the levels of POC cardiac troponins. The sensitivity and specificity depend on the antibodies and measuring system that are used. Thus, our data cannot be generalized to other POC systems. Despite these limitations, this study explained the usefulness and limitations of using the measurement of POC cardiac troponins to diagnose ACS in the ED.

**Conclusion**

When sampled > 3 hours after the onset of symptoms, the POC cardiac troponin I level is considered to be suitable for use in diagnosing ACS. However, when sampled ≤ 3 hours after the onset of symptoms, careful interpretation of POC cardiac troponins is required to rule out ACS. Increasing our understanding of the characteristics of POC cardiac troponins will aid in the diagnosis of ACS.

The authors state that they have no Conflict of Interest (COI).

**Acknowledgement**

We would like to thank Prof. Masako Nishikawa, Clinical Research Support Center, The Jikei University School of Medicine, for providing advice on the statistical analyses, and Dr. Brian Quinn, Japanese Medical Communication, for reading the manuscript.

**References**

1. O’Gara PT, Kushner FG, Ascheim DD, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 127: e362-e425, 2013.
2. Mehta SR, Granger CB, Boden WE, et al. TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 360: 2165-2175, 2009.
3. Thaygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Joint ESC/ACC/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. J Am Coll Cardiol 60: 1581-1598, 2012.
4. Vidalí M, Vertzoni E, Cabraz N, et al. “Real life use” of troponin in the emergency department: a survey of over 3000 cases. Biochem Med (Zagreb) 25: 421-429, 2015.
5. Konukai K, Ogawa T, Yagi H, et al. Renal insufficiency is related to painless myocardial infarction. Circ J 71: 1366-1369, 2007.
6. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. Eur Heart J 32: 404-411, 2011.
7. Schneider HG, Ablitz P, Taylor J. Improved sensitivity of point of care troponin I values using reporting to below the 99th percentile of normals. Clin Biochem 46: 979-982, 2013.
8. Dupuy AM, Sebbane M, Roubille F, et al. Analytical evaluation of point of care cTnT and clinical performances in an unselected population as compared with central laboratory highly sensitive cTnT. Clin Biochem 48: 334-339, 2015.
9. Diercks DB, Peacock WF 4th, Hollander JE, et al. Diagnostic accuracy of a point-of-care troponin I assay for acute myocardial infarction within 3 hours after presentation in early presenters to the emergency department with chest pain. Am Heart J 163: 74-80.e4, 2012.
10. Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145: 247-254, 2006.
11. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009.
12. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 361: 858-867, 2009.
13. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. Ann Intern Med 135: 801-811, 2001.
14. Ricciuti V, Apple FS. RNA expression of cardiac troponin T isoforms in diseased human skeletal muscle. Clin Chem 45: 2129-2135, 1999.
15. Wens SC, Schaaf GJ, Michels M, et al. Elevated plasma cardiac troponin T levels caused by skeletal muscle damage in Pompe disease. Circ Cardiovasc Genet 9: 6-13, 2016.
16. JCS Joint Working Group: Guidelines for the management of patients with ST-elevation acute myocardial infarction (JCS 2013) [internet]. [accessed 2017 Sep 13]. Available from:[http://www.j-circ.or.jp/guideline/pdf/JCS2013_kimura_h.pdf](http://www.j-circ.or.jp/guideline/pdf/JCS2013_kimura_h.pdf) (in Japanese)
17. Seino Y, Ogata K, Takano T, et al. Use of a whole blood rapid panel test for heart-type fatty acid-binding protein in patients with...
acute chest pain: comparison with rapid troponin T and myoglobin tests. Am J Med 115: 185-190, 2003.

18. Newby LK, Rodriguez I, Finkle J, et al. Troponin measurements during drug development—considerations for monitoring and management of potential cardiotoxicity: an educational collaboration among the Cardiac Safety Research Consortium, the Duke Clinical Research Institute, and the US Food and Drug Administration. Am Heart J 162: 64-73, 2011.

19. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-heart interaction: cardiac complications after stroke. Circ Res 121: 451-468, 2017.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).