Clinical and Echocardiographic Characteristics of Acute Cardiac Dysfunction Associated With Acute Brain Hemorrhage – Difference From Takotsubo Cardiomyopathy –
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Background: Cardiac dysfunction (CD) associated with brain hemorrhage is similar to that with takotsubo cardiomyopathy but still not well understood. We aimed to investigate the clinical and echocardiographic findings of acute CD (ACD) related to brain hemorrhage.

Methods and Results: Between 2013 and 2014, consecutive patients diagnosed with spontaneous and traumatic brain hemorrhage were prospectively enrolled. Electrocardiography, cardiac enzymes, and echocardiography were performed. Left ventricular (LV) systolic dysfunction on echocardiography was defined as ACD related to brain hemorrhage when all the following conditions were satisfied: abnormal ECG and cardiac troponin level, LV wall motion abnormality or decreased LV systolic function on echocardiography, and no previous history of cardiac disease. Otherwise, LV dysfunction was considered to be other CD unrelated to brain hemorrhage. In a total of 208 patients, 15 (7.2%) showed ACD. Of them, 8 patients were men and 8 showed apex-sparing LV hypokinesia and 9 died in hospital. Other cardiac abnormalities observed in the study patients were NT-proBNP elevation (n=123), QT interval prolongation (n=95), LV hypertrophy (n=89), and troponin I elevation (n=47). There were 36 in-hospital deaths (17.3%). Glasgow coma score and ACD were independently associated with in-hospital death.

Conclusions: ACD was observed in patients with various brain hemorrhages. Unlike takotsubo cardiomyopathy, high proportions of male sex, apex-sparing LV dysfunction, and in-hospital death were observed for ACD associated with brain hemorrhage. (Circ J 2016; 80: 2026–2032)

Key Words: Hemorrhagic stroke; Neurocardiology; Neurogenic stress cardiomyopathy; Takotsubo cardiomyopathy
incidence and the clinical and echocardiographic findings of CD occurring in patients with acute brain hemorrhage. We also aimed to evaluate the clinical characteristics of CD related to brain hemorrhage compared with TTC.

**Methods**

**Study Population**

From March 2013 to February in 2014, consecutive patients diagnosed with acute spontaneous or traumatic brain hemorrhage and admitted to the neurosurgical intensive care unit (NSICU) were prospectively enrolled. ECG, cardiac enzymes, and N-terminal prohormone brain natriuretic peptide (NT-proBNP) were checked on the day of admission, and echocardiography was performed within 1 week of admission in all patients (Figure 1). Follow-up examination for the initial tests and coronary examination were not included in the study protocol and the decisions were made by the neurosurgeon in charge of each patient or the cardiologists consulted for the patient. Clinical characteristics, laboratory findings, and in-hospital outcome were collected by electronic chart review. This study was approved by the ethical committee of the Institutional Review Board at the hospital and the requirement of informed consent was waived.

**Definitions**

CD was defined as left ventricular (LV) systolic dysfunction showing decreased ejection fraction (EF) or regional wall motion abnormality (RWMA) on echocardiography. Abnormal cardiac enzymes or ECG in patients showing normal LV systolic function and normal LV wall motion on echocardiography was not considered as CD. Patients with CD were considered as having acute CD (ACD) associated with brain hemorrhage if they met all of the following criteria: (1) accompanied by ECG change and abnormal cardiac troponin I (TnI) level, (2) no previous history of cardiac disease, and (3) wall motion abnormality extending beyond a single coronary arterial distribution. Otherwise, LV dysfunction was considered as other CD (OCD) unrelated to brain hemorrhage. We further classified ACD into 4 morphologic types according to the pattern of RWMA on echocardiography (Figure 2): (1) apical type (TTC pattern) showing apical or apical and mid-ventricular hypokinesia and normal or hyperkinetic motion of the basal wall, (2) mid-ventricular type showing mid-ventricular hypokinesia and preserved wall motion of the apical and basal wall, (3) reverse type (inverted TTC pattern) showing hyperkinesia of the apical wall and hypokinesia of the basal or basal and mid-ventricular wall, and (4) global type showing global hypokinesia of the LV. LV hypertrophy (LVH) was defined if the LV mass index was >115 g/m² for men, and >95 g/m² for women. On initial assessment, the patient’s consciousness was scored using the Glasgow coma scale (GCS) on a scale of 3–15 and mentation was classified as alert, drowsy, stupor, semi-coma or coma.

![Figure 1. Study flow diagram. NSICU, neurosurgical intensive care unit; NT-proBNP, N-terminal of the prohormone B-type natriuretic peptide.](image)

![Figure 2. Examples of 2 different types of acute cardiac dysfunction. (A1,2) Images captured at end-diastole and end-systole show the typical type of apical ballooning pattern. (B1,2) Images captured at end-diastole and end-systole show the reverse type with mid and basal hypokinesia.](image)
Echocardiography and Other Tests

Comprehensive echocardiographic evaluations including 2D echocardiography and color and tissue Doppler studies were performed for each patient according to the study protocol using a Vivid 7, Vivid E9, or Vivid I device (GE Vingmed, Horten, Norway). Portable echocardiography was performed for patients who were not able to be transported to the echocardiographic laboratory from the NSICU for various reasons, such as mechanical ventilation or hemodynamic instability. RWMA was evaluated and scored by visual assessment according to the established guideline of the American Society of Echocardiography by an experienced echocardiographer who was unaware of the clinical findings of the patients. LVEF was evaluated by modified Simpson’s method. LV mass was estimated using the Devereux formula and indexed to body surface area. Both TnI and creatine kinase (CK)-MB were measured with a chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA) on the day of admission. TnI elevation was defined as >0.04 ng/ml by local clinical criteria. NT-proBNP was measured with a chemiluminescence enzyme immunoassay (Mitsubishi Chemical Medience Corp, Tokyo, Japan) and was considered elevated if >125 pg/ml for patients under the age of 75 years and >450 pg/ml for patients older than 75 years by local clinical criteria. 12-lead ECGs were obtained on the day of admission. A cardiologist analyzed the ECGs by manually measuring QT intervals and evaluated ST-segment depression or elevation and T wave inversion. QTc intervals were calculated using the Bazett correction. In the cases of atrial arrhythmias, intervals were averaged over 5 beats. QT interval prolongation was defined if QTc exceeded 470 ms.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation or median (interquartile range [IQR]). Categorical variables are expressed as number and percentage. The χ² or Fisher’s exact test was used for comparison of categorical variables, and the independent t-test or Mann-Whitney test was used for continuous variables according to the results of a normality test. Univariate logistic regression analyses were carried out for all clinical, laboratory and echocardiographic variables. For multivariate logistic regression analyses, variables with significant P values on univariate analyses were included in order to identify the independent predictors of inhospital death. Statistical analyses were performed using SPSS 21.0 software (IBM, Inc, Chicago, IL, USA) and P<0.05 was regarded as significant.

Results

Clinical Characteristics

During the study period, data for 208 patients (age: 59±15 years, 123 men) with acute brain hemorrhage were collected.
All the patients had undergone ECG, routine laboratory tests including cardiac enzymes, and echocardiography according to the study protocol. Portable echocardiography was performed for 71 (34.1%) patients. A total of 15 (7.2%) patients (age: 62±12 years, 8 men) were diagnosed with ACD based on medical history, ECG, cardiac enzymes, and echocardiography (Figure 1); 9 (4.3%) patients were diagnosed with OCD, and 184 (88.5%) patients had no CD. Among the patients with ACD, 9 died in hospital (60.0%) cases, while 1 (11.1%) patient with OCD and 26 (14.1%) patients without CD died during hospitalization. The clinical characteristics presented in Table 1 were compared between the ACD group and the non-ACD group. There were no significant differences in age, sex, blood pressure, heart rate or medical history between the 2 groups. In terms of hemorrhage type, spontaneous intraventricular hemorrhage was seen more frequently in the ACD group than in the non-ACD group (20.0% vs. 1.6%, P=0.005) and other types of hemorrhage were not different between the groups. More patients in the ACD group had worse mentation evident as stupor, semi-coma, or coma (66.7% vs. 34.7%, P=0.014), but the GCS was not significantly different between the groups. In the laboratory findings, CK-MB, TnI, and NT-proBNP levels were more elevated in the ACD group compared with the non-ACD group (Table 1). The proportion of patients who underwent neurosurgery during hospitalization was not different in the 2 groups. In the ACD group, in-hospital death occurred more frequently (60.0% vs. 14.0%, P<0.001).

Cardiac Abnormalities

Observed abnormalities in cardiac evaluation of the total patient group are summarized in Table 2. In the analysis of the admission ECG, 19 (9.2%) patients showed ST-segment elevation and 11 (5.3%) patients showed ST-segment depression or T wave abnormality. QT interval prolongation was observed in 95 (45.7%) patients. In the initial laboratory tests, 11 (5.3%) patients showed LV systolic dysfunction with RWMA and 15 (7.2%) patients were classified as having ACD and 9 (4.3%) patients as having OCD by the study definitions. Table 3 shows the characteristics of 15 patients with ACD and Table S1 shows characteristics of the 9 patients with OCD. Among the 15 patients with ACD, TnI level on admission was elevated in 12 patients, but 3 patients who had initially normal TnI levels showed TnI elevation on subsequent tests. Four patients initially had normal levels of NT-proBNP. Their LVEF ranged widely [48.0% (IQR, 30.5–49.6)]. The 15 patients also showed various morphologic types of RWMA: 6 (40.0%) patients showed the reverse type and 4 (26.7%) patients showed the apical type. The other 3 (20.0%) and 2 (13.3%) patients showed global hypokinesia and mid-ventricular hypokinesia, respectively. Therefore, 8 patients had the apex-sparing pattern of LV dysfunction and 7 patients had an apex-affected pattern (mean age, 57±12.2 vs. 67±10.7, respectively, P=0.094).

In-Hospital Mortality Rate

A total of 36 patients died while hospitalized. Of them, 30 (8 in the ACD group, 22 in the non-ACD group) died from a neurogenic condition caused by acute brain hemorrhage. Among the other 6 patients, 2 (1 each in the 2 groups) died of sudden cardiac death and 1 patient died of heart failure; 2 patients died of uncontrolled sepsis and 1 patient died of aspiration pne-

<table>
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<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Hemorrhage type</th>
<th>Admit GCS</th>
<th>Admit TnI</th>
<th>Admit NT-proBNP</th>
<th>EF</th>
<th>Morphologic type</th>
<th>ECG</th>
<th>Prolonged QTc</th>
<th>Surgery</th>
<th>Death</th>
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<td>Yes</td>
</tr>
<tr>
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<td>3</td>
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<td>55.4</td>
<td>30.6</td>
<td>Reverse</td>
<td>ST depression</td>
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<td>Yes</td>
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<td>Flat T wave</td>
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<td>44.1</td>
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<td>Flat T wave</td>
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<td>50.4</td>
<td>Mid-ventricular</td>
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<td>No</td>
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<td>S-SAH</td>
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<td>S-ICH</td>
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<td>Global</td>
<td>ST elevation</td>
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<td>65</td>
<td>T-SDH</td>
<td>13</td>
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<td>116</td>
<td>49.6</td>
<td>Reverse</td>
<td>ST elevation</td>
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<td>Yes</td>
<td>No</td>
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<td>15</td>
<td>M</td>
<td>65</td>
<td>T-SDH</td>
<td>15</td>
<td>16.03</td>
<td>&gt;30,000</td>
<td>38.1</td>
<td>Apical</td>
<td>ST depression</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>

EF, ejection fraction. Other abbreviations as in Table 1.
monia. In the univariate analysis, GCS, total cholesterol, TnI, neurosurgery, and ACD were significant predictors for in-hospital death (Table 4). The other variables, including age, sex, systolic blood pressure, hemorrhagic type, heart rate, and creatinine, were not significant predictors in the univariate analysis. Medical history of hypertension, diabetes, prior stroke, prior heart disease, and smoking was not significant for predicting in-hospital death (data not shown). In the multivariate analysis, GCS (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.68–0.87, P<0.001), total cholesterol (OR 0.99, 95% CI 0.98–1.00, P=0.017) and ACD (OR 8.02, 95% CI 1.76–36.46, P=0.007) were independent risk factors for in-hospital death.

### Discussion

This prospectively enrolled study of patients with acute brain hemorrhage showed that ACD was related to acute brain hemorrhage in 7% and early TnI elevation in 23% of the patients. Of the 15 cases of ACD, 8 were males (53%) and 8 (53%) patients had the apex-sparing pattern of LV wall motion abnormality. Patients with ACD had a high in-hospital mortality rate independent of initial GCS. These results suggest that ACD related to brain hemorrhage has different clinical manifestations from the typical TTC pattern in regards to non-female dominance, more frequent apex-sparing RWMA and high rate of in-hospital death. In addition, ACD occurred not only in patients with SAH but also in patients with other types of acute brain hemorrhage with similar proportions.

To the best of our knowledge, our study is the first prospective study to investigate ACD in patients with all types of acute brain hemorrhage. Hitherto, there have been no data concerning the incidence of ACD in this population. The incidence of LV dysfunction and TnI elevation in patients with SAH has been reported in several studies. Hravnak et al reported the incidence of LV dysfunction and TnI elevation in patients with SAH has been reported in several studies. Hravnak et al reported the incidence of LV dysfunction and TnI elevation in patients with SAH. They concluded that myocardial injury was infrequent in patients with SAH. In the present study, however, 13 (21%) of 61 patients with SDH (53 traumatic and 8 spontaneous SDH cases) had initial TnI elevation and the proportion was compatible with that in patients with SAH: 9 (26%) of 35 patients with SAH had TnI elevation.

TTC is well-known for its uneven sex distribution. A recent large study reported a female-to-male ratio of 9:1 in 1,750 patients with TTC. Female predominance with a similar ratio was also reported in other studies. However, the female-to-male ratio of LV dysfunction in patients with SAH has varied in several studies and female predominance does not seem to be as clear as that found with TTC. A previous study of SAH patients reported that 31% of all female patients and 39% of all male patients had TnI elevation, and 11% of all female patients and 4% of all male patients had RWMA. Another study of patients with SAH reported that 27% and 26% of female and male patients, respectively, showed RWMA, and another study reported 24% and 9% of female and male patients, respectively, showed TnI elevation. The current study reported proportions of TnI elevation as 20% and 24% of female and male patients, respectively, and respective proportions of RWMA as 8% and 7%. The collective data indicate that CD in patients with brain hemorrhage seems to occur in both sexes at a similar rate. Why the sex distribution is different from that of TTC is unclear at this point.

Along with female predominance, TTC also features apical ballooning-type RWMA of the LV. Recent studies including a large number of patients with TTC report apical ballooning-type RWMA in 82% and 92%, respectively. Interestingly, NSC seems to have some differences in the pattern of RWMA of the LV. Two previous studies that investigated LV dysfunction in patients with SAH reported that the apex-sparing pattern of RWMA was observed in 49% and 58%, respectively.

### Table 4. Univariate and Multivariate Analyses for Predicting In-Hospital Death of the Study Patients With Acute Brain Hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>OR 95% CI P value</td>
<td>OR 95% CI P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 0.97–1.02 0.677</td>
<td></td>
</tr>
<tr>
<td>Female (vs. male) sex</td>
<td>0.79 0.37–1.65 0.524</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.01 1.00–1.02 0.086</td>
<td></td>
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<tr>
<td>T- (vs. S-) hemorrhage</td>
<td>1.15 0.54–2.48 0.714</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.02 1.00–1.03 0.090</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>0.77 0.69–0.85 &lt;0.001</td>
<td>0.77 0.68–0.87 &lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.19 0.83–1.70 0.357</td>
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<tr>
<td>Total cholesterol</td>
<td>0.99 0.98–1.00 0.009</td>
<td></td>
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<tr>
<td>TnI</td>
<td>11.02 2.21–55.11 0.003</td>
<td>2.41 0.26–22.19 0.437</td>
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<tr>
<td>Neurosurgery</td>
<td>2.73 1.21–6.15 0.015</td>
<td>1.17 0.44–3.14 0.749</td>
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<tr>
<td>Acute cardiac dysfunction</td>
<td>9.22 3.04–27.99 &lt;0.001</td>
<td>8.02 1.76–36.46 0.007</td>
</tr>
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</table>

CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,3.
Another study reported that apical involvement of RWMA in SAH patients was evident in 23–40% of the patients. Similarly, the current study showed that only 4 (27%) of 15 patients with ACD had the apical type of RWMA. Excluding 3 more patients with global hypokinesia, 8 (53%) patients showed the apex-sparing pattern of RWMA, which was similar to previous studies that included patients with SAH. In TTC, the reverse or inverted variant has been reported to be more frequently present at a younger age and to be always associated with triggering stress. One study of LV dysfunction after SAH concluded that younger age and anterior aneurysm position were independent predictors of this apex-sparing pattern. The trend of young age in patients with apex-sparing LV dysfunction was seen in this study despite statistical insignificance. From these results, young age and physical stress, especially neurogenic stress, seem to be more associated with the reverse or inverted pattern of LV dysfunction. Catecholamine cardiotoxicity has been recognized as the main pathophysiologic mechanism of LV dysfunction, but with the mid or basal myocardium, whereas other studies showed a higher density of sympathetic nerve terminals in the basal myocardium compared with the apex. This arrangement would allow balanced myocardial responses to sympathetic activation under low and medium levels. At the highest (supraphysiological) level of sympathetic stimuli, however, a disturbance of the balance and a change in the adrenergic signaling pathways for negative inotropic effect have been reported, which might cause regional LV hypokinesia. Banki et al explained that the apex-sparing pattern of LV dysfunction in patients with SAH was caused by a relative paucity of sympathetic nerve terminals in the apex. We also suspect that the LV basal segments having more sympathetic nerve endings might be more vulnerable to catecholamine toxicity under the conditions of neurogenic stress whereas the LV apex having more adrenoceptors might be more vulnerable to catecholamine toxicity under the conditions of general stress. Cimarelli et al reported that sympathetic function and glucose metabolism seem to be strictly correlated in the hypoxic myocardium. However, another small study using myocardial scintigraphy failed to show a significant difference in the sympathetic innervation between the apex-sparing and apex-affecting patterns of NSC in patients with SAH. The precise pathophysiology for the different wall motion abnormalities between TTC and NSC needs further study.

In this study, patients with ACD and acute brain hemorrhage had a high in-hospital mortality rate (60%), which was much higher than the in-hospital mortality rates of 14% or 11% in the study patients without CD or with OCD, respectively. Regarding TTC, previous studies reported in-hospital mortality rates of 8.4% and 16%, and mortality per patient-year of 5.6%. Our data showed an in-hospital mortality rate of 6.7% in 15 patients diagnosed with TTC according to Mayo clinic criteria during the same study period in our hospital (The characteristics of 15 patients are shown in Table S2). Therefore, patients with ACD and acute brain hemorrhage seem to have a poorer prognosis than patients with acute brain hemorrhage but with ACD or patients with generic TTC. Another study involving SAH patients reported a poor outcome in patients with TnI elevation compared with patients without TnI elevation (37% vs. 19%). In addition to SAH, TnI elevation in patients with ICH or ischemic stroke was also reported to be significantly associated with poor in-hospital outcome. Because poor neurologic condition is associated with the development of CD, the poor outcome in patients with neurocardiac injury is caused mainly by the underlying neurologic condition. Consistent with our findings, however, several studies have shown that poorer outcomes in patients with neurocardiac injury are independent of SAH severity. Furthermore, in the current study, LV dysfunction on echocardiography was a more powerful predictor than TnI elevation for in-hospital death.

Study Limitations
Firstly, the study patients were enrolled in a single center and for a relatively short duration, and the number of patients with ACD was too small to characterize the different types of ACD and to show a statistically significant difference among different types of ACD. Secondly, because we included heterogeneous types of brain hemorrhage we could not classify the patients by the severity of brain hemorrhage and could not investigate the relationship between severity of brain hemorrhage and incidence of ACD. Instead, we analyzed the effect of ACD on short-term outcome adjusted for initial GCS. Thirdly, we could not show long-term follow-up data because we only followed the patients until hospital discharge or death. As other limitations, we did not perform serial echocardiography for all patients but only early admission echocardiography, so we may have missed cases of ACD developing later after admission and were unable to discern the changes of cardiac function. Coronary angiography was not performed in study patients, which prevented us from defining our study patients as having stress cardiomyopathy according to the Mayo clinic criteria. Moreover, the classification of ACD and OCD in this study might be incomplete and some patients may have had both components.

Conclusions
ACD associated with acute brain hemorrhage was observed in 7% of the present study patients. In comparison with TTC, ACD in patients with brain hemorrhage occurred in both men and women at a similar rate and showed an apex-sparing pattern of LV systolic dysfunction at a higher rate. In addition, patients with ACD had a higher in-hospital mortality rate, which was independent of their initial GCS.

References


24. Ramaraj R, Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. *Congest Heart Fail* 2010; 16: 284 – 286.


**Supplementary Files**

**Supplementary File 1**

**Table S1.** Characteristics of 9 patients with cardiac dysfunction unrelated to brain hemorrhage

**Table S2.** Clinical characteristics of 15 patients diagnosed with takotsubo cardiomyopathy according to Mayo Clinic criteria during the same study period in the same hospital

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-16-0395