Summary

Acute coronary syndrome (ACS) is the major cause of out-of-hospital cardiac arrest (OHCA). The relationship between the findings from coronary images and return of spontaneous circulation (ROSC) interval is still unknown. Hence, we investigated this relationship in ACS patients with OHCA.

A cohort of 2779 patients was admitted to our emergency center due to cardiopulmonary arrest (CPA) between April 2011 and March 2015. We included ACS patients who had CPA with ventricular fibrillation (VF) as an initial rhythm, were successfully resuscitated, underwent coronary angiography (CAG), had a culprit lesion, and were diagnosed with ACS (n = 58; age, 63.7 ± 12.0 years; 93.1% male).

We divided the 58 patients into two groups, an early ROSC group (ROSC ≤ 20 minutes: E-ROSC) and a late ROSC group (ROSC > 20 minutes: L-ROSC), and then analyzed their characteristics.

The finding of a collateral artery for the culprit lesion location, Rentrop II-III, and TIMI III flow on CAG on arrival presented no significant differences between the two groups (Rentrop II-III: 25.0% versus 23.5%, P = 0.90; TIMI III: 33.3% versus 35.3%, P = 0.88). The incidence of multivessel coronary artery disease (MVD) was lower in the E-ROSC group than in the L-ROSC group (16.7% versus 58.8%, P = 0.001).

Collateral and TIMI flow were not associated with ease of resuscitation, but MVD may have a negative impact on resuscitation, especially in VF patients.

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Key words: Resuscitation, Coronary angiography, Collapse to resuscitation time

The prognosis of patients with out-of-hospital cardiac arrest (OHCA) has been poor, but the survival rates of OHCA patients have been improving due to revisions of the “chain of survival,” such as the improvement in bystander cardiopulmonary resuscitation (CPR), widespread use of automated external defibrillators, and improvement in post-cardiac arrest care.7,8

Important prognostic predictive factors are a witnessed arrest, an initial shockable rhythm, bystander-initiated CPR, and return of spontaneous circulation (ROSC).5,9 OHCA patients with an initial shockable rhythm, such as ventricular fibrillation (VF), have a higher chance of resuscitation, which leads to better neurological outcomes, than patients with non-shockable rhythms, such as pulseless electrical activity (PEA) or asystole. The likelihood of survival following out-of-hospital VF cardiac arrest improves as the interval from collapse to treatment with defibrillation decreases.9

But even in these relatively favorable situations, many patients cannot be resuscitated easily.9

Additionally, acute coronary syndrome (ACS) causes OHCA, and as recommended by guidelines, emergency coronary angiography (CAG) should be performed for OHCA patients.

The relationship between collapse to ROSC time and the findings from CAG in OHCA patients with ACS has not been reported and is still unclear.

The purpose of our study is to investigate the relationship between collapse to resuscitation time and findings from the initial CAG in OHCA patients with ACS.

Methods

Study design: The Tokyo Metropolitan Bokutoh Hospital is the only tertiary emergency center in the East Tokyo area that has approximately 1,400,000 inhabitants, and all patients with OHCA who have a chance of resuscitation are transported to our institution.7,9

We performed a retrospective analysis on all patients admitted to our institution between April 2011 and March
2015.

Inclusion criteria were age greater than 18 years and confirmation of cardiac arrest by the emergency staff. During this period, 2,779 patients with CPR were admitted and 474 patients (17%) were successfully resuscitated. The definition of resuscitation is the confirmation of stable circulation dynamics or interruption of chest compressions by the introduction of extracorporeal membrane oxygenation (ECMO).

All patients who were successfully resuscitated underwent urgent contrast-enhanced computed tomography from the head to the pelvis, and 155 patients with no obvious extra-cardiac cause of OHCA underwent emergent CAG. CAG revealed that 74 patients had a coronary culprit lesion, and they were diagnosed with ACS. We retrospectively excluded patients with non-shockable rhythms at initial rhythm check (n = 13), patients with no witnesses (n = 2), and patients who did not receive bystander CPR (n = 1) and then proceeded to analyze the remaining 58 patients.

If resuscitation takes longer than 20 minutes, the possibility of a good neurological prognosis decreases, according to previous reports.9 We therefore divided the 58 patients into two groups: the early ROSC group (ROSC ≤ 20 minutes: E-ROSC) and the late ROSC group (ROSC > 20 minutes: L-ROSC) (Figure 1). We analyzed both groups for their characteristics and findings from the initial CAG.

Prehospital care and inclusion criteria for extracorporeal cardiopulmonary resuscitation: All patients received bystander CPR and out-of-hospital resuscitation from emergency medical services (EMS) according to the Japanese CPR guidelines.

EMS can perform medical care according to basic life support guidelines, and with the instruction of a medical advisor from the control room, they can also perform tracheal intubation, intravenous line insertion, and injection of intravenous adrenaline.

We performed extracorporeal cardiopulmonary resuscitation (ECPR) for patients who had not been successfully resuscitated, regardless of the best medical practice, in cases in which the patient was less than 65 years old, collapse to hospital arrival time was less than 30 minutes, patient initially had a shockable rhythm at EMS arrival, or collapse occurred after EMS arrival to our institution.

Date collection and clinical outcome: The Institutional Review Board of our institution approved this study. Written informed consent was obtained from the patients or their family members.

Laboratory data, etiology, pre-existing co-morbidities, collapse to ROSC time, neurological outcome at 30 days, 30-day survival rate, and other factors were retrospectively collected from the medical records. Clinical outcomes were defined as neurological outcomes at 30 days after ROSC and 30-day survival. Neurological outcomes were assessed using the Glasgow-Pittsburgh cerebral performance category scale (CPC). CPC1 and CPC2 were classified as good neurological outcomes and CPC3 to CPC5 as poor neurological outcomes.10

All clinical outcomes were confirmed by reviewing medical charts and contacting the referring physician and/or the patient’s family. All events were registered by the attending physicians. The diagnosis of clinical events was adjudicated by two independent cardiologists who were blinded to the findings of the emergency procedures. Multivessel coronary artery disease (MVD) was defined as at least two major vessels (> 2 mm in diameter) with stenosis of greater than 70% of the diameter. We defined the culprit of the left main trunk (LMT) as two-vessel disease, referencing previous studies.11-14

Definition of TIMI flow and Rentrop grade: We used TIMI grade as the degree of coronary flow15 and Rentrop...
classification as the degree of collateral flow.\(^{16}\)

**Statistical analysis:** Continuous variables are expressed as mean ± SD when normally distributed and as median and interquartile range when non-normally distributed. Categorical data are presented as absolute numbers and percentages. The differences in continuous variables were assessed using the Student’s t-test or Mann-Whitney U test, as appropriate. The chi-square test or Fisher’s exact test, as appropriate, was computed to assess the differences in categorical variables. To examine the impact of collapse to ROSC time in the context of baseline clinical characteristics, logistic regression analysis was constructed for the same endpoints with the following candidate predictors: hypertension, collapse to first defibrillation countershock (DC) time, and MVD. Cumulative event rates were evaluated using Kaplan-Meier estimates and compared using the log-rank test.

A two-tailed \( P \) value less than .05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (SPSS, Inc., Chicago, IL).

**Results**

**Patient characteristics and clinical outcomes:** Of the 58 patients, 24 patients (41.4%) were resuscitated within 20 minutes (E-ROSC) and 34 patients (58.6%) needed over 20 minutes to be resuscitated (L-ROSC).

Clinical characteristics of the study population are summarized in Table I. The E-ROSC group had a higher incidence of hypertension, lower incidence of diabetes mellitus, and greater proportion of females. The collapse to first DC time was significantly shorter in the E-ROSC group than in the L-ROSC group, which was a prehospital factor. During resuscitation, the use of adrenaline and nifekalant were more frequent in the L-ROSC group than in the E-ROSC group. On the other hand, there were no significant differences in the use of amiodarone, lidocaine, and magnesium between the two groups. Moreover, ECG findings after ROSC revealed that there were no significant differences between the two groups. The E-ROSC group had more patients with 30-day survival and good neurological prognoses than the L-ROSC group (Table I). Figure 2 shows the Kaplan-Meier curve, which compares the survival rates between the E-ROSC and L-ROSC groups.

**Findings from coronary angiography:** Among the 58 patients, 20 patients (34.4%) had TIMI grade III flow in the culprit lesion at the initial CAG. There were no significant differences between the E-ROSC and L-ROSC groups regarding coronary flow (33.3% versus 35.3%), or collateral circulation. However, the L-ROSC group had a significantly higher incidence of MVD than the E-ROSC group (Table II).

In univariate analysis, the risk factors for the L-ROSC group were being male, non-hypertension, diabetes mellitus, delay to first DC time, and MVD. Unfortunately, the E-ROSC group had no patients with diabetes mellitus; we therefore could not include diabetes mellitus, which is a very strong confounding factor. After adjusting for hypertension, collapse to first DC time, and MVD, the last two factors were found to be the independent predictors of L-ROSC (Table III).

**MVD versus SVD:** We divided the patients into two groups, the culprit-only single-vessel coronary artery disease (SVD) group and the MVD group, and assessed the characteristics of the two groups (Table IV).

The MVD group had a higher incidence of diabetes

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### Table I. Characteristics of Patients and Prognosis

<table>
<thead>
<tr>
<th></th>
<th>All patient ((n = 58))</th>
<th>E-ROSC ((n = 24))</th>
<th>L-ROSC ((n = 34))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.7 ± 12.0</td>
<td>65 ± 14.3</td>
<td>63 ± 10.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>54 (93.1)</td>
<td>20 (83.3)</td>
<td>34 (100)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (24.1)</td>
<td>0 (0)</td>
<td>14 (24.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>31 (53.5)</td>
<td>17 (70.8)</td>
<td>14 (41.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>40 (69.0)</td>
<td>17 (70.8)</td>
<td>23 (67.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>32 (55.2)</td>
<td>12 (50.0)</td>
<td>20 (58.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Collapse to 1st DC time (minutes)</td>
<td>7.9 ± 4.3</td>
<td>5.3 ± 3.5</td>
<td>9.7 ± 3.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECPR, n (%)</td>
<td>19 (32.8)</td>
<td>0 (0)</td>
<td>19 (55.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, n (%)</td>
<td>26 (44.8)</td>
<td>2 (8.3)</td>
<td>24 (70.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>15 (25.9)</td>
<td>3 (12.5)</td>
<td>12 (35.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10 (17.2)</td>
<td>6 (25.0)</td>
<td>4 (11.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2 (3.4)</td>
<td>1 (4.2)</td>
<td>1 (2.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Magnesium</td>
<td>24 (41.4)</td>
<td>0 (0)</td>
<td>7 (20.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ROSC indicates return of spontaneous circulation; DC, defibrillation countershock; ECPR, extracorporeal cardiopulmonary resuscitation; ECG, electrocardiogram; and PCI, percutaneous coronary intervention.
I n tH e a r tJ
September 2019

Figure 2. A Kaplan-Meier curve. Comparison of patients with E-ROSC and L-ROSC. ROSC indicates return of spontaneous circulation; E-ROSC, early ROSC (ROSC ≤ 20 minutes); and L-ROSC, late ROSC (ROSC > 20 minutes).

Table II. Findings from Initial CAG

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All patients (n = 58)</th>
<th>E-ROSC (n = 24)</th>
<th>L-ROSC (n = 34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI III flow in culprit vessel, n (%)</td>
<td>20 (34.4)</td>
<td>8 (33.3)</td>
<td>12 (35.3)</td>
<td>0.877</td>
</tr>
<tr>
<td>Collateral Rentrop grades II-III, n (%)</td>
<td>14 (24.1)</td>
<td>6 (25.0)</td>
<td>8 (23.5)</td>
<td>0.897</td>
</tr>
<tr>
<td>MVD, n (%)</td>
<td>24 (41.4)</td>
<td>4 (16.7)</td>
<td>20 (58.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Culprit of ACS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMT, n (%)</td>
<td>4 (6.9)</td>
<td>0 (0.0)</td>
<td>4 (11.8)</td>
<td>0.080</td>
</tr>
<tr>
<td>LAD, n (%)</td>
<td>28 (48.3)</td>
<td>14 (58.3)</td>
<td>14 (41.2)</td>
<td>0.198</td>
</tr>
<tr>
<td>LCX, n (%)</td>
<td>2 (3.4)</td>
<td>1 (4.2)</td>
<td>1 (2.9)</td>
<td>0.801</td>
</tr>
<tr>
<td>RCA, n (%)</td>
<td>24 (41.4)</td>
<td>9 (37.5)</td>
<td>15 (44.1)</td>
<td>0.614</td>
</tr>
</tbody>
</table>

CAG indicates coronary angiography; ROSC, return of spontaneous circulation; MVD, multivessel coronary artery disease; ACS, acute coronary syndrome; LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; and RCA, right coronary artery.

Table III. Univariate and Multivariate Analysis of the Factors for Late ROSC

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.03</td>
<td>0.288</td>
</tr>
<tr>
<td>MVD</td>
<td>0.001</td>
<td>7.14</td>
</tr>
<tr>
<td>Onset to 1st DC time (per minute increase)</td>
<td>&lt; 0.001</td>
<td>1.41</td>
</tr>
</tbody>
</table>

ROSC indicates return of spontaneous circulation; MVD, multivessel coronary artery disease; and DC, defibrillation countershock.

Discussions

The main findings of our study can be summarized as follows.

Among OHCA patients with ACS who initially had shockable rhythms, collateral grade and recanalization were not associated with ease of resuscitation, but MVD might have a negative impact on resuscitation attempts.

Generally, about 40%-50% of ACS patients had a
In the heart J
September 2019
ASSOCIATION OF MVD WITH ROSC INTERVAL

Figure 3.

A Kaplan-Meier curve. Comparison of patients with SVD and MVD. SVD indicates single-vessel coronary artery disease and MVD, multivessel coronary artery disease.

| Table IV. Characteristics of MVD and SVD Patients and Prognosis |
|-----------------|-----------------|-----------------|-----------------|
| Age (years) | 63.7 ± 11.9 | 62.5 ± 12.7 | 65.5 ± 10.4 |
| Male, n (%) | 54 (93.1) | 30 (88.2) | 24 (100.0) |
| Diabetes mellitus, n (%) | 14 (24.1) | 4 (11.8) | 10 (41.7) |
| Hypertension, n (%) | 31 (53.4) | 18 (52.9) | 13 (54.2) |
| Smoker, n (%) | 32 (55.2) | 16 (47.1) | 16 (66.7) |
| Dyslipidemia, n (%) | 40 (69.0) | 23 (67.6) | 17 (70.8) |
| E-ROSC, n (%) | 24 (41.4) | 20 (58.8) | 4 (16.7) |
| Collapse to 1st DC time (minutes) | 7.9 ± 4.3 | 7.1 ± 4.2 | 9.1 ± 4.2 |
| Collapse to ROSC time (minutes) | 27.4 ± 17.5 | 21.1 ± 17.4 | 36.4 ± 13.2 |
| Collapse to hospital time (minutes) | 31.8 ± 9.9 | 30.9 ± 10.5 | 33.2 ± 8.8 |
| ECPR, n (%) | 19 (32.8) | 7 (20.6) | 12 (50.0) |
| STE at initial ECG, n (%) | 32 (55.2) | 17 (50.0) | 15 (62.5) |
| TIMI III flow at initial CAG, n (%) | 20 (34.5) | 10 (29.4) | 10 (41.7) |
| Rentrop II-III at initial CAG, n (%) | 14 (24.1) | 9 (26.5) | 5 (20.8) |
| Culprit of ACS LMT, n (%) | 4 (6.9) | 0 (0.0) | 4 (16.7) |
| LAD, n (%) | 28 (48.3) | 23 (67.6) | 5 (20.8) |
| LCX, n (%) | 2 (3.4) | 1 (2.9) | 1 (4.2) |
| RCA, n (%) | 24 (41.4) | 10 (29.4) | 14 (58.3) |
| Performed PCI, n (%) | 50 (86.2) | 31 (91.1) | 19 (79.1) |
| PCI success, n (%) | 48 (82.8) | 31 (91.1) | 17 (70.8) |
| 30-day survival, n (%) | 37 (63.8) | 27 (79.4) | 10 (41.7) |
| Good neurological outcome, n (%) | 26 (44.8) | 20 (58.8) | 6 (25.0) |

SVD indicates single-vessel coronary artery disease; MVD, multivessel coronary artery disease; ROSC, return of spontaneous circulation; DC, defibrillation countershock; ECPR, extracorporeal cardiopulmonary resuscitation; STE, ST-segment elevation; ECG, electrocardiogram; CAG, coronary angiography; ACS, acute coronary arteries; LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; and PCI, percutaneous coronary intervention.

coronary disease besides the culprit lesion. Approximately 75% of ACS patients with cardiogenic shock presented with MVD. Darren, et al. reported that 64% of OHCA patients with cardiogenic shock had MVD, which is a significant negative factor in 6-month survival outcome. ACS patients with MVD tend to have more unstable hemodynamic states compared with patients with SVD.

In a related study, Otani, et al. compared ECPR patients with non-ECPR patients and showed that the resistance to conventional CPR was related to ongoing myocardial ischemia. In their study, there were no significant differences in the location of the culprit lesion and the number of coronary artery stenosis between the two
groups, but patients with no recanalization during the ini-
tial CAG were significantly more common in the ECPR group than in the non-ECPR group. These findings are inconsistent with our results. Coronary flow evaluation under ECMO support is difficult, and coronary flow is often suppressed under the counterflow from ECMO. These factors might result in decreased diagnostic accuracy. Furthermore, in this study, the number of patients with ECPR, in whom ECPR was probably complicated with cardiogenic shock, was small compared with that in previous studies. Collateral flow for the culprit lesion might not be associated with the hemodynamic instability presented in a previous study.

The fact that MVD prolonged the collapse to ROSC time may be explained as follows.

We could expect early resuscitation for patients with-
out cardiogenic shock under favorable conditions for re-
suscitation, such as a relatively short collapse to first DC
time (average 8 minutes), the presence of witnesses, the
administration of bystander CPR, and an initial shockable rhythm.

Patients with cardiogenic shock might require more
time for resuscitation in terms of insufficient coronary flow, which occurs in prolonged PEA or recurrent VF. In this way, MVD may be the predictor of prolonged cardio-
genic shock under less coronary flow.

In our study, the E-ROSC group had a relatively
small proportion of MVD (17%) compared with that re-
ported in a previous report, such as post resuscitation with
prolonged cardiogenic shock (64%). Patients with SVD
may have a tendency to more easily reach a stable hem-
dynamic state and achieve early ROSC than those with
MVD, even if the former have life-threatening arrhyth-
mas.

Staged percutaneous coronary intervention (PCI) was
performed at our institution, even though it was compi-
lated by cardiogenic shock. ESC guidelines and previous
reports recommend multivessel intervention for ACS pa-
tients with cardiogenic shock. However, de Waha, et al.
and additional reports showed that performing multi-
vessel PCI provided no superiority over culprit-only
PCI. Further, Thiele, et al. reported that culprit-only PCI (with staged PCI) was superior to multivessel PCI with respect to a 30-day survival rate for patients with
MVD and acute myocardial infarction with cardiogenic
shock (CULPRIT-SHOCK Clinical Trial).

In our study, patients with MVD had a relatively fa-
vorable 30-day survival rate (41.7%) compared with that
presented in previous data. Initial culprit-only PCI with
staged PCI might be beneficial for these patients.

Clinical implication: Our study showed that MVD has
a negative impact on early resuscitation and that collateral
grade and recanalization for the culprit lesion are not
associated with ease of resuscitation among OHCA patients
with ACS who initially had shockable rhythms. To the
best of our knowledge, this is the first report in which the
relationship between collapse to ROSC time and the find-
ings from emergency CAG following ROSC was investigat-
ged.

Limitations: This is a retrospective study with a relatively
small sample size. Selection bias may have been intro-
duced because the study population included patients
treated at a tertiary referral center. Regarding the diagno-
sis of ACS, a blinded review of the cases by independent
physicians who were unaware of the conclusion was not
performed. ACS was diagnosed by more than two onsite
interventional cardiologists and intensivists on the basis of
the findings and/or CAG, but this is sometimes difficult in
clinical practice.

Due to the small sample size, there were no patients
with diabetes mellitus in the E-ROSC group and no fe-
nals in the L-ROSC group; we regretfully acknowledge
this as the most important limitation of this study. Since
we had no diabetes mellitus patients in the E-ROSC
group, we could not analyze diabetes mellitus, which is a
very strong confounding factor. Diabetes mellitus might
be associated with the factor of prolonged time to resusci-
tation, and further studies are needed to elucidate this asso-
ciation.

In the culprit lesion, we classified LMT as a two-
vessel disease. There were no obvious significant differ-
ences between the two groups with respect to the culprit
lesion; the L-ROSC group had a tendency toward the
LMT culprit. ACS patients with an LMT culprit lesion
that affected the results had poorer outcomes. Further
study is needed to eliminate the LMT culprit lesion.

In this study, we precisely analyzed the collapse to
ROSC time from EMS and hospital records. We also que-
ried patients or their families about the time from the on-
set of ACS to collapse, but the data was largely inaccurate
and could not be analyzed regardless of our best efforts.

Conclusion

Collateral flow for the culprit lesion and recanaliza-
tion were not associated with ease of resuscitation, but
MVD may have a negative impact on resuscitation, even
in cases with shockable rhythms under fully equipped
conditions.

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isted in data collection.

Disclosures

Conflicts of interest: The authors report no conflicts of
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dustry.

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