Characteristics of Patients With Cardiac Arrest Caused by Coronary Vasospasm

Nobuaki Kobayashi, MD; Noritake Hata, MD; Tetsuro Shimura, MD; Shinya Yokoyama, MD; Akihiro Shirakabe, MD; Takuro Shinada, MD; Kazunori Tomita, MD; Daisuke Murakami, MD; Masamichi Takano, MD; Yoshihiko Seino, MD; Hisashi Matsumoto, MD; Kunihiro Mashiko, MD; Kyoichi Mizuno, MD

Background: Although coronary vasospasm (CVS) would be one of the major causes of out-of-hospital cardiac arrest (OHCA), the characteristics of patients with cardiac arrest caused by CVS have not been clarified.

Methods and Results: In study 1, 1,000 consecutive patients with OHCA were retrospectively categorized based on the cause of OHCA, and the prevalence of CVS OHCA was elucidated. In study 2, 138 consecutive CVS patients were divided into 2 groups: CVS with cardiac arrest (arrest-CVS, n=12) and CVS without cardiac arrest (non-arrest-CVS, n=126). In study 1, 589 patients had OHCA caused by cardiovascular disease and 121 patients were successfully resuscitated. Among the 121 resuscitated patients, 9 had CVS OHCA. In study 2, the incidence of cardiac events (ie, cardiac arrest or chest pain) occurring on vigorous exertion, in the daytime and without prodromal chest symptoms was higher in the arrest-CVS group than in the non-arrest-CVS group.

Conclusions: CVS is an important cause of OHCA. Because significantly different characteristics are observed between CVS patients with cardiac arrest and those without, care should be taken to diagnose CVS as the cause of cardiac arrest. (Circ J 2013; 77: 673–678)

Key Words: Circadian variation; Coronary vasospasm; Out-of-hospital cardiac arrest; Prodromal chest symptoms; Vigorous exertion

Out-of-hospital cardiac arrest (OHCA) is a major public health problem and many clinical trials have been conducted to lower the mortality rate for patients with OHCA.1-2 Previous investigations have found that acute coronary syndrome (ACS) is the most frequent cause of OHCA, particularly in the elderly population.3 Meanwhile, the occurrence of OHCA in young, healthy athletes with a previous history of heart disease, electrocardiography (ECG) abnormalities or chest symptoms has been attracting attention. What are the causes of OHCA in these patients? It has previously been reported that the most common cause of OHCA in young athletes is hypertrophic cardiomyopathy,4,5 but many patients have not received a precise diagnosis as to the cause of OHCA. In addition, we question why the number of cases of OHCA in young athletes is increasing despite the increased use of screening medical examinations such as ECG. Investigation into the causes of OHCA in patients without previous cardiac history, ECG abnormalities or chest symptoms is necessary in order to decrease the incidence and improve the prognosis of OHCA.

Editorial p600

Recent studies have reported that coronary vasospasm (CVS) is another important cause of OHCA. Patients with OHCA caused by CVS tend to be relatively young,6-9 but the characteristics of patients with CVS OHCA have not been fully investigated. There may be a possibility that CVS is a considerable cause of OHCA in young, healthy individuals.

We focused on CVS as the cause of OHCA, and conducted 2 investigations, study 1 and study 2, to clarify the characteristics of patients with cardiac arrest caused by CVS. Study 1 examined the prevalence of CVS OHCA and study 2 compared the characteristics of CVS patients with cardiac arrest to those without cardiac arrest.

Received June 29, 2012; revised manuscript received September 28, 2012; accepted October 26, 2012; released online December 1, 2012  Time for primary review: 14 days
Division of Intensive Care Unit (N.K., N.H., S.Y., A.S., T. Shinada, K.T.), Cardiovascular Center (T. Shimura, D.M., M.T., Y.S.), Department of Critical Care Medicine (H.M., K. Mashiko), Chiba-Hokusoh Hospital, Nippon Medical School, Chiba; and Department of Cardiovascular Medicine, Nippon Medical School, Tokyo (K. Mizuno), Japan
Mailing address: Nobuaki Kobayashi, MD, Division of Intensive Care Unit, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamagari, Inzai, Chiba 270-1694, Japan.  Email: s5047@nms.ac.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
Methods

The present studies, study 1 and study 2, were designed as retrospective studies using medical records to collect clinical data. The Ethics Committee of Chiba-Hokusoh Hospital, Nippon Medical School, approved the study protocols.

Study 1 Subjects
We enrolled 1,000 consecutive patients with OHCA transported to the emergency room at Chiba-Hokusoh Hospital, Nippon Medical School between May 2006 and December 2011. Pediatric patients younger than 14 years of age were excluded from the present study. Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.\(^{10}\) As shown in Figure 1, all of the 1,000 enrolled patients were categorized as to the cause of OHCA. Exogenous diseases included trauma, suffocation, suicide and murder. Endogenous diseases were diagnosed based on a combination of previous disease history, present illness and examination findings such as blood examination, ECG, ultrasound, computed tomography and others. Non-cardiovascular endogenous disease included cerebrovascular disease, bleeding, cancer, infection, respiratory disease, renal disease and other. The remaining cases involved cardiovascular endogenous disease consisting of CVS, ACS, cardiomyopathy, myocarditis, primary arrhythmia, pulmonary embolism and aortic disease. Among all of the OHCA patients with cardiovascular causes, 121 were successfully resuscitated and definitively diagnosed after admission according to a combination of blood examinations, ECG, echocardiography, computed tomography, coronary angiography with or without acetylcholine provocation test and electrophysiological assessment. In the present study, to distinguish between CVS and ACS, ACS was defined as unstable angina pectoris or acute myocardial infarction caused by organic coronary artery disease, except in patients with CVS OHCA.

Study 2 Subjects
We enrolled 138 consecutive patients who underwent coronary angiography and were definitively diagnosed with CVS between May 2006 and December 2011 (same period as that in study 1) at Chiba-Hokusoh Hospital, Nippon Medical School. CVS was defined as transient total or subtotal occlusion (>90% stenosis) of the coronary artery on initial coronary angiography or acetylcholine provocation test and maximum dilatation of coronary artery after i.c. nitrate. The method used for the acetylcholine provocation test is described in the guidelines of the Japanese Circulation Society.\(^{11}\) Among the 138 CVS patients, 9 with OHCA were initially admitted to Chiba-Hokusoh Hospital, Nippon Medical School (study 1 patients); 1 with OHCA was initially admitted to another hospital and thereafter transferred to Chiba-Hokusoh Hospital; 2 experienced cardiac arrest immediately after arriving at Chiba-Hokusoh Hospital; and 126 were without cardiac arrest (so-called vasospastic angina). Because all 12 CVS patients with cardiac arrest were thought to be almost equally high-risk, they were classified into the same group. Consequently, 138 CVS patients were categorized into 2 groups: CVS patients with cardiac arrest (arrest-CVS, n=12) and CVS patients without cardiac arrest (non-arrest-CVS, n=126).

Event Onset
Event onset was defined as the onset of circulation collapse symptoms (ie, syncopal attack) or chest symptoms. To compare the situations of event onset between arrest-CVS and non-arrest-CVS, we investigated whether the cardiac events
Cardiac Arrest Caused by CVS

Cardiac Arrest Caused by CVS

Enous causes such as trauma, suffocation, suicide or murder, and 129 experienced OHCA due to non-cardiovascular endogenous causes such as cerebrovascular disease, bleeding, cancer, infection, respiratory disease, renal disease or other. The remaining 589 patients experienced OHCA caused by probable or definite cardiovascular diseases. Of those 589 patients, 468 without resuscitation were not admitted to hospital, whereas 121 patients with successful resuscitation were admitted to hospital and received precise diagnosis. The causative cardiovascular diseases in the 121 OHCA patients are shown in Figure 2. Coronary angiography was performed in the successfully resuscitated OHCA patients, except in those with pulmonary embolism (n=8) and aortic dissection (n=4) who were definitively diagnosed on computed tomography. Among the 109 patients with coronary angiography, 64 patients with ACS and 10 patients with ischemic cardiomyopathy had significant organic coronary artery stenosis, and 2 patients with CVS had total or subtotal occlusion on initial coronary angiography and maximum dilatation of coronary artery after i.c. nitrate. The remaining 33 patients had no significant coronary artery stenosis. Patients with non-ischemic cardiomyopathy (n=17) were definitively diagnosed based on echocardiography, and patients with myocarditis (n=2) were definitively diagnosed based on clinical cause, ECG or echocardiography. Among 7 patients with primary arrhythmia, 3 were definitively diagnosed based on clinical cause and ECG. Finally, 11 undiagnosed patients without significant coronary stenosis on developed on vigorous exertion or not, in the daytime or at night-time, and with or without prodromal chest symptoms. In the present study, vigorous exertion was defined as vigorous-intensity physical activity ≥6 metabolic equivalents. The intensity of physical activity was accurately established according to medical records, but when accurate physical activity was not able to be established, we choose the strongest intensity in the estimated range. Daytime and night-time were defined as from 09.00 hours to 20.59 hours, and from 21.00 hours to 08.59 hours, respectively.

Statistical Analysis

Continuous variables are presented as median and interquartile range and were compared using Mann-Whitney U-test because they were not normally distributed. Dichotomous variables were compared using Fisher’s exact test because the number of CVS OHCA patients was small. Data were statistically analyzed using SPSS version 16.0. P<0.05 was considered to be statistically significant.

Results

Prevalence of Causative Cardiovascular Diseases in OHCA (Study 1)

A flow chart to categorize the OHCA patients based on the cause of cardiac arrest is presented in Figure 1. Among the 1,000 OHCA patients, 282 experienced OHCA due to exogenous causes such as trauma, suffocation, suicide or murder, and 129 experienced OHCA due to non-cardiovascular endogenous causes such as cerebrovascular disease, bleeding, cancer, infection, respiratory disease, renal disease or other. The remaining 589 patients experienced OHCA caused by probable or definite cardiovascular diseases. Of those 589 patients, 468 without resuscitation were not admitted to hospital, whereas 121 patients with successful resuscitation were admitted to hospital and received precise diagnosis. The causative cardiovascular diseases in the 121 OHCA patients are shown in Figure 2. Coronary angiography was performed in the successfully resuscitated OHCA patients, except in those with pulmonary embolism (n=8) and aortic dissection (n=4) who were definitively diagnosed on computed tomography. Among the 109 patients with coronary angiography, 64 patients with ACS and 10 patients with ischemic cardiomyopathy had significant organic coronary artery stenosis, and 2 patients with CVS had total or subtotal occlusion on initial coronary angiography and maximum dilatation of coronary artery after i.c. nitrate. The remaining 33 patients had no significant coronary artery stenosis. Patients with non-ischemic cardiomyopathy (n=17) were definitively diagnosed based on echocardiography, and patients with myocarditis (n=2) were definitively diagnosed based on clinical cause, ECG or echocardiography. Among 7 patients with primary arrhythmia, 3 were definitively diagnosed based on clinical cause and ECG. Finally, 11 undiagnosed patients without significant coronary stenosis on
coronary angiography underwent both acetylcholine provocation test and electrophysiological assessment. Seven patients were diagnosed with CVS and 4 patients were diagnosed with primary arrhythmia.

The patients with CVS (n=9), myocarditis (n=2) or primary arrhythmia syndrome (n=7) all survived at 30 days after cardiac arrest, whereas the survival rate of the patients with pulmonary embolism (n=8) or aortic disease (n=4) 30 days after cardiac arrest was markedly low. The survival rate of the patients with ACS (n=64) or cardiomyopathy (n=27), including ischemic cardiomyopathy, 30 days after cardiac arrest was approximately 40% for both. The survival rate of all 589 patients with OHCA caused by cardiovascular disease 30 days after cardiac arrest was 10%.

**Arrest-CVS vs. Non-Arrest-CVS (Study 2)**

The baseline characteristics of the arrest-CVS and non-arrest-CVS groups are given in Table 1. The patients in the arrest-CVS group were younger than those in the non-arrest-CVS group. Event onset on vigorous exertion or in the daytime were more prevalent in the arrest-CVS group than in the non-arrest-CVS group (P=0.004 and P=0.028, respectively). Prodromal chest symptoms were more prevalent in the non-arrest-CVS group than in the arrest-CVS group (P<0.001). Angiographic findings were similar between the arrest-CVS and non-arrest-CVS groups, except that CVS on the left circumflex artery was significantly more prevalent in the arrest-CVS than the non-arrest-CVS group. All patients in study 2 were alive at the time of discharge. Table 2 lists the characteristics of each CVS patient with cardiac arrest. Patients 1 and 6 had cardiac arrest immediately after arriving at Chiba-Hokusoh Hospital, Nippon Medical School, and patient 12 had cardiac arrest and was initially admitted to another hospital and thereafter transferred to Chiba-Hokusoh Hospital.

### Discussion

The present study has shown that CVS is an important cause of OHCA. In total, 7% of cardiogenic OHCA patients with successful resuscitation have CVS as the cause of OHCA. The present study also clearly demonstrated that youth is a significant characteristic of CVS patients with cardiac arrest, similar to that reported in a previous study.9 Additionally, vigorous physical activity, even in the daytime, plays a key role in whether CVS patients develop cardiac arrest.

Although the prognosis of patients with CVS is good,13 CVS receives attention as a cause of OHCA.8,14-17 A previous study on cardiac arrest in patients without organic heart disease (ie, normal cardiac function on echocardiogram, no evidence of coronary artery disease, and normal ECG) reported that 11% of patients experience cardiac arrest caused by CVS.16 In the present study, the prevalence of CVS was 7% in cardiogenic OHCA patients with successful resuscitation. The number of CVS patients who had OHCA without successful resuscitation was unknown, but the number of CVS patients without successful resuscitation may not be small. A postmortem autopsy study showed that 12% of patients with cardiac death caused by non-atherosclerotic coronary artery disease have CVS.17 There is no doubt that CVS is a considerable cause of OHCA, and dual induction tests, both CVS with i.c. acetylcholine and ventricular fibrillation with programmed stimulation, are recommended for OHCA patients without organic heart disease.8 CVS should be remembered as a cause of OHCA in patients without organic heart disease.

The phenomenon of CVS has been recognized since 1959 to be a cause of the variant form of angina pectoris (vasospas-
tic angina), which develops at rest, particularly between midnight and early morning and is not induced by exercise during daytime. Exercise-induced variant angina and exercise-induced ventricular fibrillation, however, have been reported to be caused by CVS. Concerning the circadian variance of CVS, 1 report demonstrated that episodes of cardiac arrest triggered by CVS are more prevalent in the daytime than at night-time, which is thus different from that observed with vasospastic angina. In the present study, cardiac events induced by vigorous physical activity and those developing in the daytime were more prevalent in the arrest-CVS than in the non-arrest-CVS group. A previous multicenter study demonstrated that 8% of vasospastic angina patients experience angina attacks induced by effort only; while 36% of vasospastic angina attacks triggered by vigorous physical activity and those developing in the daytime without prodromal chest symptoms. In addition, differentiating between CVS and ACS as the cause of cardiac arrest is difficult because both CVS and ACS have similar clinical findings, including ECG abnormalities and elevation of myocardial necrotic markers. Biomarkers other than myocardial necrotic markers, however, such as soluble lectin-like oxidized low-density lipoprotein receptor-1 and matrix metalloproteinase-9 may be used to differentiate CVS from ACS in the acute phase.

Study Limitations
The present study was a retrospective, single-center study and the subject group was relatively small. Only 12 patients experienced cardiac arrest caused by CVS, but it was possible to evaluate the patient characteristics. Conducting further multicenter studies with larger sample sizes is necessary in order to confirm the current findings. In addition, 468 OHCA patients without resuscitation were excluded from detailed analysis because it was difficult to make a definitive diagnosis in these patients. As a result, the real incidence and mortality rate of CVS OHCA could not be clarified. Because the 468 OHCA patients who experienced cardiac arrest caused by CVS, but it was possible to evaluate the patient characteristics. Conducting further multicenter studies with larger sample sizes is necessary in order to confirm the current findings. In addition, 468 OHCA patients without resuscitation were excluded from detailed analysis because it was difficult to make a definitive diagnosis in these patients. As a result, the real incidence and mortality rate of CVS OHCA could not be clarified. Because the 468 OHCA patients without resuscitation included some patients with CVS, performing additional postmortem autopsy studies to examine this point would be desirable. The enrolment of the non-arrest-CVS patients in the present study as control subjects may have been biased because patients who experienced chest pain at rest and at night-time tended to undergo acetylcholine provocation test. Further examination is needed to clarify the relationship between vasospastic angina and vigorous physical activity.

A lack of prodromal symptoms in CVS patients who develop cardiac arrest is another key point. It has been widely accepted that prodromal angina attacks occurring before myocardial infarction reduce infarction size and improve long-term prognosis. This is the phenomenon of ischemic preconditioning. A lack of prodromal symptoms is a mutual exacerbation factor for many kinds of cardiovascular disease. In the present study, the lack of prodromal chest symptoms was more prevalent in the arrest-CVS than in the non-arrest-CVS group, thus indicating that a lack of prodromal chest symptoms is a key point associated with the occurrence of cardiac arrest, even in patients with CVS. A previous study similarly showed that there was no relationship between cardiac arrest and the occurrence of prodromal syncope attacks in patients with CVS.

Because significant differences between CVS as a cause of cardiac arrest and CVS as a cause of angina are observed and many CVS patients with cardiac arrest do not have prodromal chest symptoms, it is difficult to definitively diagnose OHCA patients with CVS in the clinical setting. CVS should be kept in mind as a cause of cardiac arrest, especially in young patients, even though cardiac arrest develops on vigorous exertion and in the daytime without prodromal chest symptoms. In addition, differentiating between CVS and ACS as the cause of cardiac arrest is difficult because both CVS and ACS have similar clinical findings, including ECG abnormalities and elevation of myocardial necrotic markers. Biomarkers other than myocardial necrotic markers, however, such as soluble lectin-like oxidized low-density lipoprotein receptor-1 and matrix metalloproteinase-9 may be used to differentiate CVS from ACS in the acute phase. Further studies to enable differentiation of CVS from other cardiovascular diseases as the cause of cardiac arrest are needed.

### Table 2. Characteristics of CVS Patients With Cardiac Arrest

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Coronary risk factor</th>
<th>Location</th>
<th>Vigorous exertion</th>
<th>Time of day (24-h clock)</th>
<th>Prodromal chest symptoms</th>
<th>Acetylcholine provocation test findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>Smoking</td>
<td>In hospital</td>
<td>No</td>
<td>06.08</td>
<td>No</td>
<td>Diffuse LAD, LCX</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>50</td>
<td>Smoking</td>
<td>Out of hospital</td>
<td>Yes (Running)</td>
<td>09.04</td>
<td>Yes</td>
<td>Focal LCX</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>65</td>
<td>None</td>
<td>Out of hospital</td>
<td>Yes (Playing tennis)</td>
<td>14.58</td>
<td>No</td>
<td>Diffuse RCA</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>61</td>
<td>HT/DL/Smoking</td>
<td>Out of hospital</td>
<td>No</td>
<td>07.00</td>
<td>No</td>
<td>Diffuse RCA</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>Smoking</td>
<td>Out of hospital</td>
<td>No</td>
<td>09.34</td>
<td>No</td>
<td>Diffuse LAD, LCX</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>28</td>
<td>None</td>
<td>In hospital</td>
<td>No</td>
<td>06.25</td>
<td>Yes</td>
<td>Focal LAD, LCX, RCA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>60</td>
<td>HT/DL/Smoking</td>
<td>Out of hospital</td>
<td>No</td>
<td>00.46</td>
<td>Yes</td>
<td>Focal LAD, LCX, RCA</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>67</td>
<td>HTN</td>
<td>Out of hospital</td>
<td>No</td>
<td>03.50</td>
<td>No</td>
<td>Diffuse LCX, RCA</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>66</td>
<td>HT/Smoking</td>
<td>Out of hospital</td>
<td>No</td>
<td>05.20</td>
<td>No</td>
<td>Diffuse LAD, LCX, RCA</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>52</td>
<td>HT/Smoking</td>
<td>Out of hospital</td>
<td>Yes (Bicycle riding)</td>
<td>12.10</td>
<td>No</td>
<td>Diffuse LCX, RCA</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>55</td>
<td>DL</td>
<td>Out of hospital</td>
<td>Yes (Playing tennis)</td>
<td>10.25</td>
<td>No</td>
<td>Diffuse LCX, RCA</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>33</td>
<td>None</td>
<td>Out of hospital</td>
<td>Yes (Running)</td>
<td>12.30</td>
<td>No</td>
<td>Diffuse LAD, LCX</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Conclusions

CVS is a major cause of OHCA and it should therefore be kept in mind as a considerable cause of cardiac arrest, especially in young patients, even when OHCA develops on vigorous exertion, in the daytime, or without prodromal chest symptoms.

Disclosure

None.

References