Significance of Coronary Vasospasm in the Perioperative Management of Non-Cardiac Surgery

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Background: The number of patients undergoing non-cardiac surgery has been increasing. Thus, the reduction of cardiac events is important during the perioperative period. The prevalence of Japanese patients with coronary vasospasm is higher as compared with Western countries. The present study reported the role of coronary vasospasm in the perioperative period in a Japanese university hospital.

Methods and Results: A total of 77,745 consecutive patients who underwent non-cardiac surgery in Kumamoto University Hospital between April 2003 and March 2010 were retrospectively examined. Forty-two cases in which patients underwent coronary catheterization due to cardiovascular events in the perioperative period were reviewed, and data were collected on the type of surgery, urgency of surgery, cardiac risk factors, previous history and the cardiology consultation. The Revised Cardiac Risk Index (RCRI) was also calculated. A total of 18 patients were diagnosed as having definite vasospastic angina. In the definite vasospastic angina group, 9 patients had cardiovascular events intraoperatively. Six patients were in the group undergoing high-risk surgery. The RCRI score in the definite vasospastic angina group was 0.5±0.6 (mean±SEM), and only 2 patients had a preoperative consultation with a cardiologist.

Conclusions: Coronary vasospasm is not often encountered, but it can be a cause of cardiac trouble in the perioperative period. It should be taken into consideration at the time of planning of operation in Japanese patients even if they apparently have low cardiac risk. (Circ J 2012; 76: 1965–1971)

Key Words: Coronary vasospasm; Non-cardiac surgery; Perioperative period

Recently, there have been great advances in perioperative patient management as well as surgical technology. The number of patients who undergo non-cardiac surgery has been steadily increasing. In the perioperative period, reduction of cardiac events remains a significant problem.1–3 Tools that help evaluate the risk of a major adverse cardiac event include a preoperative exercise stress test as an objective assessment of functional capacity, the Revised Cardiac Risk Index (RCRI) as a predictive measure of the risk of a cardiac event during the perioperative period,4,5 and multi-detector row computed tomography (MDCT), which has a high diagnostic accuracy for the detection of coronary artery stenosis.

In the Japanese population, the prevalence of coronary vasospasm is higher than in Western countries.6–8 Therefore, coronary vasospasm should not be overlooked in perioperative care. Coronary vasospasm can initiate angina, myocardial infarction and fatal arrhythmias.9,10 There have been several reports of perioperative vasospasm,11–18 but the prevalence of provoked coronary vasospasm in the perioperative period remains to be elucidated. We retrospectively examined the impact of coronary vasospasm on cardiac events during non-cardiac surgery.

Methods

We retrospectively examined 77,745 consecutive patients who underwent non-cardiac operations in Kumamoto University Hospital between April 2003 and March 2010. We reviewed 42 patients who underwent coronary catheterization due to cardiovascular events in the perioperative period. The interval between surgery and cardiac catheterization ranged from 40 min to 92 days (mean, 18.4 days). Cardiovascular events included myocardial infarction, fatal arrhythmias and unstable
NAGAYOSHI Y et al.

0.066
0.000
20%
-
0.000
0.130
23
15/17/10
0.141
16
No.
0.176
-
0.000
0.154
0.226
0.000
n
42
0.054
0.128
0.005
11
-
77,745
-
-
36,430   2
0.000
1966

Data given as mean ± SEM or n (%).

Table 1. Type of Surgery vs. Cardiac Events

<table>
<thead>
<tr>
<th>Department</th>
<th>No. of operations</th>
<th>No. of events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal medicine</td>
<td>352</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>General surgery</td>
<td>7,822</td>
<td>11</td>
<td>0.141</td>
</tr>
<tr>
<td>Urology</td>
<td>2,300</td>
<td>3</td>
<td>0.130</td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>3,667</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Pediatrics and pediatric surgery</td>
<td>516</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>3,884</td>
<td>6</td>
<td>0.154</td>
</tr>
<tr>
<td>Dermatology and plastic surgery</td>
<td>2388</td>
<td>3</td>
<td>0.126</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>8,896</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>3,130</td>
<td>4</td>
<td>0.128</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>2,208</td>
<td>5</td>
<td>0.226</td>
</tr>
<tr>
<td>Oral surgery</td>
<td>1,511</td>
<td>1</td>
<td>0.066</td>
</tr>
<tr>
<td>Non-cardiac interventional radiology</td>
<td>3,988</td>
<td>7</td>
<td>0.176</td>
</tr>
<tr>
<td>Endoscopic procedures</td>
<td>36,430</td>
<td>2</td>
<td>0.005</td>
</tr>
<tr>
<td>Others</td>
<td>653</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>Total</td>
<td>77,745</td>
<td>42</td>
<td>0.054</td>
</tr>
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</table>

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (M/F)</th>
<th>Age (years), range</th>
<th>Type of surgery</th>
<th>Anesthetic technique</th>
<th>Comorbidity</th>
<th>Surgery-specific cardiac risk</th>
<th>Cardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emergency</td>
<td>General anesthesia</td>
<td>High age (&gt;75 years)</td>
<td>Low/Intermediate/High</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Elective</td>
<td>Focal anesthesia</td>
<td>Hypertension</td>
<td></td>
<td>Fatal arrhythmias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current smoker</td>
<td>Diabetes mellitus</td>
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<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>42 (27/15)</td>
<td>70±9 (46–87)</td>
<td></td>
<td>Current smoker</td>
<td>Dyslipidemia</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current smoker</td>
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Table 3. Results of Cardiac Catheterization

<table>
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<tr>
<th>Cardiovascular events</th>
<th>Diagnosis confirmed on cardiac catheterization</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (n=9)</td>
<td>Myocardial infarction</td>
<td>9</td>
</tr>
<tr>
<td>Fatal arrhythmias (n=4)</td>
<td>Vasospastic angina</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Organic angina</td>
<td>1</td>
</tr>
<tr>
<td>Unstable angina (n=29)</td>
<td>Vasospastic angina</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Organic angina</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Tako-tsubo cardiomyopathy</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Undefined angina</td>
<td>1</td>
</tr>
</tbody>
</table>

angina. Unstable angina was defined according to the Braunwald classification.9 We classified asymptomatic transient ischemic ST-T changes on electrocardiogram (ECG) monitoring during the intraoperative period as unstable angina. Fatal arrhythmias associated with acute myocardial infarction were classified into the myocardial infarction group. Fatal cardiac arrhythmias included ventricular tachycardia, ventricular fibrillation, conduction disturbances and asystole. We defined the perioperative period as being from the day of admission until postoperative day 30. The perioperative period was classified into preoperative, intraoperative and postoperative phases.

We collected data on type of surgery, urgency of surgery, cardiac risk factors, previous history of angina and whether a cardiology consultation was performed. The surgery-specific cardiac risk of non-cardiac surgery was classified according to American Heart Association/American College of Cardiology guidelines.6 The patients were divided into major, intermediate, or minor perioperative risk groups based on surgery-specific risk. Diagnostic endoscopy was included in endoscopic procedures as well as in other invasive endoscopic operations. Hypertension, dyslipidemia and diabetes mellitus were diagnosed according to their guidelines, respectively.20-22 A history of angina was based on information provided by the patient.

The study protocol was approved by the Human Ethics Review Committee of Kumamoto University School of Medicine, and a signed consent form was obtained from all subjects undergoing cardiac catheterization.

Diagnostic Criteria of Vasospastic Angina

A drug-induced spasm provocation test was performed in patients who were suspected to have coronary vasospasm. The patients were diagnosed as having coronary vasospasm according to Japan Cardiology Society guidelines.23 Coronary angiography was performed using the Judkins technique. In the case of coronary artery stenosis, the spasm provocation test was performed when the lesions were not proximal lesions of the main coronary trees and/or coronary flow was not limited. Coronary spasm was provoked by i.c. injection of acetylcholine into the right and left coronaries separately.24,25 A positive angiographic finding for coronary spasm is defined as “transient, total or subtotal occlusion of a coronary artery with angina and/or ischemic ECG change, which was rapidly relieved by nitroglycerin”.

RCRI

Six independent predictors of complications were included in the RCRI: high-risk surgery defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedures; history of ischemic heart disease; history of congestive heart failure; history of cerebrovascular disease; insulin-dependent diabetes; and preoperative serum creatinine ≥2.0 mg/dl. RCRI calculates perioperative risk by the sum of these scores.

Continuous variables are presented as mean±SEM and categorical variables as percentages. Multiple group comparisons of continuous data were performed with 1-way analysis of variance, followed by Scheffe’s method to compare individual groups. Other clinical characteristics were compared by either a chi-square or Fisher’s exact test. P<0.05 was considered significant.

Results

We identified 42 cardiovascular events that occurred after a variety of non-cardiac interventions among 77,745 patients.
Coronary Vasospasm in the Perioperative Period

Figure 1. Multi-detector row computed tomography (MDCT) and electrocardiogram (ECG) monitoring of a patient with vasospastic angina. (a–c) MDCT showed no significant stenosis in the coronary arteries. In the intraoperative period, (d) ventricular tachycardia occurred repeatedly, and (e) ST-T segment elevation was observed on ECG.

Figure 2. Cardiac catheterization of a patient with vasospastic angina. Selective coronary angiography was performed using Judkins catheters. A pacing catheter was placed in the right ventricle to prevent bradycardia during acetylcholine injection. Another catheter was inserted into the coronary sinus vein for blood sampling. (a,d) Control angiogram showed no apparent organic lesion. (b,e) Coronary spasm provocation test by i.c. injection of acetylcholine indicated distal segment vasospasm of the left coronary artery and total occlusion of the right coronary artery. (c,f) Coronary vasospasm was relieved by i.c. injection of isosorbide dinitrate (ICISDN).
Cardiovascular events were as follows: myocardial infarction (n=9), fatal arrhythmias (n=4) and unstable angina (n=29). One patient died of myocardial infarction despite revascularization therapy during hospitalization. Clinical characteristics of patients with cardiovascular events are presented in Table 2.

Diagnosis on Coronary Angiography
Results of cardiac catheterization are listed in Table 3. Nine patients experienced transient myocardial ischemia associated with significant coronary artery stenosis. Spasm provocation tests were performed in 20 patients. We diagnosed 18 patients as having definite vasospastic angina in total. In 4 patients with fatal arrhythmia, 2 patients had coronary vasospasm. In 1 patient with normal coronary arteries, a spasm provocation test could not be performed because of pre-catheterization injection of isosorbide dinitrate. Four patients with suspected acute coronary syndrome were diagnosed as having tako-tsubo cardiomyopathy based on the clinical and angiographic findings.

Case Report
We present a typical case of vasospastic angina. The patient was a 61-year-old man who was admitted to Kumamoto University Hospital for treatment of pancreatic tumor. During hospitalization, he complained of transient chest discomfort. This patient had no history of heart disease. The resting 12-lead ECG was within normal limits. MDCT indicated no significant stenosis (Figures 1a–c), and the patient did not receive cardiology consultation preoperatively. Subtotal pancreatectomy with splenectomy was performed under general anesthesia. During operation, ventricular tachycardia occurred repeatedly, and ST-T segment elevation was observed on ECG (Figures 1d,e). ECG alterations were rapidly improved by continuous infusion of lidocaine (60 mg/h), nitroglycerin (0.5 μg · kg⁻¹ · min⁻¹) and diltiazem (5 μg · kg⁻¹ · min⁻¹). Elevation of cardiac enzymes was not observed. Coronary angiography was performed in the postoperative period (40 days after surgery). The control angiogram showed no apparent organic lesion, as was shown on MDCT angiography. Intracoronary injection of acetylcholine provoked total occlusion of the right coronary artery. There were no significant ECG changes during the spasm provocation test, but the patient complained of chest oppression. Neither organic stenosis nor plaque rupture was observed after i.c. injection of isosorbide dinitrate (Figure 2).

Clinical Characteristics of Patients With Definite Vasospastic Angina
Clinical characteristics of patients with definite vasospastic angina are given in Table 4. All patients with definite vasospastic angina underwent elective operation. The most prevalent risk factor was hypertension (n=7, 33%), followed by dyslipidemia and advanced age (>75 years). The prevalence of diabetes mellitus and of dyslipidemia in the definite vasospastic angina group were significantly lower than in the organic coronary disease group. Four patients were free of any apparent risk factors. Resting 12-lead ECG showed abnormalities in 2 patients. In both patients, T waves were inverted in the precordial leads. Atrial fibrillation was observed in 1 patient. There were no patients with abnormal q waves.

The characteristics of vasospastic angina are also shown in Figure 3. Surgery-specific risks were distributed equally. The

<table>
<thead>
<tr>
<th>Table 4. Clinical Characteristics: DVA vs. OOCD</th>
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<tr>
<td>n (M/F)</td>
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<tr>
<td>Age (years), range</td>
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<tr>
<td>Resting 12-lead ECG abnormalities</td>
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<tr>
<td>Type of surgery</td>
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<tr>
<td>Emergency</td>
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<td>Elective</td>
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<td>Anesthetic technique</td>
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<td>General anesthesia</td>
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<td>Focal anesthesia</td>
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<td>Comorbidity</td>
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<td>High age</td>
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<tr>
<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Current smoker</td>
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<tr>
<td>Coronary organic stenosis</td>
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<tr>
<td>Laboratory data</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
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<tr>
<td>C-reactive protein (mg/dl)</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Low-density cholesterol (mg/dl)</td>
</tr>
<tr>
<td>High-density cholesterol (mg/dl)</td>
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<tr>
<td>Triglyceride (mg/dl)</td>
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Data given as mean±SEM or n (%).

DVA, definite vasospastic angina; OOCD, other organic coronary disease (organic angina and myocardial infarction); ECG, electrocardiogram.
The majority of patients (83%) were operated upon under general anesthesia. Half of the patients had cardiovascular events during the intraoperative period. During vasospastic events, ST elevation was found in 7 patients (39%). In 2 patients, coronary vasospasm induced ventricular fibrillation and ventricular tachycardia during non-cardiac surgery. Eight patients (44%) had a history of angina, but only 2 patients (11%) had cardiology consultation.

**RCRI**
The RCRI scores are given in Figure 4. The mean RCRI score in the definite vasospastic angina group was 0.5±0.6 (mean±SEM). The majority of these patients (94%) were classified as low risk (RCRI score, 0 or 1).

**Discussion**
Coronary vasospasm is defined as an abnormal contraction of the coronary artery, which causes myocardial ischemia. In the Japanese population, coronary vasospasm plays an important role in the pathogenesis of ischemic heart disease. This study demonstrates the importance of recognizing vasospasm in the perioperative period of non-cardiac surgery. Perioperative cardiovascular events can be caused by coronary vasospasm, although this event is not often encountered.

More than half of vasospastic events were first documented...
in the intraoperative period. It is unclear whether the operative procedures are the direct cause of vasospasm, or merely coincidental. In some reports, the association of extradural anesthesia with vasospasm has been suggested. Sympathetic blockade reduces peripheral resistance. Reflex sympathetic activity induces compensatory vasoconstriction, which might cause coronary vasospasm. Sympathetic blockade, however, does not always cause coronary vasospasm. Various environmental factors seem to affect the occurrence of perioperative vasospasm. As previously reported, ischemic events are often asymptomatic in patients with vasospastic angina. ECG alterations might be observed incidentally.

In patients with coronary artery stenosis, perioperative beta blockade reduces myocardial oxygen demand. The efficacy of perioperative beta-blockers has been reported in high-risk patients. Additional plaque stabilization is an important aspect of preventing acute coronary syndrome but, unlike in coronary stenosis, coronary vasospasm is not preceded by an increase in either heart rate or blood pressure. Moreover, beta blockade is not effective for vasospasm. Myocardial ischemia due to coronary vasospasm can lead to severe arrhythmias and hypotension. In the present study, 2 patients had fatal ventricular arrhythmias due to vasospasm. Use of coronary vasodilators such as nitrates and calcium channel blockers is necessary in these cases.

Preoperative CT is one of the powerful tools for the assessment of coronary artery disease. It is difficult to detect vasospastic angina on CT because coronary vasospasm occurs transiently. For the majority of patients, intraoperative ECG monitoring is the first step in diagnosis. The specific manifestation of vasospastic angina is a transient ST elevation, indicating transmural myocardial ischemia, but ST depression is also observed frequently. Recently, Sueda et al reported that the frequency of abnormal coronary response to acetylcholine has increased in Japanese patients. The possibility of vasospasm should be anticipated at all times.

Cardiac Risk Stratification for Non-Cardiac Surgical Procedures

It is not surprising that the type of surgery independently affects the risk of perioperative cardiac complications. Myocardial ischemia can be induced by large fluid shifts or blood loss. Cardiovascular event risk is especially high in emergency surgery. Lack of appropriate preoperative preparation contributes to the higher risk of cardiac complications. Clinical perioperative cardiovascular risk is also evaluated on RCRI. The risk of cardiovascular events predicted by RCRI is known to be 0.4–11% according to an RCRI score 0–3. In the present study, there was no association between vasospastic events and surgery-specific risk. RCRI scores in the definite vasospastic angina group tended to be lower than in the other cardiovascular events group. The majority of cardiovascular events associated with vasospastic angina occurred in patients undergoing elective surgery. In addition, the prevalence of cardiovascular risk factors in the definite vasospastic angina group was lower than in the organic coronary disease group. These results show the difficulties in risk prediction of perioperative vasospastic angina. Recently, the usefulness of preoperative measurement of C-reactive protein, brain natriuretic peptide (BNP) and N-terminal proBNP has been reported. The effectiveness of these biomarkers for prediction of vasospastic angina, however, remains to be elucidated. In the present study, these levels were not measured before surgery.

Study Limitations

There were many limitations in the present study. First, the study was a retrospective single-center study. As compared with previous reports, the prevalence of cardiovascular event was low. In this study, some patients with transient ECG alterations missed cardiology consultation after surgery. Cardiac catheterization was performed only in selected patients. For better clarification of vasospastic events in the perioperative period, collaboration with anesthesiologists is necessary. Some patients with organic coronary stenosis or tako-tsubo cardiomyopathy did not undergo spasm provocation test. The

Figure 4. Revised Cardiac Risk Index (RCRI) in patients with cardiovascular events. Most of the patients with definite vasospastic angina were classified as low risk (RCRI score, 0 or 1).
Coronary Vasospasm in the Perioperative Period

incidence of coronary vasospasm might have been underesti-
mated. Long-term follow-up of perioperative vasospasm is one of
the remaining problems.

Conclusion
Coronary vasospasm is not often encountered, but can be a
cause of cardiac trouble during the perioperative period. It
should be taken into consideration at the time of planning of
operation in Japanese patients even if they apparently have
low cardiac risk.

Acknowledgments
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their important contributions.

Disclosures
There are no financial or other relationships that could lead to a conflict
of interest.

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