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Effect of coronary artery spasm on long-term outcomes in survivors of acute myocardial infarction☆

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ABSTRACT

Background: The prevalence of coronary artery spasm (CAS) inducible by intracoronary injection of acetylcholine (ACh) is high in survivors of acute myocardial infarction (AMI). Although there is a potential risk of sudden cardiac death in patients with CAS, the prognostic value of CAS was not clear. Thus, this study examined the effect of CAS on long-term prognosis in survivors of AMI in a prospective manner.
Methods: The study included a total of 437 patients with AMI who underwent a CAS provocation test using ACh. All patients were followed prospectively for 5 years or until the occurrence of the primary composite endpoint that consisted of cardiac death and acute coronary syndrome (ACS).
Results: CAS was induced in 195 (45%) of the study patients. During the follow-up period, 30 patients had a recurrent event (4 had cardiac death and 26 had ACS). Kaplan-Meier estimates in time-to-first-event analysis demonstrated a similar probability of the primary endpoint in patients with and without inducible CAS ($p = 0.13$, log-rank test). The rate of each component of the composite endpoint was also comparable between the 2 patient groups. In Cox proportional hazards risk analysis, treatment with calcium channel blockers (CCBs) negatively predicted the primary endpoints in patients with inducible CAS (HR, 0.21; 95% CI, 0.08–0.55, $p < 0.01$).
Conclusions: The presence of inducible CAS did not increase the incidence of the cardiac events in AMI survivors. Treatment with CCBs may improve outcomes in AMI survivors with inducible CAS.
Clinical trial registration: URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000021340, unique identifier: UMIN000018432.

1. Introduction

Coronary artery spasm (CAS) is involved in the pathogenesis of ischemic heart disease including acute myocardial infarction (AMI) [1,2]. In addition, CAS may cause post-infarction angina and life-threatening arrhythmias [3,4]. Previous reports demonstrated that the prevalence of the inducible CAS by an intracoronary injection of acetylcholine (ACh) or ergonovine administration was high in either Asian or Caucasian patients with a previous MI (i.e., 50–70% of the patients) [5–7]. Although patients with CAS are thought to have a better prognosis [8,9], previous retrospective studies showed that there is a risk of life-threatening arrhythmias and sudden cardiac death in patients with CAS [10–12]. However, there are few prospective studies that directly compared prognosis between patients with and without CAS. A previous report showed that a composite endpoint that consisted of various cardiovascular events was more frequent in AMI survivors with CAS induced by ACh than in those without inducible CAS [5]. However, the composite endpoint in that report [5] consisted of mainly revascularization (>80% of the composite endpoint). Revascularization procedure is partly a subjective (clinician-driven) event. Therefore, the aim of this study was to compare long-term outcomes between AMI survivors with and without ACh-inducible CAS in a prospective manner using a composite endpoint that consisted of cardiac death and acute coronary syndrome (ACS).

2. Methods

2.1. Study patients

This study initially recruited 1206 consecutive patients with a first AMI due to occlusion of a proximal segment of a major coronary artery. These patients received successful reperfusion therapy within 24 h after the onset of symptoms at Yamanashi University Hospital between January 2005 and July 2015. The diagnosis of AMI was based on the presence of each of the following criteria [13]; typical chest pain persisting for ≥30 min, ST-segment elevation of ≥0.2 mV in ≥2 contiguous leads on the standard 12-lead electrocardiogram (ECG), and creatine kinase-MB increase to ≥2 times the upper limit of normal or troponin T > 0.1 ng/mL. The exclusion criteria were as follows: 1) left main trunk disease; 2) left ventricular ejection fraction on left ventriculography or ultrasound

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cardiography < 35%; 3) congestive heart failure (New York Heart Association classification ≥ III at 1 week after AMI; 4) a paced rhythm; 5) previous coronary artery bypass surgery (CABG); 6) coronary stenosis > 75% in both 2 non-culprit major coronary arteries; 7) residual coronary stenosis > 50% in culprit coronary artery; 8) age > 80 years old; 9) valvular heart disease, secondary hypertension or renal dysfunction (serum creatinine concentration > 2.0 mg/dL); 10) major surgery, trauma or serious infectious disease within the previous four weeks; and 11) stroke on admission. Some of these exclusion criteria were set to avoid risks of complications with provocation test of CAS. After applying the exclusion criteria, the study included 445 patients, all of whom were ethnic Japanese. A flow chart of patient enrollment is shown in Supplementary Fig. 1. All participants gave written informed consent for the study protocol, which was approved by the ethics committee of Yamanashi University Hospital. The investigation conformed to the principles outlined in the 1975 Declaration of Helsinki.

2.2. Provocation test of coronary artery spasm (CAS)

The provocation test for CAS was performed using intracoronary injection of ACh at 10–15 days (mean, 13 ± 2.6 days) after the onset of AMI, according to our previous reports [14,15] and the Japanese Circulation Society (JCS) guidelines [16]. Briefly, after baseline coronary angiography, incremental doses of 50 and 100 μg of ACh chloride were injected into the left coronary artery over a period of 30 s each, and coronary angiography was performed 1 min after the start of each injection. ACh at a dose of 50 μg was injected into the right coronary artery. The culprit coronary artery was first tested. Nitrates were injected into the coronary artery tested first in the following cases at the provocation test: 1) persistence of CAS > 5 min; 2) reduction of systolic blood pressure requiring systemic administration of noradrenalin; 3) atrial fibrillation; 4) life-threatening arrhythmias; 5) strong chest pain; 6) rejection by patient for the subsequent ACh provocation test; 7) discretion by physician. When this occurred, the subsequent provocation test was not done in the other coronary artery. Vasodilators including calcium channel blockers (CCBs) and nitrates, except for sublingual nitroglycerin, were discontinued >48 h before the provocation test.

CAS positive test was defined as transient total occlusion or subtotal occlusion with washout delay of contrast in at least one major coronary artery. In these cases, CAS provocation test was considered as positive irrespective of chest symptom and ECG changes. In addition, CAS provocation test was positive when ACh induced a transient severe constriction (99% - 90% narrowing) in at least one major coronary artery accompanied by both typical chest pain and ischemic ECG changes [16,17]. Multi-vessel CAS was present when ≥2 major epicardial coronary arteries had CAS [12,15].

2.3. Prospective follow-up study

This study was registered at URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000021340 (unique identifier: UMIN000018432). All patients were prospectively followed-up every 2 months at a hospital by each patient's primary physician for a period of up to 5 years, with a minimum follow-up of 1 year or until the occurrence of one of the following events: cardiac death or ACS (non-fatal MI or unstable angina pectoris [uAP]). The primary endpoint was a composite endpoint that consisted of cardiac death and ACS. The secondary endpoint was also a composite endpoint that consisted of non-cardiac death, cardiac death and ACS. In addition, information on the occurrence of coronary revascularization including percutaneous coronary intervention and CABG was collected during the follow-up period. Cardiac death was confirmed by hospital records. uAP was defined by the requirement of hospitalization, presence of ischemic ECG changes, and the following angina: 1) angina lasting ≥ 20 min at rest; 2) new-onset angina of at least Canadian Cardiovascular Society (CCS) Class III; or 3) increasing angina, i.e., increased by ≥1 CCS class to at least CCS Class III severity [18]. All patients received standard medical therapy to prevent recurrent cardiac events according to the NCEP guidelines [19]. Prescription of cardiac medications and revascularization of residual coronary stenosis or de novo coronary lesions were performed at the discretion of attending physicians.

2.4. Definition of coronary risk factors

Risk factors for cardiovascular disease were defined as current smoking (≥10 cigarettes/day for > 10 years), hypertension (blood pressure > 140/90 mm Hg or taking antihypertensive medications), dyslipidemia (high-density lipoprotein [HDL] cholesterol < 40 mg/dL, low-density lipoprotein [LDL] cholesterol ≥ 140 mg/dL, or triglycerides ≥ 150 mg/dL or taking medications for dyslipidemia) and diabetes mellitus (fasting plasma glucose level ≥ 126 mg/dL, 2-hour post-load ≥ 200 mg/dL in a 75-g oral glucose tolerance test, casual plasma glucose level of ≥200 mg/dL, hemoglobin A1c ≥ 6.5%, or taking medications for diabetes mellitus) [20]. The presence of a family history of coronary artery disease (CAD) was defined as MI, cardiac death or need for coronary revascularization in a first-degree relative.

2.5. Statistical analysis

All descriptive data were expressed as either the mean value ± SD, median and interquartile range or frequency (%). The Shapiro-Wilk test showed that body mass index (BMI), levels of LDL-cholesterol, HDL-cholesterol, triglyceride, estimated glomerular filtration rate (eGFR), hemoglobin A1c, C-reactive protein (CRP) and brain natriuretic peptide (BNP) were not distributed normally. These variables were therefore expressed as the median and interquartile range (25th and 75th percentiles). Continuous variables were compared between the two groups using an unpaired *t*-test or Mann-Whitney *U* test, where appropriate. Frequencies were compared using a chi-square test.

Kaplan-Meier estimates of time-to-first-event analysis were performed, and a log-rank test was used to compare survival curves. The association of inducible CAS with various factors was assessed by univariate and multivariate logistic regression analyses. The predictive values of inducible CAS and the other clinical variables were assessed by univariate Cox proportional hazards analysis. In these analyses, dichotomous variables were coded as 1 (present) or 0 (absent).

All probabilities were expressed as two-tailed values, with statistical significance inferred at $p < 0.05$. All confidence intervals were computed at the 95% level. The statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX, USA).

On the basis of our and other's previous reports [5,21], we proposed that the primary composite endpoint would occur in approximately 15% of patients with AMI and inducible CAS, and in 5% of those without inducible CAS. Thus, it was estimated that 161 patients would be needed in each group ($n = 322$, total) to detect a significant difference in the primary composite endpoint between the two groups with a two-tailed α of 0.05 and a power of 0.80 ($\beta = 0.20$). On the assumption that CAS would be induced in 50%–60% of AMI survivors [5,7], this justified the number of patients ($n = 445$) included in this prospective study.

3. Results

3.1. Provocation of coronary artery spasm (CAS)

Eight patients were withdrawn from the study after enrollment since they could no longer be contacted, and a total of 437 patients completed the follow-up study (Supplementary Fig. 1). Baseline clinical characteristics of patients at the discharge are shown in Table 1. CAS was induced in 195 (45%) of the total study patients. CAS occurred in 139 (32%) of 437 infarct-related culprit coronary arteries and 111 (15%) of 720 non-infarct-related arteries tested ($p < 0.01$, by chi-square test). Multi-vessel CAS was observed in 50 (17%) of the 303 patients who had a provocation test in both the left and right coronary arteries. Total occlusion or subtotal occlusion with contrast washout delay of a major coronary artery in response to ACh was observed in 48 (25%) and 135 (69%) of the 195 patients with inducible CAS, respectively. Both total and subtotal (contrast washout delay) coronary occlusion in the different coronary arteries occurred in 11 (6%) of the 195 patients. ACh-induced severe narrowing with a magnitude of 99–90% occurred in at least one major coronary artery in 171 patients who had neither total nor subtotal (contrast washout delay) coronary occlusion. Among these 171 patients, 48 (28%) patients had chest pain alone during the provocation test, 39 (23%) patients had ischemic ECG changes alone, 23 (13%) patients had both chest pain and ischemic ECG changes, and 61 (36%) patients had neither chest pain nor ischemic ECG changes. During the provocation test, ventricular tachycardia or fibrillation requiring electrical defibrillation occurred in 6 (1.3%) of the total study patients. Neither death nor MI occurred during the provocation test.

3.2. Comparison of baseline characteristics at discharge between patients with and without inducible CAS

Patients with inducible CAS had a higher prevalence of current smoking, lower prevalence of hypertension, and fewer multi-vessel CAD than those without inducible CAS at baseline (Table 1). The use of CCBs at the discharge was significantly higher in patients with than without inducible CAS (Table 1). The use of angiotensin converting enzyme inhibitor (ACE-I) and/or angiotensin II receptor blocker (ARB) was higher in patients without inducible CAS, compared with that in those with CAS, probably because the prevalence of hypertension was higher in patients without CAS, compared with those with CAS. Six months after AMI, the frequency of CCBs usage remained similar to that at discharge in the respective groups of the patients (Supplementary Table 1).

Multivariate logistic regression analysis showed that inducible CAS was associated positively with current smoking (OR, 1.84; 95% CI, 1.22–2.75, $p < 0.01$) and negatively with hypertension (OR, 0.64; 95% CI, 0.42–0.96, $p = 0.03$) and multi-vessel CAD (OR, 0.45; 95% CI, 0.27–0.77, $p < 0.01$) in AMI survivors (Supplementary Table 2).