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The impact of myocardial bridge on coronary artery spasm and long-term clinical outcomes in patients without significant atherosclerotic stenosis

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ABSTRACT

Background and aims: Myocardial bridge (MB) and coronary artery spasm (CAS) can induce a sustained chest pain, acute coronary syndrome (ACS) and even sudden cardiac death. The aim of this study is to evaluate the relationship between MB and CAS and its impact on long-term clinical outcomes.
Methods: A total of 812 patients with MB without significant coronary artery disease (CAD), who underwent acetylcholine (ACH) provocation test, were enrolled. Significant CAS was defined as ≥70% temporary narrowing by ACH test, and MB was defined as the characteristic phasic systolic compression of the coronary artery with a decrease of more than 30% in diameter on the angiogram after intracoronary nitroglycerin infusion. To adjust baseline confounders, logistic regression analysis was performed. The primary endpoint was incidence of CAS, and secondary endpoints were major adverse cardiac events (MACE) and recurrent angina requiring repeat coronary angiography (CAG) at 5 years.
Results: MB is closely implicated in a high incidence of CAS, spontaneous spasm, ischemic ECG change and chest pain during ACH provocation test. In addition, MB of various severity and reference vessel size was substantially implicated in CAS incidence, and severe MB was a strong risk factor of CAS. MB patients with CAS were shown to have a higher rate of recurrent angina compared with MB patients without CAS, up to a 5-year follow-up. However, there were no differences regarding the incidence of MACE.
Conclusions: Severe MB was associated with high incidence of CAS, and MB patients with CAS were likely to have a higher incidence of recurrent angina. Intensive medical therapy and close clinical follow-up are needed for better clinical outcomes in MB patients with CAS.

1. Introduction

Myocardial bridge (MB), a congenital abnormality of coronary arteries, is frequently found through coronary angiography (CAG) and computed tomographic (CT) angiography in patients who complain of chest pain [1–4]. MB is known to be substantially implicated in high incidence of coronary artery spasm (CAS), which can induce sustained chest pain, acute coronary syndrome (ACS) and even sudden death [3–10]. However, there are limited data regarding the relationship between different types of MB (with varying bridging lengths, bridging severity, and reference vessel sizes) and CAS incidence and its impact on long-term clinical outcomes in Asian patients. Therefore, we attempted to evaluate the impact of MB on CAS and its impact on 5-year clinical outcomes in patients without significant coronary stenosis, who underwent CAG and acetylcholine (ACH) provocation test.

2. Materials and methods

The design of this registry has been introduced before [11–14].

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In brief, it is a single-center, prospective, all-comers registry designed to reflect the "real world" practice since 2004. Data were collected by a trained study coordinator, with a standardized case report form. Standardized definitions for all patient-related variables and clinical diagnoses were used. The participants or their legal guardians were given a thorough literal and verbal explanation of the study procedures before granting a written consent to participate in the study. Institutional Review Board (IRB) of Korea University Guro Hospital (KUGH) approved all of the consenting procedures. The authors of this manuscript have certified that the information contained herein is true and correct as reflected in the records of the IRB (#KUGH10045). KUGH-IRB specifically approved the entire study. A total of 812 patients diagnosed with myocardial bridge (MB), who were enrolled in this study, had a typical or atypical chest pain without significant CAD (defined as having a stenosis diameter of more than 70% on the quantitative coronary angiography (QCA), prior coronary artery bypass graft (CABG) or prior percutaneous coronary intervention (PCI)).

2.1. Study definition

MB was defined as having a characteristic phasic systolic compression of the coronary artery, with a decrease of more than 30% in diameter on the CAG after intracoronary nitroglycerin infusion, which is exclusively located in the left anterior descending coronary artery (LAD), mostly in anterior-posterior (AP) cranial or right anterior oblique (RAO) cranial projections. Significant CAS was defined as having greater than 70% luminal narrowing of the artery during ACH provocation test regardless of ischemic ECG changes or presence of chest pain. The multi-vessel spasm was defined as having significant CAS in more than two major epicardial arteries. The diffuse spasm was defined as having a significant CAS with a site length of more than 30 mm. The spontaneous spasm was defined as having focal or diffuse narrowing of greater than 30% in baseline CAG, compared to the reference vessel diameter, after nitroglycerin administration into the intracoronary route. Deaths were regarded to be of cardiac cause unless a non-cardiac cause could be confirmed. Repeated CAG (mostly due to recurrent angina) was performed in patients who complained of recurrent angina despite adequate antianginal medication for at least 6 months since the onset of first CAG. In this case, the physician assumed that CAS may be progressed or there may be newly developing atherosclerotic coronary artery disease (CAD). Major adverse cardiovascular events (MACE) were defined as the composite of total death, recurrent MI, and revascularization including PCI and CABG.

2.2. Acetylcholine provocation test

The design of the ACH provocation test has been previously introduced [5,12–14]. Initial investigation for CAG included clinical history of non-invasive stress tests such as treadmill test, stress echocardiography, and radionuclide study. CAG was performed to confirm the presence of significant CAD. However, CAG was immediately done without functional studies in case of typical resting ischemic chest pain to confirm VSA. Vasodilators or vasoconstrictors such as nitrates, calcium channel blockers (CCB), beta blockers, nicorandil, and molsidomine were discontinued for at least 72 h before CAG. CAS induction was tested by an intracoronary injection of ACH immediately after diagnostic angiography by either a trans-radial or trans-femoral approach. ACH was injected by incremental doses of 20 (A1), 50 (A2) and 100 (A3) μg/min into the left coronary artery over a 1-min period with 5-min intervals, up to the maximally tolerated dose under a continuous monitoring with electrocardiogram and measurement of blood pressure. Routine provocation test of the right coronary artery was not done due to safety issues regarding the higher prevalence of advanced atrioventricular (AV) block, which needs a temporary pacemaker for maintaining adequate ACH infusion rate, and cost-effectiveness for diagnosis and management of significant CAS. Angiography was repeated after each ACH dose until a significant focal or diffuse narrowing greater than 70% was observed. If significant focal or diffuse vasoconstriction (>70%) of coronary arteries was induced at any dose, ACH infusion was stopped. An intracoronary injection of 0.2 mg of nitroglycerine was administered after completing the ACH provocation test, followed by CAG 2 min later. End-systolic images for each segment of the left coronary artery were chosen, according to the corresponding points on the electrocardiographic trace (QRS onset or end of T wave), and analyzed using the proper QCA system of the catheterization laboratory (FD-20, Phillips, Amsterdam, The Netherlands). Coronary artery diameters were measured by QCA before and after the administration of ACH at the site that showed the greatest changes following drug administration. Reference vessel diameters were measured at the proximal and distal portions of each artery. The mean reference vessel diameter was used to assess diameter narrowing by QCA.

2.3. Statistical analysis

For continuous variables, differences between the two groups were evaluated by the unpaired *t*-test or Mann-Whitney rank test. Data were expressed as mean ± standard deviations. For discrete variables, differences were expressed as counts and percentages and analyzed with $\chi 2$ or Fisher's exact test between the two groups. To adjust for any potential confounders, multivariable Cox-regression analysis, which includes baseline confounding factors, was used for assessing independent impact factors. We tested all available variables that could be of potential relevance: age, sex, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, cerebrovascular accidents, peripheral artery occlusive disease, chronic kidney insufficiency, current smokers, current alcohol drinkers and insignificant coronary stenosis). Various clinical outcomes were estimated with the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Single or multivariable Cox-proportional hazard models were used to assess the hazard ratio of the CAS group compared with the non-CAS group adjusted for various confounders. For all analyses, a two-sided $p < .05$ was considered statistically significant. All data were processed with SPSS (version 20.0, SPSS-PC, Inc. Chicago, Illinois).

2.4. Study endpoints

Primary endpoint was the incidence of CAS, total death, MI, *de novo* PCI, and MACE. The secondary endpoint was the incidence of recurrent angina requiring repeat CAG. In this study, the mean follow-up period was 1327 ± 548 days, and we could follow up on the clinical data of all enrolled patients through medical chart reviews, telephone contacts and face-to-face interviews at the regular outpatient clinic.

3. Results

In the present study, a total of 812 MB patients without significant stenosis, who underwent ACH provocation test, were enrolled. As shown a Fig. 1, of the 812 patients, 59.1% (n = 480) were diagnosed with CAS by ACH provocation test. As shown in Table 1, regarding baseline clinical characteristics, the CAS group had a significantly higher incidence of old age, lower heart rate, and more peripheral artery occlusive disease compared with the non-CAS group. Moreover, the CAS group had a significantly higher number of prescribed anti-anginal medication, such as calcium channel