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Impact of alcohol drinking on acetylcholine-induced coronary artery spasm in Korean populations

Sung Min Sohn [a, 1], Byoung Geol Choi [b, 1], Se Yeon Choi [b], Jae Kyeong Byun [b], Ahmed Mashaly [c], Yoonjee Park [c], Won Young Jang [c], Woohyeun Kim [c], Jah Yeon Choi [c], Eun Jin Park [c], Jin Oh Na [c], Cheol Ung Choi [c], Hong Euy Lim [c], Eung Ju Kim [c], Chang Gyu Park [c], Hong Seog Seo [c], Dong Joo Oh [c], Seung-Woon Rha [c, *]

[a] Department of Medicine, Korea University College of Medicine, South Korea
[b] Department of Medicine, Korea University Graduate School, Seoul, South Korea
[c] Cardiovascular Center, Korea University Guro Hospital, Seoul, South Korea

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ABSTRACTS

Background and aims: Generally, immoderate alcohol consumption is associated with variant angina and accepted as one of the risk factors for coronary artery spasm (CAS), but evidence is lacking in this regard. The aim of this study is to evaluate the impact of alcohol consumption and drinking pattern on CAS by acetylcholine (ACH) provocation test and long-term clinical outcomes.

Methods: A total of 5491 patients with typical or atypical chest pain, without significant coronary artery disease, who underwent intracoronary ACH provocation test, were enrolled prospectively, and retrospectively analyzed in this study. They were divided into two groups according to their alcohol drinking status; the current alcohol (CA) drinking group (n = 1792), and non-CA group (n = 3699). To adjust for potential confounders, a propensity score matching (PSM) 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: After PSM analysis, alcohol consumption was a strong risk factor for CAS. Furthermore, excessive alcohol consumption was correlated with a higher risk for CAS. As compared with the non-CA group, the CA group showed worse angiographic and clinical findings, including higher incidence of CAS (58% *vs.* 62%, $p = 0.016$), spontaneous spasm (17% *vs.* 22%, $p = 0.004$), multi-vessel spasm (31% *vs.* 37%, $p = 0.009$), proximal epicardial spasm (39% *vs.* 46%, $p = 0.002$), ischemic electrocardiography changes such as T-inversion (0.4% *vs.* 1.2%, $p < 0.001$) and chest pain (42% *vs.* 46%, $p = 0.047$) during ACH provocation test. However, the status and pattern of alcohol drinking had no influence on long-term clinical outcomes such as MACE or recurrent angina.

Conclusions: Alcohol consumption is a strong risk factor for CAS, and excessive alcohol consumption was correlated with a higher risk for CAS. Further well-designed studies are needed to confirm the results.

1. Introduction

Patients who complain of resting chest pain are frequently found to have apparently normal coronary arteries, as seen by the coronary angiography (CAG), and have had no history of gastrointestinal disorders [1,2]. These patients are frequently diagnosed with coronary artery spasm (CAS) by intracoronary provocation test using acetylcholine (ACH) or ergonovine [3–6]. It is well-documented that obstructive CAS, which is closely implicated in endothelial dysfunction, can induce acute coronary syndrome, vasospastic angina (VSA) and even sudden cardiac death [2,6].

Generally, age, smoking, high sensitivity C-reactive protein (hsCRP), remnant lipoproteins, myocardial bridge and insignificant coronary stenosis are well-known significant risk factors for CAS

* Corresponding author. Cardiovascular Center, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul, 08308, South Korea.
E-mail address: swrha617@yahoo.co.kr (S.-W. Rha).
[1] These authors contributed equally to this work.

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[4,7–12]. In addition, immoderate alcohol consumption is associated with variant angina, and accepted as one of the risk factors for CAS, but evidence is lacking in this regard [4,13–15]. In published studies, the effect of alcohol consumption on cardiovascular disease (CVD), which varies according to the status and drinking pattern (acute or chronic, immoderate or not), remains ambiguous [16–22]. Therefore, the aim of this study is to evaluate the impact of alcohol consumption and drinking pattern on CAS by ACH provocation test and long-term clinical outcomes.

2. Materials and methods

The design of this registry has been introduced before [7–10,23,24]. 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 this entire study.

A total of 10,177 patients with typical or atypical chest pain, who underwent CAG at the Cardiovascular Center of KUGH, Seoul, South Korea, between November 2004 and May 2014, were enrolled in this study. Among these, 6430 patients with typical or atypical chest pain without significant CAD (defined as having a stenosis diameter of less than 70% on the quantitative coronary angiography) underwent intracoronary ACH provocation test. The design of the ACH provocation test was previously explained. Patients were excluded if they had any of the following conditions: coronary artery bypass graft (CABG), prior percutaneous coronary intervention (PCI), stroke, advanced heart failure (New York Heart Association class III or IV) or serum creatinine $\geq$ 2 mg/dl, because these conditions could be major causes of adverse cardiovascular events and could bias the results.

2.1. Study definition

In the present study, to define varying consumption levels, we accounted for the different percentages of alcohol contained in various types of alcohols (i.e. beer, wine, rice wine, whiskey and etc.) by converting them all into a single unit of grams/day (g/day). Moderate consumption was defined as < 40 g/day in men, < 20 g/day in women; and high consumption was defined as $\geq$ 40 g/day in men, $\geq$ 20 g/day in women [25]. Significant CAS was defined as greater than 70% luminal narrowing of the artery during ACH provocation test regardless of ischemic electrocardiography (ECG) changes or presence of chest pain. Major adverse cardiovascular events (MACE) were defined as the composite of total death, myocardial infarction (MI), and revascularization including PCI and CABG. Deaths were regarded to be of cardiac cause unless a non-cardiac death 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 CAD.

2.2. Statistical analysis

For continuous variables, differences between groups were evaluated by 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 groups. To adjust for any potential confounders, propensity score matching (PSM) analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, sex, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, current smokers and alcohol consumption), angiographic and clinical parameters (myocardial bridge, insignificant stenosis). Matching was performed with 1:1 matching protocol without a replacement (nearest neighbor matching algorithm), with caliper width equal to 0.01 of the standard deviation of the propensity score. Various clinical outcomes were estimated with the Kaplan-Meier method, and differences between groups were compared with the log-rank test before and after PSM. Cox-proportional hazard models were used to assess the hazard ratio for CAS according to the state of alcohol consumption and pattern (low, high and unknown consumption). For all analyses, a two-sided $p < 0.05$ was considered statistically significant. All data were processed with SPSS (version 20.0, IBM, Armonk, New York).

2.3. Study endpoints

Primary endpoint was the incidence of CAS during ACH provocation test, and secondary endpoint was the incidence of total death, MI, *de novo* PCI, and MACE, and third endpoint was recurrent angina requiring repeat CAG. In this study, the mean follow-up period was 1218 ± 577 days (after PSM: 1235 ± 581) and we could follow up on the clinical data of all enrolled patients through face-to-face interviews at the regular outpatient clinic, medical chart reviews, and telephone contacts.

3. Results

We enrolled a total of 5491 patients. They were divided into two groups according to their alcohol drinking status: 1) the current alcohol (CA) drinking group (n = 1792), and 2) non-CA group (n = 3699). To adjust for potential confounders, a PSM analysis was performed using the logistic regression model. After PSM analysis, two propensity-matched groups (1391 pairs, total = 2782) were generated.

3.1. Baseline clinical and laboratory characteristics

As shown in Table 1, in the entire population, there were considerable differences between the two groups in baseline characteristics such as age, sex, body mass, hypertension, history of smoking, lipid profile (HDL and LDL-cholesterol) and glycemic profile (fasting glucose and hemoglobin A1c). However, after PSM analysis, these were well-balanced baseline characteristics, except current smoker, and fasting glucose level was higher in the CA group than in the non-CA group.

3.2. Baseline angiographic and clinical parameters at acetylcholine provocation test

As shown in Table 2, in the entire population, the CA group had a significantly higher incidence of CAS, spontaneous spasm and myocardial bridge compared with the non-CA group. In addition, after PSM analysis, the CA group had a significantly higher incidence of CAS, spontaneous spasm, ischemic ECG change such as T-