Impact of old age on clinical and angiographic characteristics of coronary artery spasm as assessed by acetylcholine provocation test

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Abstract

Background Smoking and other risk factors have been well known as important factors of variant angina or coronary artery spasm (CAS). However, clinical features related to age on coronary artery spasm have been rarely evaluated. Methods We evaluated 3155 consecutive patients with insignificant coronary artery lesion. Patients underwent Acetylcholine (Ach) provocation test for induction of CAS. CAS was defined as > 70% luminal narrowing of coronary arteries during Ach provocation test. The results of Ach provocation test were compared among age groups; < 45 years (Group 1), 45–54 years (Group 2), 55–64 years (Group 3), and ≥ 65 years (Group 4). Results Older patients had higher incidence of hypertension, diabetes, but lower incidence rate of current smoking, male sex compared with younger patients. Positive Ach provocation test finding was frequently showed with aging (47.36% vs. 58.3% vs. 62.6% vs. 61.5%; P < 0.001). Multivariate logistic analysis showed that age, male, and myocardial bridge were independent predictors of CAS induced by Ach provocation test.

Conclusion Our present study showed that old age was independent predictor for Ach-induced significant coronary artery spasm.

Keywords: Acetylcholine; Age factor; Coronary vasospasm

1 Introduction

Coronary artery spasm (CAS) has an important role in the pathogenesis of variant angina as well as acute myocardial infarction, and sudden cardiac death.[1–3]

In real world clinical practice, vasospastic angina has been suspected in relatively younger patients with resting chest pain during the early morning hours, particularly when occurring during sobriety.[4] However, in recent times, elderly patients have occasionally been diagnosed as significant CAS in especially Asian patients. Given the recent and forward increases in the number of elderly population, it is reasonable to evaluate CAS in the elderly patients. Only several studies have shortly investigated the importance of age on CAS.[5–7] There is no earlier study that analyzed CAS based on the age classification.

Therefore, in this study, we evaluated any impact of age on CAS and its related angiographic and clinical parameters as compared among age groups by intracoronary acetylcholine (Ach) provocation test.

2 Methods

2.1 Study population

We enrolled 5,314 patients who had chest pain and had been diagnosed as insignificant coronary artery disease defined as the diameter stenosis less than 50% on quantitative coronary angiography (QCA) from November 2004 to January 2013 in the Korea University Guro Hospital. Exclusion criteria included the presence of history of implantation of coronary stent, stage III or IV heart failure, history of coronary artery bypass surgery, cerebrovascular disease, chronic kidney disease, peripheral artery disease, because these states may be important causes of adverse cardiovascular events and could serve as the significant bias due to
pre-existed endothelial dysfunction or advanced atherosclerotic changes in the cardiovascular system. Finally, 3155 patients were divided into four groups according to age: < 45 years (Group 1), 45–54 years (Group 2), 55–64 years (Group 3), and ≥ 65 years (Group 4).

2.2 Ach provocation test

After diagnostic coronary angiography, CAS was induced by intracoronary Ach infusion. The Ach provocation test details were reported earlier. In short, β-blockers, calcium channel antagonists or blockers (CCBs), renin angiotensin system blockers such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARB), nitrates, and vaso-active drugs were stopped before the catheterization during at least three days. Under continuous monitoring, Ach with doses of 20, 50 and 100 µg/min was incrementally infused into the left coronary artery over a 60 s with 5 min intervals until the tolerated dose as much as possible. After then, an intracoronary nitroglycerin (NTG) 0.2 mg was infused. Final angiogram was done 2 min later. If more than 70% epicardial coronary artery vasoconstriction was induced with any Ach dose, the provocation test was terminated for safety issues. Because of safety concerns by higher chance of advanced atrio-ventricular (AV) block which needs temporary pacemaker for maintaining adequate Ach infusion rate and subsequent cost effectiveness for diagnosis and management of significant CAS, Ach provocation test for right coronary artery was not routinely performed. The coronary arteries were analyzed utilizing the QCA system (FD-20, Philips, Amsterdam, Netherlands). Two independent experts analyzed the angiographic images. The percent diameter change was estimated at the most significantly narrowed site of the spasm-induced artery.

2.3 Study definitions

Significant CAS was defined as a 70% or more than stenosis of the coronary arterial luminal diameter irrespective of chest pain and/or ECG change. We did not perform higher Ach dose to achieve transient subtotal or total occlusion for patient’s safety. Less than 20% luminal narrowing on coronary angiogram by QCA was defined as normal coronary appearance. When comparing with the after intracoronary NTG infusion, ≥ 30% narrowing of coronary artery before the Ach provocation test was defined as baseline spasm. Myocardial bridge (MB) was defined as a > 30% decrease in coronary artery diameter during systole after intracoronary NTG injection. Diffuse CAS was defined as ≥ 20 mm lesion measured for entire diffuse lesion by QCA. CAS of ≥ 2 epicardial coronary arteries was defined as multi-vessel spasm.

2.4 Ethics statement

The study protocol was approved by the Ethics Committee of Korea University Guro Hospital (IRB approval No. KUGH10045-003), and patient provided written informed consent before coronary angiography by one of the investigators.

2.4 Statistical analysis

The statistical analyses using SPSS 11.0 (SPSS Inc., Chicago, USA) were performed. Data were presented as mean ± SD, P < 0.05 were considered statistically significant. ANOVA test was performed for continuous variables among groups. Differences were expressed as counts and percentages for discrete variables and used with Chi-square (or Fisher’s exact) test. Chi-square test for linear trend was used to assess whether the incidence of CAS increased gradually with age. Multivariate logistic regression analysis was performed for identifying the independent impact of age on Ach-induced CAS.

3 Result

Hypertension, diabetes, hyperlipidemia were more frequent with aging, but current smoking was less frequent with old patients (36.2% vs. 25.0% vs. 17.4% vs. 11.7%; P < 0.001). Elderly patients group have taken drugs with higher rates of aspirin, cilostzol, CCB, ARBs and statins than did younger patients. There was no significant difference in the lipid parameters among the four groups, which might result from the higher statin use rate in elderly patients. However, the high-sensitivity C-reactive protein (hs-CRP) level was higher in the older patient groups and incidence of male patients underwent Ach provocation test were decreased with aging. The clinical characteristics of study patients are presented in Table 1.

The incidences of Ach-induced significant CAS were significantly higher in the elderly patients than younger patients (47.3% vs. 38.3% vs. 62.6% vs. 61.5%, P < 0.001). The prevalence of CAS tended to increase with age (Chi-square test for linear trend, P < 0.001). The reference diameters (mm) by NTG injection and narrowing (%) of the coronary artery diameters by Ach induced spasm were decreased with aging. But diameter narrowing was similar among age groups. The incidences of ECG change, and AV block were not different among the groups during Ach provocation test. However, there was less frequency rate of chest pain in the most elderly patients (Group 4). The incidence of angiographic MB was more frequent in the younger patients (Group 4) compared with the older patients (Group 3, 4). There was no serious complication like acute
myocardial infarction, ventricular tachycardia/fibrillation, need for pacing. The results of Ach provocation test were presented in Table 2.

In patients who had significant CAS, the older patients groups required a more low to intermediate Ach dose (50 µg) to induce significant CAS than younger patients, suggesting more vulnerable response to Ach than the younger patients groups. There was similar angiographic characteristics including spasm type in the patient groups but spasm vessel numbers were more frequent in group 3. CAS at left anterior

Table 1.  The baseline characteristics of the study groups.

| Variables | Group I (<45 yrs) (n = 825) | Group II (45–54 yrs) (n = 1272) | Group III (55–64 yrs) (n = 1272) | Group IV (≥65 yrs) (n = 936) | P value |
|-----------|-----------------------------|-------------------------------|--------------------------------|-------------------------------|--------|
| Age, yrs  | 36.7 ± 7.3                  | 50.4 ± 2.8                    | 59.9 ± 2.9                     | 71.1 ± 4.6                    | <0.001 |
| Male      | 507 (61.5%)                 | 630 (49.5%)                   | 510 (40.1%)                    | 340 (36.3%)                   | <0.001 |
| BMI, kg/m²| 23.9 ± 3.7                  | 24.3 ± 3.1                    | 24.5 ± 2.9                     | 24.2 ± 3.3                    | 0.05   |
| DM        | 36 (4.4%)                   | 121 (9.5%)                    | 187 (14.7%)                    | 175 (18.7%)                   | <0.001 |
| HTN       | 209 (25.3%)                 | 493 (38.8%)                   | 670 (52.7%)                    | 566 (60.5%)                   | <0.001 |
| Dyslipidemia | 62 (7.5%)                | 169 (13.3%)                   | 214 (16.8%)                    | 171 (18.3%)                   | <0.001 |
| Smoking   | 283 (34.3%)                 | 312 (24.5%)                   | 208 (16.4%)                    | 95 (10.1%)                    | <0.001 |
| Laboratory finding |                |                               |                               |                               |        |
| hs-CRP, mg/dL | 2.3 ± 7.7                | 2.2 ± 6.5                     | 2.8 ± 10.4                     | 4.6 ± 14.6                    | <0.001 |
| TC, mg/dL  | 170.3 ± 44.3               | 179.0 ± 44.9                  | 178.9 ± 46.8                   | 174.3 ± 46.7                  | 0.944  |
| TG, mg/dL  | 122.2 ± 102.5              | 127.6 ± 97.8                  | 124.8 ± 87.3                   | 117.7 ± 78.3                  | 0.083  |
| LDL-C, mg/dL | 104.8 ± 37.7             | 109.72 ± 39.3                | 108.8 ± 39.91                  | 103.1 ± 39.8                  | 0.472  |
| HDL-C, mg/dL | 50.0 ± 15.3              | 50.73 ± 14.8                 | 49.9 ± 15.0                    | 49.7 ± 15.1                   | 0.426  |
| Medication history |                 |                               |                               |                               |        |
| Aspirin   | 4 (0.5%)                    | 7 (0.6%)                      | 25 (2.0%)                      | 28 (3.0%)                     | <0.001 |
| Cilostazol | 0 (0%)                      | 3 (0.2%)                      | 9 (0.9%)                       | 12 (1.3%)                     | <0.001 |
| β-blockers | 16 (1.9%)                  | 25 (2.0%)                     | 38 (3.0%)                      | 44 (4.7%)                     | <0.001 |
| CCB       | 39 (4.7%)                   | 89 (7.0%)                     | 105 (8.3%)                     | 79 (8.4%)                     | 0.008  |
| ACEi      | 8 (1.0%)                    | 10 (0.8%)                     | 14 (1.1%)                      | 11 (1.2%)                     | 0.797  |
| ARB       | 19 (2.3%)                   | 54 (4.2%)                     | 75 (5.9%)                      | 48 (5.1%)                     | 0.008  |
| Nitrates  | 156 (18.9%)                 | 228 (17.9%)                   | 234 (18.4%)                    | 150 (16.0%)                   | 0.389  |
| Nicorandil | 4 (0.5%)                   | 21 (1.7%)                     | 27 (2.1%)                      | 34 (3.6%)                     | <0.001 |
| Statins   | 18 (2.2%)                   | 73 (5.7%)                     | 93 (7.3%)                      | 73 (7.8%)                     | <0.001 |

Data are presented as mean ± SD or n (%). ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CCB: calcium channel blockers; DM: diabetes mellitus; HDL-C: high density lipoprotein cholesterol; hs-CRP: high sensitivity C reactive protein; HTN: hypertension; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

Table 2. Characteristics of Ach provocation test in study population.

| Variables                  | Group I (<45 yrs) (n = 825) | Group II (45–54 yrs) (n = 1272) | Group III (55–64 yrs) (n = 1272) | Group IV (≥65 yrs) (n = 936) | P value |
|---------------------------|-----------------------------|-------------------------------|--------------------------------|-------------------------------|--------|
| RD after NTG infusion, mm | 2.51 ± 0.58                 | 2.45 ± 0.60                   | 2.42 ± 0.91                    | 2.27 ± 0.53                   | <0.001 |
| MD after Ach infusion, mm | 0.76 ± 0.36                 | 0.70 ± 0.37                   | 0.69 ± 0.38                    | 0.66 ± 0.32                   | <0.001 |
| DN after Ach infusion     | 69.9% ± 12.8%               | 70.7% ± 13.3%                 | 70.9% ± 13.4%                  | 71.1% ± 12.7%                 | 0.124  |
| Ach-induced CAS          | 382 (46.3%)                 | 731 (57.5%)                   | 772 (60.7%)                    | 566 (60.5%)                   | <0.001 |
| Baseline spasm           | 158 (19.2%)                 | 260 (20.4%)                   | 282 (22.2%)                    | 169 (18.1%)                   | 0.664  |
| ST-segment change        | 17 (2.1%)                   | 49 (3.9%)                     | 43 (3.4%)                      | 30 (3.2%)                     | 0.152  |
| Chest pain               | 365 (44.2%)                 | 585 (46.0%)                   | 596 (46.9%)                    | 381 (40.7%)                   | 0.171  |
| Atrioventricular block   | 237 (28.7%)                 | 387 (30.4%)                   | 395 (31.1%)                    | 291 (31.1%)                   | 0.669  |
| Myocardial bridge        | 179 (21.7%)                 | 250 (19.7%)                   | 204 (16.0%)                    | 134 (14.3%)                   | <0.001 |

Data are presented as mean ± SD or n (%). Ach: Acetylcholine; CAS: coronary artery spasm; DN: diameter narrowing; MD: minimal diameter; NTG: nitroglycerine; RD: reference diameter. *P < 0.001 by chi-square for linear trend among all groups.
descending artery was more occurred in the group 1, 4 compared with group 2, 3 (Table 3).

In order to evaluate independent predictive factors for CAS induced by Ach, first, we adjusted baseline confounding factors, which is hypertension, dyslipidemia, high density lipoprotein cholesterol (HDL-C), gender, diabetes mellitus, age, current smoking, and angiographic baseline spasm and MB using univariate logistic regression analysis. Second, multivariate logistic analysis showed that old age, male, baseline spasm, and MB were independent predictive factors for CAS induced Ach provocation test (Table 4). Other risk factors including smoking, diabetes mellitus, HDL-C and dyslipidemia were not independent predictors in this study cohort.

| Table 3. Characteristics of acetylcholine provocation test in patients with significant coronary artery spasm. |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Variables                        | Group I (≤ 45 yrs) (n = 825) | Group II (45–54 yrs) (n = 1272) | Group III (55–64 yrs) (n = 1272) | Group IV (≥ 65 yrs) (n = 936) | P value |
| Maximal tolerable dose of Ach    |                  |          |                |                  |             |
| 20 µg/min                        | 15 (3.9%)       | 37 (5.1%) | 43 (5.6%)      | 27 (4.8%)       | 0.675     |
| 50 µg/min                        | 106 (27.7%)     | 246 (33.7%) | 280 (36.3%) | 201 (35.6%) | 0.05     |
| 100 µg/min                       | 261 (68.3%)     | 447 (61.2%) | 448 (58.1%) | 336 (59.6%) | 0.008    |
| Spasm types                      |                  |          |                |                  |           |
| Focal                            | 66 (17.3%)      | 118 (16.1%) | 123 (15.9%) | 76 (13.4%) | 0.381    |
| Diffuse                          | 316 (82.7%)     | 613 (83.9%) | 649 (84.1%) | 490 (86.6%) | 0.381    |
| Spasm vessel number              |                  |          |                |                  |           |
| One vessel                       | 273 (71.5%)     | 489 (66.9%) | 508 (65.8%) | 399 (70.5%) | 0.119    |
| Multi-vessel                     | 109 (28.5%)     | 242 (33.1%) | 264 (34.2%) | 167 (29.5%) | 0.119    |
| Spasm site                       |                  |          |                |                  |           |
| LM                               | 2 (0.5%)        | 2 (0.3%) | 2 (0.3%)       | 1 (0.2%)       | 0.797    |
| LAD                              | 257 (67.3%)     | 440 (60.2%) | 462 (59.8%) | 383 (67.7%) | 0.570    |
| LCX                              | 15 (3.9%)       | 39 (5.3%) | 43 (5.6%)      | 16 (2.8%)      | 0.072    |
| RCA                              | 1 (0.3%)        | 10 (1.4%) | 2 (0.3%)       | 0              | 0.012    |
| LCA + RCA                        | 2 (0.5%)        | 1 (0.1%) | 4 (0.5%)       | 0              | 0.220    |

Data are presented as n (%). Ach: acetylcholine; LAD: left anterior descending; LCA: left coronary artery; LCX: left circumflex; LM: left main; RCA: right coronary artery.

| Table 4. Univariate and multivariable logistic analysis of the predictors of acetylcholine induced coronary artery spasm. |
|---------------------------------|----------------|----------------|-----------------|
| Variables                        | Univariate   | Multivariate (adjusted) | OR 95% CI |
| Ages                            | P-value      | P-value          | Adjusted       |
| ≤ 45 yrs                        | < 0.001      | < 0.001          | 1.86 1.50–2.294 |
| 45–54 yrs                       | < 0.001      | < 0.001          | 2.40 1.92–2.988 |
| 55–64 yrs                       | < 0.001      | < 0.001          | 2.60 2.01–3.244 |
| ≥ 65 yrs                        | < 0.001      | < 0.001          | 1.59 1.34–1.872 |
| Male                            | < 0.001      | < 0.001          | 1.00 1.00–1.002 |
| Baseline spasm                  | < 0.001      | < 0.001          | 2.07 1.73–2.484 |
| Hypertension                    | 0.600        | 0.153            | 0.90 0.77–1.042 |
| Diabetes mellitus               | 0.556        | 0.739            | 1.04 0.82–1.309 |
| Dyslipidemia                    | 0.012        | 0.316            | 1.01 0.90–1.357 |
| Smoking                         | < 0.001      | 0.079            | 1.08 0.97–1.477 |
| Myocardial bridge               | < 0.001      | < 0.001          | 1.58 2.10–3.162 |
| hs-CRP                          | 0.327        | 0.485            | 1.00 0.99–1.010 |
| HDL cholesterol                | < 0.001      | 0.285            | 0.99 0.92–1.002 |

hs-CRP: high sensitivity C reactive protein; HDL: high density lipoprotein.

4 Discussion

The major results of our study are as below: (1) the elderly patients had a significantly higher incidence of significant CAS as compared with young patients by intracoronary Ach provocation test; (2) in elderly patients, significant CAS occurred more frequently at lower Ach dose, suggesting they may have more vulnerability than younger patients; (3) the elderly patients had less frequent rate of chest pain than in younger patients during Ach provocation test, suggesting less chance of ischemic symptoms even during the significant CAS than younger patients; and (4) the old age was an independent predictor of Ach induced CAS.

Advanced age is one of the important risks for the development of cardiovascular diseases. Aging is well known for phenotypic changes that render the cardiovascular system prone to disease state even without of well-known risk factors. With aging, age-specified mortality rates from cardiovascular diseases rise exponentially throughout the advanced age, occupying for more than 40% of all deaths between 65–74 years and almost 60% at over 85 years.
Our hypothesis is that the advancing age is partly attributable to the development of vascular endothelial dysfunction and might be a cause of CAS. Results about both human beings and experimental animals indicate that impaired endothelial dependent vasodilatation with aging is mediated by a reduction in nitric oxide (NO) availability.\cite{13,14} Vasospastic angina is known to have endothelial dysfunction because of decreased NO availability, too.\cite{15} Therefore, in this context, our study investigated the hypothesis that elderly populations might have more frequent CAS contrast with young populations and attempted to reveal significance of aging on CAS and its associated parameters including the elderly CAS patients’ clinical and angiographic characteristics by Ach provocation test.

In addition, the background of old age on CAS could be suggested as bellows. First, atherosclerotic disease affecting large coronary arteries can modify their vascular tone and reactivity.\cite{16,17} About 88% of localization of CAS had an atherosclerotic lesion.\cite{18} Intravascular ultrasound study have revealed atherosclerotic plaques in just adjacent spastic portion.\cite{19} When we consider that the elderly patients have higher prevalence of diffuse atherosclerosis in their major epicardial arteries, there will be higher chances of significant CAS in the elderly patients. Second, vascular oxidative stress rises with age as a result of more development of reactive oxygen species without an increased compensation in antioxidant defenses. Several experimental evidences indicate that dysfunction of vascular endothelium develops with advanced age in humans in the absence of definite cardiovascular diseases and important risk factors for cardiovascular systemic disease.\cite{20} Deteriorated dysfunction of endothelium, raised leucocyte adhesion, decreased fibrinolytic function have been showed in advanced aged population contrast with young populations.\cite{21} Third, one recent study reported that chronic low-grade inflammation plays an important role in pathogenesis of coronary vasospasm.\cite{22} Hung, et al\cite{23} prospectively investigated the association of hs-CRP with coronary artery vasospasm and reported that hs-CRP level was independently associated with CAS. Brachial flow mediated dilatation is reversely related to plasma inflammation markers including ICAM-1 (intercellular adhesion molecule-1), interleukin-6, and CRP among middle and advanced adults in the Framingham Heart Study.\cite{24} In our study, hs-CRP was more higher in the elderly patients compared with younger patients, suggesting importance of chronic inflammation in pathogenesis of significant endothelial dysfunction in the elderly patients.

There was discrepancy between significant CAS and ischemic chest pain in our study. In the guidelines, vasospastic angina is defined as “transient, total, or sub-total occlusion of a coronary artery with a sign/symptoms of myocardial ischemia by the Ach or ergonovine coronary spasm test.”\cite{25} However, we did not perform higher Ach dose to achieve transient subtotal or total occlusion for patient’s safety. Significant CAS was defined as > 70% luminal narrowing irrespective of ischemic ECG change, or chest pain in our study. This definition might bring results of significant coronary spasm without ischemic chest pain. In addition, silent ischemia in elderly patients with diabetes mellitus or female gender might be attributed to CAS without ischemic chest pain.

The current study has some limitations. First, event through we tried to minimize effect from the confounding biases using the multivariate logistic analysis, some potential confounders cannot be completely ruled out. For example, smoking has been known as a major risk factor for coronary artery spasm. But, smoking was not independent risk factor in our study. Smoking incidence was significantly lower in the older age group (Group 3, 4) compared with younger age group (Group 1, 2) in our study population. However, the results were based on a relatively large patient population which has effect in eliminating the baseline biases. Second, we did not simultaneously performed Ach provocation test and ergonovine test. Although Ach is now frequently used to provoke CAS, it has been reported that there is a discrepancy between Ach provocation and ergonovine test.\cite{20} In order to evaluate definite CAS of a patient, the two provocation tests should be performed respectively. However, that way is not practically feasible in real world practice. Some atypical chest patient might have coronary endothelial dysfunction and suffer coronary artery spasm by Ach provocation test irrespective of anginal chest pain. Therefore, incidence of the coronary artery spasm could be overestimated.

In conclusion, our present study showed that the elderly patients had significantly more frequent CAS but less incidence of ischemic chest pain as compared with young patients induced by Ach provocation test. Old age was an independent risk factor for Ach-induced significant CAS. Therefore, in elderly patients, CAS might be a frequent etiology of ischemic chest pain and should be considered as a differential etiology.

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