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Gender differences in the presentation of chest pain in obstructive coronary artery disease: results from the Korean Women's Chest Pain Registry

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Background/Aims: Chest pain in patients with obstructive coronary artery disease (OCAD) is affected by several social factors. The gender-based differences in chest pain among Koreans have yet to be investigated.

Methods: The study consecutively enrolled 1,549 patients (male/female, 514/1,035; 61 ± 11 years old) with suspected angina. The predictive factors for OCAD based on gender were evaluated.

Results: Men experienced more squeezing type pain on the left side of chest, while women demonstrated more dull quality pain in the retrosternal and epigastric area. After adjustment for risk factors, pain in the retrosternal area (odds ratio [OR], 1.491; 95% confidence interval [CI], 1.178 to 1.887) and aggravation by exercise (OR, 2.235; 95% CI, 1.745 to 2.861) were positively associated with OCAD. In men, shorter duration (OR, 1.581; 95% CI, 1.086 to 2.303) and dyspnea (OR, 1.610; 95% CI, 1.040 to 2.490) increased the probability for OCAD, while left-sided chest pain suggested a low probability for OCAD (OR, 0.590; 95% CI, 0.388 to 0.897). In women, aggravation by emotional stress (OR, 0.348; 95% CI, 0.162 to 0.746) and dizziness (OR, 0.457; 95% CI, 0.246 to 0.849) decreased the probability for OCAD.

Conclusions: This is the first study to focus on gender differences in chest pain among Koreans with angina. Symptoms with high probability for OCAD were different between sexes. Our findings suggest that patient's medical history in pretest assessment for OCAD should be individualized considering gender.

Keywords: Chest pain; Sex characteristics; Coronary artery disease; Angina pectoris

INTRODUCTION

Chest pain is a common chief complaints and reason for referral to cardiology clinic. A wide range of diseases including coronary artery disease (CAD) may trigger chest pain. It is well known that careful history and identifying typical chest pain is the cornerstone of the diagnosis of CAD [1]. In most cases, it is possible to differentiate patients with CAD even based on the patient's history alone [2].

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Angina is typically described as a squeezing and heavy sensation. The site of chest pain is usually retrosternal and the pain typically occurs under exertion or emotional stress; however, the typical description of angina is based on previous studies from Western countries [3-6]. Various factors including language, cultural syndrome and gender may contribute to the presentation of chest pain. Korea has its own culture and language, and the study about chest pain characteristics in Korean population is warranted. Furthermore, gender differences in the presentation of chest pain affect angina diagnosis and management [7-9]. However, chest pain characteristics of Koreans with angina, and symptoms suggestive of CAD, especially considering gender differences, have yet to be reported.

Therefore, our nation-wide, multicenter, prospective design study aims to evaluate whether gender difference exists in the description of angina symptoms. We further evaluated which symptoms are independently associated with the presence of obstructive coronary artery disease (OCAD) on coronary angiography (CAG).

METHODS

Subjects

The Korean Women's Chest Pain Registry (KoROSE) is a nation-wide, multicenter, prospective study evaluating patients who visited outpatient clinic with chest pain. The detailed protocol of the registry has been previously published [10,11]. The registration started from January 2012. The registry also enrolled men from February 2014 for comparison between sexes. Patients from 25 tertiary medical centers were registered until May 2018. Exclusion criteria were a history of myocardial infarction, or any coronary revascularization, or malignancy, or inflammatory diseases, or chronic kidney disease on dialysis. This study enrolled consecutive patients in the registry who underwent invasive CAG.

Clinical characteristics including age, gender, anthropometric parameters, and medical history of cardiovascular risk factors were investigated. Hypertension was defined by treatment with anti-hypertensive medications, and a systolic blood pressure (BP) ≥ 140, or diastolic BP ≥ 90 mmHg. Diabetes mellitus (DM) was defined by treatment with insulin or oral hypoglycemic agents

or fasting blood glucose ≥ 126 mg/dL. This study protocol was approved by the Institutional Review Boards of all participating centers (IRB No. 2012AN0011). Written informed consent was obtained from all participants.

Chest pain questionnaires

Detailed chest pain questionnaires were obtained from all the patients by physicians. Six aspects of chest pain were evaluated as follows: (1) pain quality, (2) pain location, (3) pain duration, (4) aggravating factors, (5) location of radiating pain, and (6) associated symptoms. Pain quality was described as squeezing, pressure, and stinging, burning or dull pain. Patients were asked to point to painful locations on the body. The duration of pain was classified into three categories: shorter than 5 minutes, longer than 5 minutes and shorter than 15 minutes, longer than 15 minutes and shorter than 1 hour, and longer than 1 hour. Patients were asked to select the aggravating factors from the list: exercise, meal, emotional stress, low temperature, alcohol or other. The location of radiating pain was investigated among left arm, right arm, neck or back. Patients were also asked to indicate any associated symptoms from the list: palpitation, dizziness, headache, dyspnea, or syncope.

Invasive coronary angiography

To evaluate OCAD, invasive CAG was performed in each patient for the following indications: (1) typical angina, (2) angina with abnormal function test result, and (3) angina not evaluable with functional testing. Invasive CAG was performed via femoral or radial artery using a standard protocol. The percentage of coronary artery stenosis was determined by the ratio of the diameter of the stenotic lesion and normal site just proximal to the lesion. OCAD was defined as ≥ 70% stenosis in a proximal or middle epicardial coronary artery or major branch.

Statistical analysis

Categorical variables were presented with frequencies (percentages) and continuous variables were presented with mean ± standard deviation. The differences in baseline and chest pain characteristics were compared between genders and according to the presence of OCAD using the independent t test or chi-square test. Multivariable logistic regression was performed to investigate the impact of each chest pain characteristic for

OCAD after adjustment for age, gender, hypertension, DM, dyslipidemia, smoking, and family history of CAD. SPSS version 24 (IBM Co., Armonk, NY, USA) was utilized for statistical analysis. A $p < 0.05$ was considered statically significant.

RESULTS

Baseline characteristics of total population, men and women

The study enrolled 1,549 consecutive patients (mean age 61.1 ± 11.2 years, 514 males and 1,035 females). Table 1 lists the clinical demographics of the total study population. The mean age of men was younger than that of women (59.4 ± 11.1 years vs. 61.9 ± 11.1 years, $p < 0.001$). The prevalence of current smoking was higher in men compared

Table 1. Baseline characteristics of study population

Characteristic	Total (n = 1,549)	Men (n = 514)	Women (n = 1,035)	p value[a]
Age	61.1 ± 11.2	59.4 ± 11.1	61.9 ± 11.1	< 0.001
Cardiac risk factor				
BMI, kg/m²	25.1 ± 3.5	25.2 ± 2.9	25.0 ± 3.7	0.496
BMI ≥ 25 kg/m²	723 (46.7)	253 (49.2)	470 (45.4)	0.087
Hypertension	797 (51.5)	264 (51.4)	533 (51.5)	0.501
Diabetes mellitus	311 (20.1)	104 (20.2)	207 (20.0)	0.482
Dyslipidemia	305 (19.7)	92 (17.9)	213 (20.6)	0.118
Family history	275 (17.8)	103 (20.0)	172 (16.6)	0.057
Current smoking	210 (13.6)	167 (32.5)	43 (4.2)	< 0.001
Marital status				
Married	976 (80.2)	294 (89.6)	682 (76.7)	< 0.001
Single	49 (4.0)	17 (5.2)	32 (3.6)	0.140
Divorced	38 (3.1)	11 (3.4)	27 (3.0)	0.451
Widowed	154 (12.7)	6 (1.8)	148 (16.6)	< 0.001
Occupational history				
Production worker	282 (18.2)	131 (25.5)	151 (14.6)	< 0.001
Office worker	229 (14.8)	138 (26.8)	91 (8.8)	< 0.001
None or housewife	1,038 (67.0)	245 (47.7)	793 (76.6)	< 0.001
Medications				
ACEi	78 (5.0)	28 (5.4)	50 (4.8)	0.341
ARB	400 (25.8)	135 (26.3)	265 (25.6)	0.412
BB	320 (20.7)	96 (18.7)	224 (21.6)	0.098
CCB	446 (28.8)	146 (28.4)	300 (29.0)	0.430
Diuretics	106 (6.8)	32 (6.2)	74 (7.1)	0.286
Aspirin	588 (38.0)	182 (35.4)	406 (39.2)	0.080
Clopidogrel	352 (22.7)	107 (20.8)	245 (23.7)	0.115
Statins	661 (42.7)	225 (43.8)	436 (42.1)	0.286

Values are presented as mean ± SD or number (%).
BMI, body mass index; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker.
[a]The result of independent t test or chi-square test between men and women.

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Table 2. Chest pain characteristics of study population

Characteristic	Total (n = 1,549)	Men (n = 514)	Women (n = 1,035)	p value[a]
Pain quality				
Squeezing	568 (36.7)	207 (40.3)	361 (34.9)	0.022
Pressure	396 (25.6)	128 (24.9)	268 (25.9)	0.361
Stinging	261 (16.8)	93 (18.1)	168 (16.2)	0.197
Burning	68 (4.4)	20 (3.9)	48 (4.6)	0.297
Dull	237 (15.3)	59 (11.5)	178 (17.2)	0.002
Pain location				
Retrosternal	817 (52.7)	256 (49.8)	561 (54.2)	0.057
Left side of chest	368 (23.8)	160 (31.1)	208 (20.1)	< 0.001
Right side of chest	47 (3.0)	17 (3.3)	30 (2.9)	0.382
Epigastric	317 (20.5)	81 (15.8)	236 (22.8)	0.001
Pain duration				
< 5 min	719 (46.4)	249 (48.4)	470 (45.4)	0.142
5–15 min	281 (18.1)	99 (19.3)	182 (17.6)	0.230
15 min–1 hr	159 (10.3)	55 (10.7)	104 (10.0)	0.376
> 1 hr	390 (25.2)	111 (21.6)	279 (27.0)	0.012
Aggravating factors				
Exercise	449 (29.0)	161 (31.3)	288 (27.8)	0.086
Meal	35 (2.3)	12 (2.3)	23 (2.2)	0.509
Stress	122 (7.9)	36 (7.0)	86 (8.3)	0.214
Low temperature	32 (2.1)	11 (2.1)	21 (2.0)	0.510
Alcohol	10 (0.6)	6 (1.2)	4 (0.4)	0.074
Location of radiating pain				
Left arm	128 (8.3)	37 (7.2)	91 (8.8)	0.165
Right arm	42 (2.7)	9 (1.8)	33 (3.2)	0.067
Neck	99 (6.4)	32 (6.2)	67 (6.5)	0.473
Back	148 (9.6)	29 (5.6)	119 (11.5)	< 0.001
Associated symptoms				
Palpitation	168 (10.8)	43 (8.4)	125 (12.1)	0.016
Dizziness	164 (10.6)	55 (10.7)	109 (10.5)	0.491
Syncope	27 (1.7)	9 (1.8)	18 (1.7)	0.566
Dyspnea	369 (23.8)	115 (22.4)	254 (24.5)	0.190
Headache	88 (5.7)	19 (3.7)	69 (6.7)	0.010

Values are presented as number (%).

[a] The result of chi-square test between men and women.

to women. However, other cardiovascular risk factors including hypertension, DM and dyslipidemia, and cardiovascular medications were not different between the genders.

Chest pain characteristics

Six chest pain characteristics including quality, duration, location, radiation, aggravation, and associated symptoms are listed in Table 2. Among all the enrolled patients, 568 patients (30.7%) described squeezing qual-

ity, and 817 patients (52.7%) manifested pain in the retrosternal area. Pain duration shorter than 5 minutes was the most common (719 patients, 46.4%), and was aggravated by exercise in 449 patients (29.0%).

When chest pain characteristics were compared between genders, men experienced more squeezing chest pain, while women experienced more dull pain. Men complained more of left-sided chest pain, and women presented with epigastric pain. Pain duration exceeding one hour was more common in women than in men. More women described chest pain radiating to back with accompanying palpitation and headache.

Chest pain related to OCAD

OCAD on CAG was found in 425 patients (27.4%).Chest pain was compared between patients with non-OCAD and OCAD (Table 3). Typical symptoms for angina were observed more in patients with OCAD compared with non-OCAD. In patients with OCAD, squeezing pain was more common than in patients with non-OCAD (171 [40.2%] vs. 397 [35.3%], $p = 0.042$). Based on location, pain in the retrosternal area was predominant; however, left-sided pain in the chest was less common in patients with OCAD compared with non-OCAD (pain in retrosternal area: 251 [59.1%] vs. 566 [50.4%], $p = 0.001$; left side of chest: 83 [19.5%] vs. 285 [25.4%], $p = 0.009$). Duration of chest pain did not differ according to the presence of OCAD. Pain was aggravated by exercise more frequently, and less by emotional stress in patients with OCAD compared with non-OCAD (exercise: 175 [41.2%] vs. 274 [24.4%], $p < 0.001$; emotional stress: 18 [4.2%] vs. 104 [9.3%], $p < 0.001$). The location of radiating pain showed no difference according to the presence of OCAD. Among the associated symptoms, patients with OCAD complained of less palpitation and dizziness compared with patients with non-OCAD (palpitation: 26 [6.1%] vs. 142 [12.6%], $p < 0.001$; dizziness: 26 [6.1%] vs. 138 [12.3%], $p < 0.001$).

To investigate the independent association between each chest pain characteristic and OCAD, a multivariate logistic regression including age, gender, hypertension, DM, dyslipidemia, smoking, and family history of CAD was performed (Table 4). The analysis revealed that pain in the retrosternal area and aggravation by exercise increased the probability of OCAD, while palpitation decreased the probability of OCAD (pain in retrosternal area: odds ratio [OR], 1.491; 95% confidence interval [CI], 1.178 to 1.887, $p = 0.001$) (exercise: OR, 2.235; 95% CI, 1.745 to 2.861, $p < 0.001$) (palpitation: OR, 0.476; 95% CI, 0.304 to 0.746; $p = 0.001$).

Gender differences in chest pain characteristics and OCAD

OCAD on CAG was more prevalent in men compared with women (175 [34.0%] vs. 250 [24.2%], $p < 0.001$). Men and women displayed differences in chest pain characteristics according to the presence of OCAD. In men, typical symptoms for angina were more commonly observed in patients with OCAD compared with non-OCAD, while in women, a component of typical symptom was less commonly observed in patients with OCAD compared with non-OCAD. Quality of chest pain was not related to OCAD in both men and women. Left-sided chest pain was less commonly observed in men with OCAD compared with non-OCAD (42 [24.0%] vs. 118 [34.8%], $p = 0.008$). However, the location of chest pain was not related to OCAD in women. In terms of duration, only men demonstrated that shorter duration was related to OCAD (97 [55.4%] vs. 152 [44.8%], $p = 0.014$). Among aggravation factors of chest pain, emotional stress was less frequent in women with OCAD compared with non-OCAD (8 [3.2%] vs. 78 [9.9%], $p < 0.001$), but the association was not significant in men. Among associated symptoms of chest pain, dyspnea was more common in men with OCAD compared with non-OCAD (49 [28.0%] vs. 66 [19.5%], $p = 0.019$) and dizziness was less common in women with OCAD compared with non-OCAD (13 [5.2%] vs. 96 [12.2%], $p = 0.001$).

In men and women, multivariate logistic regression was performed to investigate the association between chest pain and OCAD after adjustment for age, hypertension, DM, dyslipidemia, smoking, and family history of CAD. Shorter duration of chest pain (less than 5 minutes) and dyspnea increased the probability of OCAD only in men (shorter duration: OR, 1.581; 95% CI, 1.086 to 2.303; $p = 0.017$) (dyspnea: OR, 1.610; 95% CI, 1.040 to 2.490; $p = 0.033$). Left-sided chest pain decreased the probability of OCAD in men (OR, 0.590; 95% CI, 0.388 to 0.897; $p = 0.014$), while aggravation by emotional stress and dizziness decreased the probability of OCAD in women (emotional stress: OR, 0.348; 95% CI, 0.162 to 0.746; $p = 0.007$) (dizziness: OR, 0.457; 95% CI, 0.246 to 0.849; $p = 0.013$).

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Table 3. Chest pain characteristics according to the presence of obstructive coronary artery disease

Characteristic	Total (n = 1,549)			Men (n = 514)			Women (n = 1,035)		
	Non-OCAD (n = 1,124)	OCAD (n = 425)	p value[a]	Non-OCAD (n = 339)	OCAD (n = 175)	p value[a]	Non-OCAD (n = 785)	OCAD (n = 250)	p value[a]
Pain quality									
Squeezing	397 (35.3)	171 (40.2)	0.042	133 (39.2)	74 (42.3)	0.283	264 (33.6)	97 (38.8)	0.079
Pressure	292 (26.0)	104 (24.5)	0.295	89 (26.3)	39 (22.3)	0.190	203 (25.9)	65 (26.0)	0.513
Stinging	200 (17.8)	61 (14.4)	0.061	64 (18.9)	29 (16.6)	0.303	136 (17.3)	32 (12.8)	0.054
Burning	49 (4.4)	19 (4.5)	0.510	13 (3.8)	7 (4.0)	0.550	36 (4.6)	12 (4.8)	0.502
Dull	175 (15.6)	62 (14.6)	0.347	40 (11.8)	19 (10.9)	0.437	135 (17.2)	43 (17.2)	0.534
Pain location									
Retrosternal	566 (50.4)	251 (59.1)	0.001	157 (46.3)	99 (56.6)	0.017	409 (52.1)	152 (60.8)	0.010
Left side of chest	285 (25.4)	83 (19.5)	0.009	118 (34.8)	42 (24.0)	0.008	167 (21.3)	41 (16.4)	0.055
Right side of chest	36 (3.2)	11 (2.6)	0.329	12 (3.5)	5 (2.9)	0.451	24 (3.1)	6 (2.4)	0.386
Epigastric	237 (21.1)	80 (18.8)	0.181	52 (15.3)	29 (16.6)	0.404	185 (23.6)	51 (20.4)	0.171
Pain duration									
<5 min	518 (46.1)	201 (47.3)	0.356	152 (44.8)	97 (55.4)	0.014	366 (46.6)	104 (41.6)	0.094
5–15 min	206 (18.3)	75 (17.6)	0.409	70 (20.6)	29 (16.6)	0.160	136 (17.3)	46 (18.4)	0.381
15 min–1 hr	112 (10.0)	47 (11.1)	0.292	39 (11.5)	16 (9.1)	0.254	73 (9.3)	31 (12.4)	0.099
>1 hr	288 (25.6)	102 (24.0)	0.278	78 (23.0)	33 (18.9)	0.166	210 (26.8)	69 (27.6)	0.426
Aggravating factors									
Exercise	274 (24.4)	175 (41.2)	<0.001	91 (26.8)	70 (40.0)	0.002	183 (23.3)	105 (42.0)	<0.001
Meal	26 (2.3)	9 (2.1)	0.495	8 (2.4)	4 (2.3)	0.612	18 (2.3)	5 (2.0)	0.506
Stress	104 (9.3)	18 (4.2)	<0.001	26 (7.7)	10 (5.7)	0.264	78 (9.9)	8 (3.2)	<0.001
Low temperature	19 (1.7)	13 (3.1)	0.072	5 (1.5)	6 (3.4)	0.131	14 (1.8)	7 (2.8)	0.225
Alcohol	7 (0.6)	3 (0.7)	0.547	4 (1.2)	2 (1.1)	0.667	3 (0.4)	1 (0.4)	0.670
Location of radiating pain									
Left arm	93 (8.3)	35 (8.2)	0.536	24 (7.1)	13 (7.4)	0.507	69 (8.8)	22 (8.8)	0.542
Right arm	32 (2.8)	10 (2.4)	0.368	5 (1.5)	4 (2.3)	0.367	27 (3.4)	6 (2.4)	0.279
Neck	70 (6.2)	29 (6.8)	0.373	21 (6.2)	11 (6.3)	0.553	49 (6.2)	18 (7.2)	0.342
Back	112 (10.0)	36 (8.5)	0.214	21 (6.2)	8 (4.6)	0.295	91 (11.6)	28 (11.2)	0.484
Associated symptoms									
Palpitation	142 (12.6)	26 (6.1)	<0.001	35 (10.3)	8 (4.6)	0.016	107 (13.6)	18 (7.2)	0.003
Dizziness	138 (12.3)	26 (6.1)	<0.001	42 (12.4)	13 (7.4)	0.055	96 (12.2)	13 (5.2)	0.001
Syncope	21 (1.9)	6 (1.4)	0.357	7 (2.1)	2 (1.1)	0.358	14 (1.8)	4 (1.6)	0.552
Dyspnea	263 (23.4)	106 (24.9)	0.283	66 (19.5)	49 (28.0)	0.019	197 (25.1)	57 (22.8)	0.259
Headache	66 (5.9)	22 (5.2)	0.348	11 (3.2)	8 (4.6)	0.300	55 (7.0)	14 (5.6)	0.269

Values are presented as number (%).

OCAD, obstructive coronary artery disease.

[a]The result of chi-square test between men and women.

Table 4. Clinical characteristics associated with obstructive coronary artery disease by gender

Characteristic	Total			Men			Women		
	OR	95% CI	p value[a]	OR	95% CI	p value[a]	OR	95% CI	p value[a]
Age ≥ 65 yr	1.970	1.545–2.513	< 0.001	1.511	1.017–2.244	0.041	2.225	1.625–3.047	< 0.001
Women	0.663	0.510–0.862	0.002						
Hypertension	1.297	1.011–1.664	0.041	0.864	0.586–1.274	0.459	1.694	1.218–2.356	0.002
Diabetes mellitus	1.975	1.496–2.607	< 0.001	1.590	0.996–2.539	0.052	2.201	1.558–3.109	< 0.001
Current smoking	1.801	1.279–2.536	0.001	1.712	1.155–2.536	0.007	1.652	0.821–3.327	0.160
Quality: squeezing	1.238	0.976–1.572	0.079	1.195	0.817–1.749	0.358	1.244	0.912–1.696	0.169
Quality: stinging	0.839	0.607–1.160	0.288	0.878	0.537–1.436	0.604	0.818	0.528–1.267	0.368
Location: retrosternal	1.491	1.178–1.887	0.001	1.553	1.066–2.260	0.022	1.454	1.072–1.972	0.016
Location: left chest	0.676	0.507–0.901	0.008	0.590	0.388–0.897	0.014	0.761	0.514–1.125	0.171
Duration: <5 min	1.043	0.826–1.318	0.724	1.581	1.086–2.303	0.017	0.820	0.605–1.112	0.202
Duration: >1 hr	0.923	0.704–1.211	0.564	0.764	0.480–1.214	0.254	1.024	0.731–1.435	0.890
Aggravation by exercise	2.235	1.745–2.861	< 0.001	1.908	1.285–2.835	0.001	2.501	1.817–3.443	< 0.001
Aggravation by emotional stress	0.485	0.286–0.822	0.007	0.755	0.350–1.627	0.473	0.348	0.162–0.746	0.007
Radiation to back	0.877	0.581–1.324	0.532	0.717	0.305–1.686	0.446	0.936	0.582–1.507	0.786
Other symptom: palpitation	0.476	0.304–0.746	0.001	0.423	0.189–0.944	0.036	0.521	0.302–0.899	0.019
Other symptom: dizziness	0.480	0.306–0.752	0.001	0.591	0.304–1.149	0.121	0.457	0.246–0.849	0.013
Other symptom: dyspnea	1.029	0.784–1.350	0.837	1.610	1.040–2.490	0.033	0.801	0.560–1.144	0.222

The following variables were selected for multivariable analysis: age ≥ 65 years, gender, body mass index ≥ 25 kg/m^2, hypertension, diabetes mellitus, dyslipidemia, current smoking, and family history of coronary artery disease.

OR, odds ratio; CI, confidence interval.

[a]The result of chi-square test between men and women.

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DISCUSSION

This is the first study to demonstrate gender differences in the presentation of chest pain and the risk for OCAD in Koreans with suspected angina. Our study demonstrated the following findings. (1) Men showed higher degrees of left-sided chest pain with a squeezing quality, while women presented with more dull pain in retrosternal and epigastric areas, radiating to the back, with palpitations and headache. (2) In both genders, pain in the retrosternal area and aggravation by exercise were independently associated with OCAD. (3) In men, duration shorter than 5 minutes and dyspnea increased the probability for OCAD, while left-sided chest pain had a low probability for OCAD. (4) In women, aggravation by emotional stress and dizziness lowered the probability for OCAD.

Our study has several strengths. This is a prospective study with a sufficient sample size to access gender differences in chest pain among patients with suspected angina in an outpatient setting. Furthermore, as a gold standard for the diagnosis of OCAD, invasive CAG was performed in all patients.

In patients with stable angina, women tend to be older than men, have more comorbidity such as hypertension, DM, dyslipidemia except for current smoking [12]. In this study, the mean age of women were older than men; however, other cardiovascular risk factors were well balanced between men and women except for current smoking. This population with relatively balanced risk factors between men and women could be an appropriate model to analyze gender difference of chest pain characteristics minimizing confounding factors.

Chest pain and OCAD

Stable angina is characterized by retrosternal squeezing, heaviness, and burning. It may radiate to arms, neck, jaw, and is triggered by exercise or emotional stress [2]. In the total study population, pain in retrosternal area and aggravation by exercise were associated with a high probability of OCAD. The results are compatible with the traditional description of stable angina. However, palpitation was negatively associated with OCAD. Palpitation is a common non-pain symptom [13]. However, the clinical implications of palpitation are unclear in patients with non- acute coronary syndrome. Our findings suggest that palpitation in patients with suspected angina may be an atypical symptom with a low probability of OCAD.

Gender differences in chest pain

Current practice guidelines in cardiovascular diseases (CVDs) are based on previous studies conducted primarily in men. For example, in the 2007 American Heart Association guidelines for the prevention of CVD in women, women constituted only 30% of all patients in clinical trials [14]. In a decade, numerous remarkable studies focused on clinical characteristics and outcomes of CVD in women [15-18]. In chest pain characteristics, gender differences have been reported variously according to study design (acute coronary syndrome or stable angina setting, patient population and methods to investigate chest pain characteristics). Although there are reports that chest pain characteristics were not significantly different between men and women with OCAD [19], women tend to have less specific and more non-cardiac symptoms compared with men [7,8,13,20]. Compared to men, CAD in women presents later in their lifespan. Because symptoms become less specific with aging, the differences in the distribution of age in men and women with CAD contribute to gender differences in chest pain presentation. The findings of current study that women older than men, and men presents more typical chest pain with squeezing quality and women manifest more dull pain and non-cardiac symptoms such as palpitation and headache is consistent with previous studies.

Although the gender differences in chest pain have been reported in patients with CAD, their clinical implications and association with CAD are scarce. Majority of previous studies were performed in acute coronary syndrome setting, ant these studies demonstrated that diagnostic probability of chest pain characteristics are not significantly different between men and women [21,22]. In the current study among Koreans with stable chest pain in a tertiary care setting, the gender differences in symptoms for including or excluding CAD have been demonstrated.

Typically, a pain duration more than 30 minutes was the strong negative predictor for CAD [23]. In men from this study, shorter pain duration was positively associated with CAD. However, this association was not observed in women from this study. Similarly, the study

with 1,212 German patients with chest pain in the primary care setting, also demonstrated that in men, shorter pain duration was positively associated with CAD, while pain duration exceeding 1 hour was associated with CAD in women [24]. Even though our findings were consistent with previous study, the underlying mechanism remains unclear.

In this study, only men showed left-sided chest pain was negatively associated with CAD. Bosner et al. [24] reported localized muscle tension in men was negatively associated with CAD. Because men tend to be more active in physical activity than women, it is possible that localized muscle tension, not CAD, may present as a left-sided chest pain. Simple physical examination such as chest wall tenderness on palpation is required to rule out the probability of CAD in these cases.

In men from this study, dyspnea was positively associated with CAD. The reason of association between dyspnea and CAD in men was not clear. But, smoking rate was much higher in men compared to women. As smoking is a potent common risk factor for both CAD and pulmonary disease, high smoking rate in men may be one cause of the association between dyspnea and CAD.

In women, aggravation by emotional stress was negatively associated with CAD. Although emotional stress is a traditional aggravation factor of angina [1], it is notable that in women from this study, pain worsening with emotional stress suggested a low probability of OCAD. In Western countries, somatization is more prevalent in women compared to men [25]. Higher frequency of depressive disorder in women also support the psychological etiology of chest pain in women [26]. Bosner et al. [24] also reported that in German population, women have more psychogenic disorder as the etiology of chest pain compared to men. Hwabyung is a Korean cultural syndrome and its prevalence in general population is 4.1% [27]. It is prevalent in middle-aged or older women. Chest pain in Korean women without OCAD may be explained as one of the somatization symptoms of Hwa-byung. The traditional notion that emotional stress is a predictor of CAD may be a misguided concept that has been derived from previous studies which had been conducted in population mainly composed of men rather than women. Further studies are needed to elucidate the psychological causes of chest pain in women.

Underlying mechanisms for gender differences

Currently, the underlying mechanism of gender difference in chest pain characteristics has not been clearly investigated; however, several mechanisms have been suggested. Firstly, gender differences in pain perception can be one mechanism. In positron emission tomography study, the gender difference of neurophysiological response by painful heat stimulation was observed and women perceive more intense pain than men [28]. In a population study, women tend to have more frequent and severe pain with more referring to greater portion of body region [29]. Second, coronary microvascular dysfunction is reported to be more common in women with suspected angina [30]. This difference of microvascular dysfunction may result in gender difference of chest pain characteristics. Lastly, on the inferior and posterior surface of heart, parasympathetic afferent nerves predominate while sympathetic nerves mainly innervate the anterior surface of heart. In women, right coronary dominance is more prevalent compared to men [31]. The proximal stenosis of a right coronary dominant artery may provoke myocardial ischemia on both anterior and posterior-inferior walls, and activate both sympathetic and parasympathetic nerve. Compared to men with a left coronary dominant system, women with right coronary artery stenosis have more probability to manifest autonomic symptoms such as nausea and emesis [31,32]. These anatomical and physiologic differences may explain the more observed autonomic symptoms such as epigastric pain, palpitation and dizziness in women of present study.

Limitations

Our study has several limitations. First, despite the growing concern about microvascular angina [33,34], our study did not investigate functional ischemia or microvascular dysfunction. We intend to conduct a coronary flow reserve test for additional patients enrolled. Our future study will investigate chest pain characteristics in patients with microvascular angina. Second, the number of men was relatively smaller than women in our study, suggesting a possible attenuation in the association between chest pain and OCAD in men. Finally, although this study suggested psychological causes as the non-cardiac factors in women's chest pain, our study did not conduct a psychological analysis.

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In conclusion, this is the first study to focus on gender differences in chest pain among Koreans with angina. Symptoms with high probability for OCAD varied between sexes. Our findings suggest that history taking in pretest assessment for OCAD should be individualized according to gender.

KEY MESSAGE

1. Although chest pain in patients with obstructive coronary artery disease (OCAD) is affected by several social factors, gender differences in the presentation of chest pain has not been evaluated in Koreans with suspected angina.
2. In men, duration shorter than 5 minutes and dyspnea increased the probability for OCAD, while left-sided chest pain had a low probability for OCAD.
3. In women, aggravation by emotional stress and dizziness lowered the probability for OCAD.
4. In pretest assessment for Korean patients with suspected angina, history taking should be individualized according to gender.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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