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Diagnostic utility of chest pain characteristics in discriminating obstructive coronary artery disease: A 'Historic' Dilemma

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Abstract

Chest pain (CP) is the major presenting symptom of coronary artery disease (CAD) wherein history remains to be a fundamental and challenging diagnostic step. Despite the clarity of 'typical' CP characteristics in guidelines; interpretation and description of CP by patients are open to wide variations. The aim of this study was to define the components of CP that most closely associate to presence of obstructive CAD and determine the influence of gender on CP features. Herein, consecutive patients with suspected stable CAD who were scheduled for a coronary angiography (CAG) were prospectively enrolled. The data on demographic and pain characteristics were collected by a questionnaire. Patients were categorized into 'CAD' and 'Normal' groups with respect to presence of obstructive CAD in CAG. Among 402 patients, 86 had chest discomfort or equivalent symptoms but denied 'CP'. Patients with CAD were more commonly male; with older age, lower BMI, more frequent prior revascularization, clopidogrel use, higher creatinine and lower HDL levels. When classical features of CP such as quality; location, duration, relationship to exertion were compared; stabbing/sharp pain, CP related to cold or emotional stress and CP that radiates to back were significant factors against CAD; while absence of precipitating factors was related to CAD. Yet, none of the features of typical angina pectoris were significantly related to presence of CAD. Determinants of CAD were; prior revascularization (OR= 22.7, p=0.021), body mass index (OR=1.4, p=0.007), clopidogrel use (OR=55.5, p=0.018) and blood glucose (OR=1.02, p=0.046) in women; and age (OR=1.2, p=0.029) was the single predictor of CAD in men. This study demonstrated no association between classical features of typical CP and presence of CAD in patients with stable angina pectoris. Clinical factors that influenced presence of CAD in different genders were also different.

Keywords: Chest pain, typical angina pectoris, coronary artery disease

Introduction

Chest pain (CP) is the major presenting symptom of patients with coronary artery disease (CAD) at the outpatient and/or emergency clinics. [1] Nevertheless, not all patients presenting with CP are of cardiac origin. Physical, psychological and socio-economic factors play significant role in perception and description of pain by patients. [2] Physicians, on the other hand, have to rely on patients' description of pain, to proceed with the diagnostic steps. Herein, history remains to be the fundamental and the most challenging diagnostic step.

Angina pectoris is the CP of ischemic origin. [3] The characteristics of typical angina pectoris are clearly outlined in the guidelines and are distinct in terms of quality, duration and location. [1] Diagnosis and treatment of coronary artery disease depends on the correct interpretation of CP as a symptom. This, however, is not straightforward; as CP is a subjective symptom with many influencing factors. Several studies failed to prove discriminatory

value of CP characteristics on prediction of significant CAD in acute coronary syndromes. [4-6] The data on chronic angina pectoris is limited, and there is no literature published in Turkish population.

This study aimed to define the features of the CP in patients with obstructive CAD and determine the components that most closely associate to presence of obstructive CAD. We also sought to evaluate whether CP characteristics differed among genders.

Material and Methods

A total of 402 consecutive patients with CP and suspected stable CAD who were scheduled for a routine coronary angiography (CAG) were prospectively enrolled. Patients with episodes of CP suggestive of unstable angina pectoris such as new (within 2 weeks) onset, those with rest angina, with acute coronary syndromes or recent (within 6 months) revascularization were not included to the study. Patient enrollment was started after approval from local Ethics Committee and covered a period between September 2017 and January 2018.

The data on demographic characteristics and features of CP were evaluated by a questionnaire, prior to the coronary angiography.

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The biochemical parameters such as fasting blood glucose, white blood cell (WBC) count, hemoglobin (Hb), Platelet count (PLT) creatinine, low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TC) and triglyceride were recorded. Weight and height were measured to calculate body mass index (BMI; kg/m²). Patients were categorized into 'obstructive CAD' and 'Normal' groups with respect to presence of CAD that causes luminal stenosis of $\geq 50\%$ on coronary angiogram.

CP questionnaire

The questionnaire was divided into two parts wherein the first part consisted of questions about the demographic data with possible influence on perception of CP such as level of education, working status, history of cardiovascular risk factors, history of prior revascularization and drugs used.

The second part of the questionnaire was about important features of CP such as quality, location, duration, precipitating and relieving factors, radiation, number of locations that pain radiates, accompanying symptoms and the severity graded by the patient. Guidelines of stable coronary artery disease classifies stable angina pectoris according to the following 3 criteria [1]:

1. Substernal chest discomfort of characteristic quality and duration
2. Provoked by exercise or emotional stress
3. Relieved by rest or nitrates.

In 'typical' angina pectoris, CP features fulfill all three criteria while those that fulfill 2 are classified as 'atypical' CP and those that fulfill one or none are classified as 'noncardiac'. We, therefore,

utilized the same criteria in the CP questionnaire.

Statistical Analysis

The categorical variables were expressed as percentages (%), n) and continuous variables were expressed as mean \pm standard deviation or as median (min-max) as appropriate. The normality of distribution in continuous variables were tested by Kolmogorov-Smirnov test. The 'Obstructive CAD' and 'Normal' groups were compared using either independent samples t test in case or Mann Whitney U test as appropriate. The categorical variables were compared by Chi-Square. Pearson's Chi square was used when the expected frequencies in the 2x2 contingency tables were >25 ; A continuity correction chi square was used when the expected frequencies were between 5 and 25 and Fisher's exact test was used when the expected frequencies were <5 . With stratifying study group by gender and setting presence of obstructive CAD as the dependent variable, multivariate logistic regression analysis was conducted. All variables that had $p \leq 0.10$ in the univariate analyses were included into the model, by stepwise method, to determine the predictors of presence of obstructive CAD. A p value of <0.05 was considered significant.

Results

Of 402 patients (48% women; mean age 61.2 ± 10.9 years), 86 patients negatively replied to the question on whether they had experienced chest pain before. These patients denied to have 'CP' but complained of subtle chest discomfort (59.3%), dyspnea (25.6%), fatigue (11%), sweating (1.9%) and syncope (1.9%). The data on patients without chest pain are presented in Table 1.

Table 1. Baseline characteristics of the patients who denied to have CP

Baseline Characteristics	Overall study opulation n=86	Obstructive CAD n=44	Normal n=42	p value	
Age, years	63.7 \pm 11.4	64.5 \pm 10.8	63 \pm 12.1	0.55	
Female Gender, %(n)	40.7 (35)	29.5(13)	52.4(22)	0.053*	
Education, %(n)	Primary school	73.3(63)	77.3(34)	0.44	
	High school	10.5(9)	11.4(5)	9.5(4)	
	University	16.3(14)	11.4(5)	21.4(42)	
Work status, %(n)	26.7(23)	20.5(9)	33.3(14)	0.26	
BMI, kg/m ²	28.5(18.3-44.4)	28.4(18.3-44.4)	29.3(20.9-42.5)	0.27	
Hypertension, %(n)	48.8(42)	50(22)	47.6(20)	0.99	
Diabetes mellitus, %(n)	26.7(23)	25(11)	28.6(12)	0.89	
Hyperlipidemia, %(n)	32.6(28)	31.8(14)	33.3(14)	1	
Smoking status, %(n)	25.6(22)	27.3(12)	23.8(10)	0.90	
Family history, %(n)	48.8(42)	47.7(21)	50(21)	1	
Prior revascularization, %(n)	43(37)	63.6(28)	21.4(9)	<0.001	
Medications, %(n)	ASA	50(43)	65.9(29)	33.3(14)	0.05
	Clopidogrel	17.4(15)	27.3(12)	7.1(3)	0.03
	Beta blockers	41.9(36)	47.7(21)	35.7(15)	0.36
	RAAS blockers	47.7(41)	59.1(26)	35.7(15)	0.051
	CCB	15.1(13)	20.5(9)	9.5(4)	0.26
	Statin	27.9(24)	34.1(15)	21.4(9)	0.28
	OAD	19.8(17)	20.5(9)	19(8)	1
	Insulin	4.7(4)	6.8(3)	2.4(1)	0.61*
	Nitrates	3.5(3)	4.5(2)	2.4(1)	1*
	Glucose	111(68-379)	114(87-356)	110(68-379)	0.44
White blood cell, x10 ³	7.5(3.7-12.7)	7.3(4.1-11.5)	7.6(3.7-12.7)	0.19	
Hemoglobin, gr/dL	13.2(9-17.7)	13.3(9-16.6)	13.2(9.1-17.7)	0.61	
Platelet, x10 ³	237.5(121-457)	220(141-432)	262(121-457)	0.019	
Creatinine	0.9(0.6-6.8)	0.88(0.59-2.0)	0.91(0.56-6.8)	0.56	
LDL, mg/dL	104(27-357)	102(27-176)	106(40.8-358)	0.71	
HDL, mg/dL	44(25-99)	43(25-99)	45(29-80)	0.38	
T. cholesterol, mg/dL	183(98-439)	183(101-275)	194(98-439)	0.82	
Triglyceride, mg/dL	158(14.2-527)	167.5 (14.2-527)	149(60-518)	0.13	
Predominant symptom	Dyspnea	25.6 (22)	22.7(10)	28.6(12)	0.41
	Pre/syncope	0.01(1)	-	0.02(1)	
	Sweating	0.01 (1)	0.02(1)	-	
	Fatigue	25.6 (11)	9.1(4)	16.7(7)	
	Chest discomfort	59.3 (51)	65.9(29)	52.4(22)	

CAD: Coronary artery disease, BMI: Body mass index, ASA: Acetylsalicylic acid, RAAS: renin-angiotensin-aldosterone system, CCB: calcium channel blockers, OAD: oral antidiabetic drugs, LDL: low density lipoprotein, HDL: high density lipoprotein. Categorical variables are compared by continuity correction chi square; continuous variables are compared by independent samples t test or Mann Whitney U as appropriate. *indicates p values calculated by Fishers exact test

Table 2. Baseline characteristics of patients with chest pain

Baseline Characteristics	Overall study populationn=316	Obstructive CAD n=165	Normal n=151	p value
Age	60.4±10.7	62.9±10.3	57.7±10.5	<0.001
Female Gender, %(n)	50(158)	35.8(59)	65.6(99)	<0.001
Education, %(n)				
Primary school	85.1(269)	86.1(142)	84.1(127)	0.9
High school	11.1(35)	10.9(18)	11.3(17)	
University	3.8(12)	3(5)	4.6(7)	
Work status, %(n)	30.4(96)	30.3(50)	30.5(46)	0.97
BMI	29.2 (18.5-48.8)	28.2 (19.4-45.5)	31.1 (18.5-48.8)	0.004
Hypertension, %(n)	54.7(173)	55.2(91)	54.3(82)	0.88
Diabetes mellitus, %(n)	30.7(97)	31.5(52)	29.8(45)	0.74
Hyperlipidemia, %(n)	31.6(100)	30.9(51)	32.5(49)	0.76
Current Smoker, %(n)	28.5(90)	28.4(41)	32.5(49)	0.13
Family history, %(n)	55.4(175)	51.5(85)	59.6(90)	0.149
Prior revascularization, %(n)		55.8(92)	32.5(49)	<0.001
Medications, %(n)				
ASA	50.3(159)	54.5(90)	45.7(69)	0.11
Clopidogrel	22.5(71)	33.9(56)	9.9(15)	<0.001
Beta blockers	51.3(162)	50.9(84)	51.7(78)	0.89
RAAS blockers	41.5(131)	45.5(75)	37.1(56)	0.13
CCB	16.5(52)	14.5(24)	18.5(28)	0.33
Statin	26.3(83)	30.3(50)	21.9(33)	0.09
OAD	21.5(68)	21.2(35)	21.9(33)	0.89
Insulin	8.2(26)	9.1(15)	7.3(11)	0.70*
Nitrates	4.7(15)	5.5(9)	4(6)	0.72*
Glucose	112(62-419)	113(77-419)	110(62-346)	0.07
White blood cell, x10 ³	7.2(3.4-15.5)	7.3(3.4-15.5)	7.2(3.5-14.4)	0.50
Hemoglobin, gr/dL	13.4(9.2-18.6)	13.5(9.2-18.6)	13.3(9.7-18)	0.50
Platelet, x10 ³	243(108-547)	231(114-475)	259(108-547)	0.051
Creatinine	0.85(0.5-2.2)	0.87(0.54-2.2)	0.81(0.52-1.56)	0.02
LDL, mg/dL	116(25-269)	114(25-269)	116(28-247.5)	0.46
HDL, mg/dL	44(21-104.5)	42(21-104.5)	46.1(25-93.2)	0.013
T. cholesterol, mg/dL	198(96-356)	193(110-359)	202(96-353)	0.33
Triglyceride, mg/dL	171(48-743)	176(48-722)	167(54-743)	0.74

CAD: Coronary artery disease, BMI: Body mass index, ASA: Acetylsalicylic acid, RAAS: renin-angiotensin-aldosterone system, CCB: calcium channel blockers, OAD: oral antidiabetic drugs, LDL: low density lipoprotein, HDL: high density lipoprotein. Categorical variables are compared by chi square; continuous variables are compared by independent samples t test or Mann Whitney U as appropriate. * indicates p values calculated by continuity correction.

Among 86 patients who denied to have CP, 51% (n=44) was revealed to have obstructive CAD. Patients in obstructive CAD group differed from normal group, only in terms of prior revascularization; there were more patients with prior revascularization in obstructive CAD group. Patients with obstructive CAD but no CP also had more frequent clopidogrel use and lower platelet number than normal CAG patients.

The presenting symptom of 78.6%(n=316) of patients was CP. The baseline characteristics of these patients are presented in Table 2. When compared to patients with normal CAG; obstructive CAD patients were more frequently male (35.8 vs 65.7%, p<0.001), with older age (62.9±10.3 vs 57.7±10.5, p<0.001), lower BMI (28.2 vs 31.1 kg/m², p=0.004), more common prior revascularization (55.8 vs 32.5%, p<0.001) and clopidogrel use (33.9 vs 9.9%, p<0.001), higher creatinine (0.85 vs 0.81, p=0.02) and lower HDL(42 vs 46.1 mg/dL, p=0.013). There was no statistically significant difference in terms of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, smoking; the medications; or the biochemical parameters such as WBC, Hb, PLT, LDL, TC and TG between patients with and without obstructive CAD (p>0.05).

Table 3 summarizes the pain characteristics of patients with CP. Notably, most patients described typical angina pectoris in terms of quality, location, duration and related factors. Nevertheless, only 52.2% of CAG revealed obstructive CAD. CP characteristics of patients with and without CAD were comparable in terms of localization, duration, relieving factors, accompanying symptoms and severity of pain (p>0.05). Patients with obstructive CAD, however, less frequently had stabbing/sharp pain (7.3 vs 15.2%, p=0.03), CP that is precipitated by cold (24.8 vs 37.7%, p=0.013) or emotional stress(47.9 vs 68.2%, p<0.001), and that radiates to back (42.4 vs 55.6%, p=0.014).

As previous studies have established the role of gender as a significant predictor of CP characteristics; we have stratified patient population by gender to determine the predictors of presence of CAD. Logistic regression analysis showed that prior revascularization (OR= 22.7, p=0.021), body mass index (OR=-1.4, p=0.007), clopidogrel use(OR=55.5, p=0.018) and blood glucose (OR=1.02, p=0.046) were significant predictors of CAD in women while age (OR=1.2, p=0.029) was the single predictor of CAD in men.

Table 3. Characteristics of chest pain in patients with and without CAD

Characteristics of chest pain		Overall study population n=316	Obstructive CAD n=165	Normal n=151	p value
Quality, %(n)	squeezing/pressure*	46.5(147)	47.3(78)	45.7(69)	0.77
	ache/burn	21.2(67)	21.8(36)	20.5(31)	0.78
	needling	21.2(67)	23.6(39)	18.5(28)	0.26
	stabbing/sharp	11.1(35)	7.3(12)	15.2(23)	0.03
Localization, %(n)	anterior thorax*	94(297)	93.3(154)	94.7(143)	0.78
	epigastric	2.8(9)	2.4(4)	3.3(5)	0.74
	back	3.2(10)	4.2(7)	2(3)	0.34
Duration, %(n)	few seconds	20.3(64)	20(33)	20.5(31)	0.80
	<5 min*	34.2(108)	36.4(60)	31.8(48)	
	5-10 min*	25(79)	23.5(39)	26.5(40)	
	30 min< hours	12(38) 6.3(20)	13.3(22) 5.5(9)	10.6(16) 7.3(11)	
Precipitating factors, %(n)	none identified	18.4(58)	23.6(39)	12.6(19)	0.011
	exercise*	67.7(214)	64.2(106)	71.5(108)	0.167
	cold*	31(98)	24.8(41)	37.7(57)	0.013
	emotional stress*	57.6(182)	47.9(79)	68.2(103)	<0.001
Relieving factors, %(n)	none	15.8(50)	17.6(29)	13.9(21)	0.61
	rest*	79.1(250)	77(127)	81.5(123)	
	nitrates*	5.1(16)	5.5(9)	4.6(7)	
Radiation, %(n)	none	21.2(32)	26.1(43)	21.2(32)	0.4
	back	48.4(153)	42.4(70)	55.6(84)	0.014
	shoulders	26.6(84)	25.5(42)	27.8(42)	0.58
	arms	41.5(131)	38.8(64)	44.4(67)	0.26
	jaw	24.7(78)	23(38)	26.5(40)	0.43
Accompanying symptoms , %(n)	None	18(57)	20(33)	15.4(24)	0.34
	Dyspnea	49.1(155)	46.1(76)	52.3(79)	0.26
	nausea	19.9(63)	20(33)	19.9(30)	0.97
	pre/syncope	11.7(37)	9.1(15)	14.6(22)	0.18
	cold sweating	50.9(161)	49.1(81)	53(80)	0.49
	fatigue	63.9(202)	63(104)	64.9(98)	0.72
Scale		5(1-10)	5(2-10)	5(1-10)	0.9

* indicates the features on typical angina pectoris. CAD: Coronary artery disease

Discussion

This study has demonstrated that classical features of typical angina pectoris were not associated with obstructive CAD in patients with stable angina pectoris. Moreover, pain that radiates to back or that is exacerbated by cold or emotional stress was associated with absence of CAD. Logistic regression analysis proved that clinical factors which influenced presence of CAD were different between the two genders and none of the CP characteristics was independently associated with CAD in either gender.

The characteristics of CP that favors angina pectoris was defined long ago and have been used in clinical practice since then [1,7,8]. Nevertheless, CP is a subjective symptom for which the utility of this classification is questionable [9]. Carlton et al have studied the discriminatory value of 'typicality of CP' in acute CP patients and showed that it was not of value in acute coronary syndromes [4]. This was also proved by a study, in which categorical definition of typical CP yielded very low sensitivity and specificity. (48% and 66% respectively) in patients with acute CP [5]. Sephehrvand et al have gone one step further, omitted CP characteristics and tested the accuracy of different management protocols in the emergency setting ignoring CP features. They showed that management protocols performed well without CP characteristics in decision-

making [6]. The data on the chronic stable CP is scarce and there is no published data in Turkish population indeed.

Comparison of CP features between patients with and without CAD showed that, most of the features of chronic stable CP were similar between the two groups. An exception was the stabbing/sharp pain that is already known to be an unusual symptom in the CAD. Although pain 'exacerbated by emotional stress or cold' constitutes one of the components of typical angina pectoris, it was less common in CAD patients in our study. Previous studies suggested that patients with non-obstructive CAD and psychological stress have greater incidence of persistent chest pain [10,11]. Concomitant stress, may have therefore, triggered the anginal symptoms in patients without CAD in our study as well. Pain that radiates to back was also found to be associated with absence of CAD in the present study. Radiation of angina to the back is a common presentation that can easily be misinterpreted for back pain. In logistic regression analysis, when all clinical factors were evaluated together with the CP characteristics, this study evidenced that, none of the pain characteristics were among significant predictors of CAD.

Gender is a major cardiovascular risk factor. It has shown to profoundly influence perception and description of CP [12-14]. We

therefore have analyzed current data in men and women separately, in an effort to describe the predictors of CAD precisely. Among all clinical and CP characteristics, age was the single, independent, significant predictor of CAD in male patients. For women, the p value for age in regression analysis was 0.07 and it did not reach statistical significance. The mean age of women and men with CP was 61 ± 10.3 vs 59.9 ± 11.2 . ($p > 0.05$)

In women, significant predictors of CAD were found to be prior revascularization (for longer than 6 months), clopidogrel use, blood glucose and BMI. Need for repeat revascularization after an initial procedure is a common outcome of percutaneous coronary interventions as clearly demonstrated by the SYNTAX trial [15]. Clopidogrel use was independently associated with CAD; as patients with more severe anginal symptoms may have been prescribed to have clopidogrel. Blood glucose was also positively associated with CAD. Higher BMI seemed to be protective of CAD in women; as previously demonstrated by obesity paradox [16,17]. Nevertheless, BMI is not a good surrogate of obesity and cannot discriminate the subtypes of obesity and adipose tissue with varying metabolic rates [18].

Another important finding in our study was high percentage of patients who denied to have 'CP'. They described chest discomfort using different terminology. Considerable amount of these patients without CP had indeed CAD revealed by CAG. These patients with atypical symptoms are those with worse prognosis.[19] The major limitation of the study was the fact that study population consisted only of patients with CP who were referred to CAG. This was inevitable since there is no study to have CAG for all patients presenting with CP. Moreover, CAG has provided a gold standard method to conclude on presence of CAD.

Conclusion

This study has several clinical implications to the clinical practice as we have demonstrated no association between classical features of typical CP and presence of CAD in patients with stable angina pectoris. Pain that radiates to back; that is exacerbated by cold or emotional stress was associated with absence of CAD, in the present study. Different clinical factors influenced presence of CAD in different genders; yet none of the CP characteristics was independently associated with CAD in either gender.

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Ethical approval

Before the study, permissions were obtained from local ethical committee.

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