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ORIGINAL ARTICLE

Tools to improve the diagnostic accuracy of exercise electrocardiograms in patients with atypical angina pectoris

Atipik angina pektorisi olan hastalarda efor testinin tanısal doğruluğunu arttıracak araçlar

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ABSTRACT

Objective: Although frequently utilized, an exercise electrocardiogram (ECG) provides limited diagnostic accuracy in patients with atypical angina pectoris. The purpose of this study was to determine the possible incremental value of pretest probability (PTP) scores and exercise parameters in discriminating coronary artery disease (CAD) and to identify PTP cutoff values.

Methods: In a retrospective cohort of 207 patients with atypical angina (76 women, 131 men; mean age: 57.6±8.2 years) who underwent coronary angiography (CAG) after a positive exercise ECG, the PTP was calculated according to the CAD Consortium basic and clinical models along with exercise parameters of blood pressure (BP), heart rate (HR), exercise duration, maximal metabolic equivalents (METs), HR reserve, HR recovery, chronotropic index, BP reserve, BP recovery, and ST/HR ratio. Patients were categorized into true positive (TP) or false positive (FP) groups, depending on the ultimate determination of a presence of obstructive CAD.

Results: A TP result was associated with older age, male gender, hypertension, diabetes, hyperlipidemia, and higher basic and clinical PTP, as well as higher maximal BP, maximal ST deviation and ST/HR, but lower maximal METs, chronotropic index, and HR recovery. The basic and clinical PTP, and the chronotropic index could predict a TP test result irrespective of gender. Logistic regression analysis revealed that clinical PTP was the only independent predictor of TP results. A cutoff score of 18 for the basic and 21 for the clinical PTP were determined to discriminate CAD.

Conclusion: This study has shown that, among various electrocardiographic and hemodynamic parameters, the clinical PTP and the chronotropic index are the most helpful tools to discriminate patients with CAD among patients with atypical angina.

ÖZET

Amaç: Efor testi, sık kullanılmakla beraber, atipik angina pektorisi olan hastalarda kısıtlı tanısal doğruluğa sahiptir. Bu çalışmada, test-öncesi olasılık skorları (TOS) ile çeşitli egzersiz parametrelerinin, koroner arter hastalığını (KAH) tanımada, ilave değeri olup olmadığını ve TOS sınır değerlerini belirlemeyi amaçladık.

Yöntemler: Atipik angina pektorisi olup pozitif efor testi sonrası koroner anjiyografi (KAG) yapılan, 207 hastalık geriyedönük kohort çalışmamızda (76 kadın, 131 erkek; ortalama yaş 57.6±8.2) CAD konsorsiyumu tarafından önerilen 'temel' ve 'klinik' TOS ile; egzersiz süresi, maksimal metabolik eşdeğer (MET), kalp hızı (KH) rezervi, KH derlenmesi, kronotropik indeks, kan basıncı (KB) rezervi, KB derlenmesi, ST/KH oranı gibi egzersiz KB ve KH parametreleri değerlendirildi. Hastalar tıkayıcı KAH varlığına göre gerçek pozitif (GP) ve yalancı pozitif (YP) gruplarına ayrıldı.

Bulgular: Gerçek pozitif test sonuçları ile yaş, erkek cinsiyet, hipertansiyon, diyabet, hiperlipidemi; yüksek temel ve klinik TOS, egzersiz KB, ST deviyasyonu, ST/KH oranı arasında pozitif, MET, kronotropik indeks ve KH derlenmesi arasında negatif yönde ilişki bulundu. Temel ve klinik TOS değerleri, cinsiyetten bağımsız olarak, GP test sonucu için öngörücü idi. Lojistik regresyon analizi, klinik TOS'un GP sonuç için tek öngörücü olduğunu göstermiştir. Temel TOS için 18, klinik TOS için ise 21 değerlerinin KAH için ayırt edici sınır değerler olduğu saptanmıştır.

Sonuç: Çalışmamızda birçok elektrokardiyografik ve hemodinamik parametrenin arasında, klinik TOS ve kronotropik indeksin atipik angina pektorisi olan hastalarda KAH'ı ayırt edici özelliği olduğu gösterilmiştir.

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An exercise electrocardiogram (ECG) is the preferred initial method to evaluate ischemic chest pain. Although it provides a noninvasive, low-cost, and rapid method of assessment, its diagnostic accuracy is limited, especially in patients with atypical angina. The overall sensitivity and specificity of an exercise ECG is 68% and 77%, respectively.[1,2] Yet patient characteristics or the pretest probability (PTP) may also influence the test results and interpretation. A positive exercise ECG result is a challenge for the interpreter and may not always translate into the presence of significant coronary artery disease (CAD) in patients with a relatively low risk profile.

More than 3 decades ago, Diamond and Forrester[3] developed a simple method of predicting exercise ECG PTP to avoid the confusion of false negative (FN) test results in high-risk individuals and false positive (FP) test results in low risk individuals. In 2011, this score was revised by the CAD Consortium Group, which developed a basic model to calculate the PTP of patients in an effort to minimize errors in the diagnosis of CAD.[4] The current European Society of Cardiology guidelines support the use of the basic PTP score for risk stratification.[5] This score, however, was recently updated by the same group, incorporating cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia, and smoking into the basic model, to produce the advanced clinical model.[6] Yet, the accuracy of this novel, advanced clinical PTP score and the cutoff values among low-intermediate or high-risk patients are not well-defined.

Although variables of exercise capacity, heart rate (HR) and blood pressure (BP) responses provide valuable information for prognosis, the magnitude of ST depression is the primary criterion for the diagnosis of ischemia on an exercise ECG.[1,2] However, the sensitivity and specificity of ST segment evaluation in an exercise ECG are low.[7] Numerous studies have addressed the utility of different parameters beyond ST depression, but no consistent improvement in diagnostic accuracy has yet been demonstrated.[5,8] Exercise-induced ST segment depression leading to a FP test result is a particular concern in patients with a low-intermediate PTP and in women.[9–11]

Therefore, subjects presenting with atypical angina and a non-high PTP of CAD represent the gray zone in the interpretation of an exercise ECG. In this study population, the possible incremental value of integrating exercise parameters related to HR and BP, PTP score, and ST segment changes to improve diagnostic yield and the positive predictive value of an exercise ECG was evaluated.

Abbreviations:

AUC	*Area under the curve*
BMI	*Body mass index*
BP	*Blood pressure*
CAD	*Coronary artery disease*
CAG	*Coronary angiography*
CI	*Confidence interval*
CTA	*Computed tomographic angiography*
DM	*Diabetes mellitus*
ECG	*Electrocardiogram*
FP	*False positive*
HR	*Heart rate*
MET	*Metabolic equivalent*
OR	*Odds ratio*
PTP	*Pretest probability*
TP	*True positive*

METHODS

A cohort of 207 patients (131 men and 76 women; mean age 57.6±8.2 years) who presented with atypical angina pectoris and underwent coronary angiography (CAG) after a positive exercise ECG was retrospectively evaluated. Patients with known CAD, prior stent or coronary artery bypass grafting, or with an acute coronary syndrome or congestive heart failure were excluded from the study. Patients with an uninterpretable baseline ECG, and those with resting ST segment abnormalities, such as an ST segment depression (≥0.1 mV), complete bundle branch block, left anterior or posterior hemiblock, preexcitation, digoxin use, or ventricular paced rhythm were also excluded. The patients' descriptions of the chest pain were obtained from the medical records and pain suggestive of ischemic origin was classified as typical, atypical, and nonspecific, as outlined in previous guidelines.[1,5] Only patients with atypical chest pain symptoms that included 2 of the 3 following components were enrolled in the study: Substernal chest discomfort of characteristic quality and duration, provoked by exercise or emotional stress, and relieved by rest or nitrates. Patient characteristics of age, gender, height, weight, and cardiovascular risk factors of hypertension, diabetes mellitus (DM), hyperlipidemia, current smoking, and family history were recorded. Body mass index (BMI, kg/m^2) was calculated as weight divided by height squared. Hypertension was defined as either a systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or antihypertensive use. DM was determined by antidiabetic medication use or prior physician diagnosis. Hyperlipidemia was diagnosed as defined by the current guidelines.[12] These data were used to calculate individual PTPs according to the 2 CAD Consortium models. The basic model suggests the use of age, gender, and type of chest pain data to construct the basic probability, while the clinical model uses additional data on cardiovascular risk factors of hypertension, DM, hyperlipidemia, and smoking status to construct an advanced clinical PTP score.[6] Obstructive CAD was determined based on CAG results demonstrating a diameter narrowing of ≥50% in an epicardial coronary artery.

Exercise electrocardiogram and exercise parameters

A treadmill exercise test using the Bruce protocol was scheduled for patients presenting with chest pain at the physician's discretion. Data related to age, gender, height, weight, and cardiovascular risk factors, as well as a description of the chest pain were recorded for every patient prior to the exercise ECG. For the purpose of the study, the exercise ECG recordings were retrospectively analyzed by a doctor blinded to the CAG results. The total duration of exercise, the metabolic equivalents (METs) achieved by the patient, and BP and HR changes during exercise and recovery were recorded in detail. An index of maximal predicted HR was derived from the ratio of maximal HR to that of age-predicted maximal HR (220-age). HR reserve, the increase in HR with exercise, was calculated as peak HR minus resting HR. HR recovery, which is the response of HR after the cessation of exercise, was calculated as HR at peak exercise minus HR at 1 minute after cessation of exercise.[13] The chronotropic index, the index of maximal predicted HR reserve, was determined by the formula: HR at peak exercise-resting HR/([220-age]-resting HR). Similarly, BP reserve was defined as peak systolic BP-resting systolic BP. BP recovery was defined as the ratio of systolic BP at the third minute of recovery to systolic BP at peak exercise. A ratio of <0.9 is considered abnormal BP recovery.[14] A Duke Treadmill Score was calculated for each patient as exercise time in minutes - 5x (ST segment deviation in mm) - 4x (angina index), in which the angina index is 0 if there is no angina, 1 if angina is present, and 2 if angina stops the exercise.[15] The ratio of ST segment to HR index (ST/HR) provided an adjustment of ST segment to the HR. We also calculated the maximal ST segment deviation to change in BP to determine a ST to BP ratio.

An exercise ECG test was interpreted as ischemic, or positive, if a horizontal or down-sloping ST segment depression of ≥1 mm or elevation of at least 60–80 milliseconds was observed after the J point, or if ischemic chest pain occurred.[1] The CAG was carried out using the standard protocol and the patients were classified as having either a TP or FP test result, depending on the existence of a diameter stenosis of ≥50%.

Statistical analysis

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc software (MedCalc Software, Ostend, Belgium) were used for the statistical analysis. Continuous variables were expressed either as mean±SD or as mean (min-max), while categorical variables were expressed as a number (percentage). The variables were tested for normality of distribution using the Kolmogorov-Smirnov test. The TP and FP patient groups were compared using an independent samples t-test for normally distributed variables, and the Mann-Whitney U test for variables without normal distribution. The categorical variables were compared with a chi square test. Pearson's chi square test 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 frequency was <5. Receiver operating curves for basic and advanced clinical PTP scores were constructed and areas under the curve (AUC) were calculated with MedCalc software. With a TP result as the dependent variable, multivariate logistic regression analysis was conducted and all variables with a p value <0.25 were included in the model using the backward logistic regression method. Age, gender, hypertension, DM, hyperlipidemia, BMI, basic PTP score, clinical PTP score, exercise duration, maximal METs, maximal BP, HR reserve, BP reserve, chronotropic index, resting BP, HR recovery, maximal ST deviation, BP recovery, and ST/HR index were the possible variables that were included in the model to determine the predictors of TP results. A p value of <0.05 was considered significant.

RESULTS

A total of 207 patients with atypical angina pectoris and a positive exercise ECG were enrolled in the study. The mean age of the study population was 57.6±8.2 years. In 79 of 207 patients, the CAG revealed obstructive CAD, yielding a positive predictive value of the exercise ECG of 38.2%. The demographic characteristics and exercise ECG parameters of patients with respect to CAG results are shown in Table 1. Notably, the patients with obstructive CAD (i.e., a TP test result) were older (61.4±6.79 *vs*. 55.3±8.25 years; p<0.001), more likely to have hypertension (65.8% *vs*. 50%; p=0.026), DM (65.8% *vs*. 50.7%; p=0.034), hyperlipidemia (77.2% *vs*. 58.5%; p=0.006), and less likely to be female (20.2% *vs*. 46%; p<0.001). The basic and clinical CAD consortium model estimates of PTP were higher in patients with TP test results. (25.3 [4.0–47.0] *vs*. 10.0 [2.0–46.0]; p<0.001 and 35.0 [3.0–71.0] *vs*. 15.6 [2.0–52.0]; p<0.001, respectively).

When patients with TP and FP tests were compared in terms of exercise parameters, patients with obstructive CAD (TP test) had a lower maximal MET (7.7±0.82 *vs*. 8.1±1.14; p=0.005), chronotropic index (0.6 [0.1–1.2] *vs*. 0.7 [0.3–5.3]; p=0.002), and HR recovery (14.0 [0–35.0] *vs*. 17.0 [0–60.0] beats; p=0.015), but a higher maximal BP (195.0 [114.0–244.0] *vs*. 184.5 [110.0–254.0] mm Hg; p=0.005), maximal ST segment deviation (2 [1–4] *vs*. 2 [1–4] mm; p=0.011) and ST/HR ratio values (3.1 [0.5–15.4] *vs*. 2.4 [0.3–8.5] µV/bpm; p<0.001) (Table 1).

Table 1. Comparison of demographic characteristics, pretest probability scores, and exercise variables in the false positive and true positive groups

	False positive (n=128)			True positive (n=79)			*p*
	n	%	Mean±SD Median (Min-Max)	n	%	Mean±SD Median (Min-Max)	
Age (years)			55.3±8.25			61.4±6.79	<0.001*
Female gender	60	46		16	20.2		<0.001**
Hypertension	64	50		52	65.8		0.026**
Diabetes mellitus	65	50.7		52	65.8		0.034**
Hyperlipidemia	75	58.5		61	77.2		0.006**
Current smoking	36	28.1		28	35.3		0.268**
Family history	40	32.2		22	27.8		0.604**
Body mass index (kg/m^2)			29.0 (18.6–45.6)			28.0 (21.5–45.3)	0.186***
Basic PTP score			10.0 (2.0–46.0)			25.3 (4.0–47.0)	<0.001***
Clinical PTP score			15.6 (2.0–52.0)			35.0 (3.0–71.0)	<0.001***
Exercise duration (min)			8.5 (1.0–15.0)			8.0 (1.4–14.3)	0.191***
Maximal METs			8.1±1.14			7.7±0.82	0.005*
Maximal predicted HR (bpm)			89.8±10.24			90.8±11.56	0.506*
Maximal BP (mm Hg)			184.5 (110–254)			195.0 (114–244)	0.005***
HR reserve (beats)			63.9±17.26			60.9±19.35	0.240*
BP reserve (mm Hg)			46.0 (41.0–210.0)			53.5 (9.0–109.0)	0.062***
Chronotopic index			0.7 (0.3–5.3)			0.6 (0.1–1.2)	0.002***
Resting HR (bpm)			85.6±13.65			84.3±13.91	0.471*
Resting BP (mm Hg)			135.8±23.34			140.8±18.92	0.188*
HR recovery (beats)			17.0 (0–60.0)			14.0 (0–35.0)	0.015***
Maximal ST deviation (mm)			2.0 (1.0–4.0)			2.0 (1.0–4.0)	0.011***
Duke Treadmill Score			-1.8±4.17			-2.46±4.44	0.364*
BP recovery			0.9 (0.6–1.7)			1.0 (0.7–2.1)	0.091***
ST/HR index (µV/bpm)			2.4 (0.3–8.5)			3.1 (0.5–15.4)	<0.001***
ST/BP index (µV/mm Hg)			0.04 (0–0.2)			0.03 (0–0.3)	0.786***

*Indicates p values compared using an independent samples t-test.
**Indicates p values compared using chi square test (expected frequencies in 2x2 contingency tables >25).
***Indicates p values compared using the Mann-Whitney U-test.
Bpm: Beats per minute; METs: Metabolic equivalents; HR: Heart rate; BP: Blood pressure; PTP: Pretest probability; Min: Minimum; Max: Maximum.

Table 2. Comparison of exercise variables between the true positive and false positive groups stratified by gender

	Gender	False positive n=128 (68 male, 60 female)	True positive n=79 (63 male, 16 female)	*p*
Age (years)	Male	55.5±8.8	62.1±6.8	<0.001
	Female	55.0±7.6	58.0±6.2	0.081
Hypertension, n (%)	Male	32/68 (47)	43/63 (68.2)	0.014*
	Female	32/60 (53.3)	9/16 (56.2)	1**
Diabetes mellitus, n (%)	Male	29/68 (42.6)	40/63 (63.5)	0.017*
	Female	36/60 (60)	12/16 (75)	0.416**
Hyperlipidemia, n (%)	Male	40/68 (58.8)	46/63 (73)	0.127**
	Female	35/60 (58.3)	15/16 (93.7)	0.018**
Current smoking, n (%)	Male	19/68 (27.9)	25/63 (39.7)	0.216**
	Female	17/60 (28.3)	3/16 (18.8)	0.537***
Family history, n (%)	Male	21/68 (30.8)	18/63 (28.6)	0.922**
	Female	19/60 (31.7)	4/16 (25)	0.763***
Body mass index (kg/m^2)	Male	28.6 (21.3–38.2)	27.8 (21.5–45.3)	0.203
	Female	29.3 (18.6–45.6)	28.9 (24–36)	0.949
Basic PTP score	Male	18.5 (8–46)	27 (8–47)	<0.001
	Female	6 (2–19)	8 (4–11)	0.047
Clinical PTP score	Male	22.5 (4–52)	39 (13–71)	<0.001
	Female	9.5 (2–35)	15.5 (3–23)	0.037
Exercise duration (min)	Male	10 (2.5–15)	8.4 (1.4–14.3)	0.002
	Female	6.2 (1–13.5)	6.1 (2–10)	0.411
Maximal METs	Male	8.6±0.9	7.8±0.7	<0.001
	Female	7.5±1.0	7.1±0.8	0.078
Maximal BP (mm Hg)	Male	188 (136–250)	196 (114–244)	0.084
	Female	176 (110–254)	183 (142–216)	0.537
Maximal predicted HR (bpm)	Male	91.1±8.7	92.6±11.1	0.404
	Female	88.6±12.2	84.8±11.7	0.272
HR reserve (beats)	Male	65.0±16.7	62.9±19.1	0.495
	Female	62.8±17.7	53.3±19.0	0.064
BP reserve (mmHg)	Male	52 (-41–210)	55.5 (10–109)	0.177
	Female	44 (6–112)	41 (9–83)	0.975
Chronotropic index	Male	0.63 (0.3–2.9)	0.55 (0.1–5)	0.043
	Female	0.64 (0.3–5.2)	0.52 (0.2–1.2)	0.025
HR recovery (beats)	Male	18 (0–45)	14 (0–35)	0.080
	Female	16.5 (0–60)	12 (2–31)	0.079
Maximal ST deviation (mm)	Male	2 (1–4)	2 (1–4)	0.103
	Female	1.5 (1–2.5)	2 (1–2)	0.169
Duke's Treadmill Score	Male	-0.5±3.9	-1.8±4.3	0.066
	Female	-3.2±3.9	-4.3±4.5	0.358
BP recovery (mm Hg)	Male	0.9 (0.6–1.7)	0.95 (0.7–2.1)	0.683
	Female	0.89 (0.7–1.2)	1 (0.7–1.5)	0.017
ST/HR index (µV/bpm)	Male	2.4 (0.3–8.5)	3.1 (0.2–15.4)	0.011
	Female	2.3 (0.3–5.4)	2.9 (1.2–4.9)	0.070
ST/BP index (µV/mm Hg)	Male	0.03 (0.02–0.2)	0.03 (0–0.3)	0.788
	Female	0.03 (0–0.2)	0.04 (0–0.2)	0.453

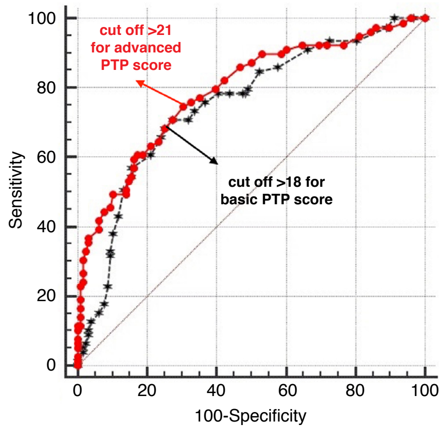
Categorical variables were compared using Pearson's chi square test, continuity correction chi square, or Fisher's exact test, as appropriate, and an independent samples t-test and the Mann-Whitney U test were used to compare continuous variables.
*Indicates p values from Pearson's chi square; **Indicates p values from continuity correction chi square; ***Indicates p values from Fisher's exact test.
Bpm: Beats per minute; MET: Metabolic equivalents; HR: Heart rate; BP: Blood pressure.

Gender has a substantial influence on the results of an exercise ECG. Therefore, the impact of this variable on the predictive value of an exercise ECG was analyzed in separate subgroups of female and male patients. To exclude unintended bias, demographic characteristics were first compared in terms of gender, which revealed that the men were older than the women (58.7±8.5 *vs*. 55.6±7.5 years;

Table 3. Sensitivity, specificity, and +/– predictive values for given cutoff values in the basic and advanced clinical pretest probability scores

	Sensitivity	95% CI	Specificity	95% CI	+ Predictive value	– Predictive value
Basic pretest probability score						
>15	75.95	65.0–84.9	63.28	54.3–71.6	56.1	81.0
>16	73.42	62.3–82.7	66.41	57.5–74.5	57.4	80.2
>17	70.89	59.6–80.6	67.97	59.1–75.9	57.7	79.1
>18	70.89	59.6–80.6	72.66	64.1–80.2	61.5	80.2
>19	68.35	56.9–78.4	75.00	66.6–82.2	62.8	79.3
>20	65.82	54.3–76.1	75.78	67.4–82.9	62.7	78.2
>21	60.76	49.1–71.6	78.91	70.8–85.6	64.0	76.5
>22	56.96	45.3–68.1	84.37	76.9–90.2	69.2	76.1
>23	54.43	42.8–65.7	84.37	76.9–90.2	68.3	75.0
>25	50.63	39.1–62.1	86.72	79.6–92.1	70.2	74.0
Advanced clinical pretest probability score						
>18	79.75	69.2–88.0	60.16	51.1–68.7	55.4	82.8
>19	77.22	66.4–85.9	64.84	55.9–73.1	57.5	82.2
>20	75.95	65.0–84.9	67.19	58.3–75.2	58.8	81.9
>21	74.68	63.6–83.8	69.53	60.8–77.4	60.2	81.7
>22	70.89	59.6–80.6	72.66	64.1–80.2	61.5	80.2
>23	68.35	56.9–78.4	75.00	66.6–82.2	62.8	79.3
>24	64.56	53.0–75.0	76.56	68.3–83.6	63.0	77.8
>25	63.29	51.7–73.9	78.91	70.8–85.6	64.9	77.7
>27	60.76	49.1–71.6	81.25	73.4–87.6	66.7	77.0
>28	60.76	49.1–71.6	82.81	75.1–88.9	68.6	77.4
>29	59.49	47.9–70.4	83.59	760.–89.5	69.1	77.0
>30	56.96	45.3–68.1	83.59	76.0–89.5	68.2	75.9
>31	54.43	42.8–65.7	84.37	76.9–90.2	68.3	75.0
>32	53.16	41.6–64.5	85.16	77.8–90.8	68.9	74.7
>33	50.63	39.1–62.1	85.94	78.7–91.4	69.0	73.8
>34	49.37	37.9–60.9	85.94	78.7–91.4	68.4	73.3
>35	49.37	37.9–60.9	89.84	83.3–94.5	75.0	74.2
>36	45.57	34.3–57.2	90.62	84.2–95.1	75.0	73.0
>37	44.30	33.1–55.9	92.19	86.1–96.2	77.8	72.8
>38	41.77	30.8–53.4	93.75	88.1–97.3	80.5	72.3
>39	39.24	28.4–50.9	93.75	88.1–97.3	79.5	71.4
>40	36.71	26.1–48.3	96.87	92.2–99.1	87.9	71.3

CI: Confidence interval.



	Basic PTP Score	Advanced PTP Score
AUC	0.75	0.79
p value	<0.001	<0.001
95% CI	0.686–0.808	0.728–0.843
Optimal cut-off points	>18	>21
Sensitivity, % (95% CI)	71 (59.6–80.6)	75 (63.6–83.8)
Specificity, % (95% CI)	73 (64.1–80.2)	70 (60.8–77.4)

Figure 1. Comparison of the basic and advanced clinical pretest probability scores.

p=0.015), but the groups were otherwise similar in terms of the prevalence of hypertension, DM, hyperlipidemia, current smoking, and family history. Next, the association of exercise variables between the TP and the FP groups was compared stratified by gender (Table 2). Of cardiovascular risk factors, older age and the presence of hypertension and DM were associated with TP test results only in men, while hyperlipidemia was associated with TP test results only in women. Men who could exercise for a shorter du-

Table 4. **Multiple logistic regression analysis for predictors of true positive test results**

Variables	Odds ratio	95% Confidence Interval	*p*
First step			
Age	0.901	0.345–2.357	0.832
Female gender	6.192	0.016–2327.189	0.547
Hypertension	1.345	0.581–3.113	0.479
Diabetes mellitus	1.403	0.466–4.226	0.547
Hyperlipidemia	0.645	0.257–1.616	0.350
Body mass index	0.953	0.873–1.042	0.291
Basic pretest probability score	0.936	0.758–1.156	0.538
Clinical pretest probability score	1.110	1.026–1.201	0.009
Exercise duration	0.890	0.749–1.059	0.189
Maximal metabolic equivalents	0.274	0.000–272.428	0.713
Maximal blood pressure	0.999	0.977–1.022	0.924
Heart rate reserve	0.993	0.963–1.024	0.672
Blood pressure reserve	1.005	0.988–1.023	0.548
Chronotropic index	1.749	0.790–3.874	0.168
Resting blood pressure			
Heart rate recovery	0.980	0.935–1.027	0.398
Maximal ST deviation	1.884	0.827–4.294	0.132
Blood pressure recovery	1.891	0.242–14.754	0.543
ST to heart rate	1.016	0.698–1.478	0.935
Last step			
Clinical pretest probability score	1.086	1.059–1.114	<0.001

ration and fewer METs, and who had a greater ST deviation when indexed to HR (higher ST/HR ratio), had more TP exercise ECG results. In women, the BP recovery ratio tended to be higher (i.e., BP recovery was slower), than in men who had TP test results. The parameters that were associated with a TP exercise ECG in both males and females were basic and clinical probability scores for CAD as determined by the CAD Consortium formulae and a lower chronotropic index.

Between the 2 scores used to estimate PTP, the advanced clinical score could discriminate obstructive CAD better than the basic score (AUC: 0.750, 95% confidence interval [CI]=0.686–0.808; $p<0.001$ for the basic model and AUC: 0.790, 95% CI=0.728–0.843; $p<0.001$ for the advanced clinical model) (Fig. 1). Table 3 illustrates the sensitivity and specificity of different cutoff values of PTP scores indicating that a basic score of >18 had a 71% sensitivity and 73% specificity to determine a TP test result, while an advanced clinical score of >21 had a 75% sensitivity and 70% specificity to determine a TP test result. Logistic regression analysis also revealed that the advanced clinical PTP was the only variable to independently predict a TP test result (OR: 1.086; 95% CI 1.059–1.114; $p<0.001$) (Table 4).

DISCUSSION

This study, in which all subjects had a PTP score <85%, has several implications for clinical practice: (1) It provides insights into the role of an exercise ECG in patients with atypical angina and a low to intermediate risk profile, especially in women; (2) it reveals that the clinical PTP model constructed by the CAD Consortium performs better in discriminating CAD than basic model; (3) it provides discriminatory cutoff values of 18 and 21 for the basic and clinical CAD scores, respectively; (4) it allows us to demonstrate and compare the predictive role of variables associated with HR and BP in conjunction with ST segment deviation.

An exercise ECG provides invaluable data for both the diagnosis of CAD and the prognosis of patients evaluated for chest pain. Its major drawback is decreased diagnostic accuracy in patients with a lower cardiovascular risk burden and in women. Consequently, the current guidelines recommend an individualized approach to patients with chest pain and emphasize the role of considering PTP before proceeding to diagnostic testing.[5,16] The CAD Consortium's basic score is used as surrogate model of estimating PTP in the 2012 European Society of Cardiology Guidelines for the management of stable angina pectoris and further diagnostic testing is recommended for those in the intermediate risk category (15–85%).[5] Previous guidelines of the American College of Cardiology had supported the same approach, but proposed a different PTP model and different cutoff numbers for intermediate risk patients.[16] In our study, all of the patients had a PTP score below 85%.

The prevalence of obstructive CAD, and thus the positive predictive value of the exercise ECG in our study population with atypical angina pectoris was 38.4%. In this study, the inclusion of mostly intermediate risk patients with a lower cardiovascular risk profile and atypical angina pectoris explains the low rate of obstructive CAD. In the CONFIRM study (Clinical Outcomes: An International Multicenter Registry), which examined suspected CAD and coronary stenosis using coronary computed tomographic angiography (CTA), researchers reported a prevalence as low as 23% in men and 13% in women with atypical angina pectoris.[17] Interestingly, the prevalence of CAD in patients with nonanginal chest pain or patients without symptoms was greater than expected in this study, blurring a clear distinction between the low and intermediate risk groups.[17]

Evidence from the Partners Registry suggests that the advanced clinical CAD Consortium score, in which clinical risk factors like hypertension, DM, hyperlipidemia, and smoking status are added to the basic model, is more accurate to predict CTA-proven significant CAD.[18] With invasive CAG, the gold standard method of CAD evaluation, we have also shown that the advanced clinical PTP score is better than the basic score in predicting CAD. Moreover, we have demonstrated that the advanced clinical PTP score was the only parameter significantly associated with a TP test (CAD) in multivariate logistic regression analysis in both men and women.

Identifying CAD in women with chest pain is a challenge.[19] Although the prevalence of CAD is lower in women than in men, the CAD mortality is higher in women.[20] It is interesting that in our study population there was a weaker association between cardiovascular risk factors with the prevalence of CAD and predicting outcomes in women. The mean age of the women in our study was 55.6±7.5 years, which represents the peri-menopausal period. The prevalence of CAD rises steeply with age after menopause and the inclusion of younger women may have diluted this effect. Nevertheless, advanced clinical CAD score could still detect CAD in women.

In this study, we also evaluated and compared the effect of hemodynamic responses in the predictive value of an exercise ECG. An abnormal HR response to exercise was expressed as chronotropic index, HR reserve, and HR recovery, all of which have previously been shown by individual studies to be associated with TP results. We demonstrated that chronotropic index, a measure of chronotropic incompetence, was associated with TP results, irrespective of gender. An appropriate decrease in HR after the cessation of exercise is related to parasympathetic tone and is known to be associated with decreased mortality.[21] Similarly, an attenuated HR response is associated with CAD.[22] An abnormal BP response was expressed as maximal BP, BP reserve, and BP recovery ratio. The maximal BP was significantly higher in patients with CAD and the BP recovery was impaired. Of electrocardiographic changes, an ST segment deviation was more pronounced and the index of ST deviation to HR was significantly higher in the TP group. The superior diagnostic capability of the ST segment/HR index has previously been established.[23] The subgroup analysis of these parameters in male and female patients revealed that, among these variables, only the chronotropic index was consistently associated with a TP test in both genders.

The main limitation of this study is its retrospective design, the small number of study participants, and the involvement of women who were younger than the men. Gender is an important cardiovascular risk factor; however, different cutoff values for each gender were not set since gender consideration is included in the calculation of PTP score.

Conclusion

During the evaluation of angina pectoris, one has to consider the balance between effective utilization of resources and accuracy in diagnosis. Our study has demonstrated that, among the various electrocardiographic and hemodynamic parameters, the clinical PTP score of the CAD Consortium and the chronotropic index are the most helpful tools in discriminating patients with CAD from FP exercise ECG results, even in patients with atypical angina pectoris. This may assist in clinical decision-making.

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