ORIGINAL ARTICLE

The Analysis of the Corrected QT-Interval Increases Exercise Stress Test Capability to Detect Significant Coronary Artery Disease

El análisis del intervalo QT corregido incrementa la capacidad de la ergometría para diagnosticar enfermedad arterial coronaria significativa

NORMA CRUDO[MTSAC], JUAN GAGLIARDI[MTSAC], JOSÉ L. CASTELLANO[MTSAC], ALFREDO PIOMBO[MTSAC], MIGUEL A. RICCITELLI[MTSAC]

ABSTRACT

Background: The clinical usefulness of exercise stress testing to indicate the presence and functional severity of coronary artery stenoses is limited by the relatively low sensitivity and specificity of ST-segment depression. Therefore, the modifications of other electrocardiographic variables during exercise, which may provide additional and complementary information to ST-segment depression, should be investigated. It has been demonstrated that the corrected QT interval (QTc) prolongation is the earliest event during the first stage of transmural ischemia.
Objectives: The aim of this study was to investigate whether modifications of the QTc interval induced by maximal exercise ($QTc_{máx}$) together with ST-segment depression ≥ 1 mm can increase the capability of the stress test to detect significant coronary artery disease and if other signs may also provide useful information to identify these patients.
Methods: One hundred and sixty six patients with ST-segment depression ≥ 1 mm during exercise or during the recovery stage of a stress test underwent coronary angiography. They were divided into two groups: Goup I (GI): 118 patients with $QTc_{máx}$ interval prolongation and Group II (GII): 48 patients with normal $QTc_{máx}$ shortening. Clinical, stress test-related and electrocardiographic parameters and coronary angiography were analyzed to identify the presence of significant coronary artery disease.
Results: Significant coronary artery disease was detected in 102 of the 166 patients included in the study (61.4%), all from GI. Group I showed high prevalence of patients with significant coronary artery disease (86.4% vs. 0%; $p < 0.001$), low ischemic threshold, late recovery of ST-segment depression, wider $QRS_{máx}$ complex, chronotropic incompetence and low exercise capacity. During graded exercise stress testing, GII patients presented greater prevalence of severe hypertension and ST-segment depression < 1 mm two minutes after exercise. Increased $QTc_{máx}$ interval resulted as an independent predictor of coronary artery disease ($p < 0.001$).
Conclusions: $QTc_{máx}$ prolongation plus ST-segment depression ≥ 1 mm produced a considerable increase in the capability of exercise stress testing to detect significant coronary artery disease, which was absent in all the patients with ST-segment depression and normal $QTc_{máx}$ shortening.

Key words: Exercise Stress Test - QTc Interval - ST-segment Depression.

RESUMEN

Introducción: La utilidad clínica de la capacidad de la ergometría para indicar la presencia y gravedad funcional de las obstrucciones coronarias se ve limitada por las relativamente bajas sensibilidad y especificidad del infradesnivel del segmento ST (infra-ST), lo cual hace necesaria la investigación de las modificaciones de otras variables electrocardiográficas durante el esfuerzo que puedan aportar información adicional y complementaria a la del infra-ST. Se ha demostrado que el evento más temprano en la primera fase de la lesión transmural es la prolongación del intervalo QT corregido (QTc).
Objetivos: Investigar si las modificaciones del intervalo QTc inducidas por el esfuerzo máximo ($QTc_{máx}$) sumadas al infra-ST ≥ 1 mm permiten incrementar la capacidad de la ergometría para diagnosticar la presencia de enfermedad arterial coronaria significativa y si otros signos pueden aportar también información útil para identificar a estos pacientes.
Material y métodos: Ciento sesenta y seis pacientes con infra-ST ≥ 1 mm durante la fase de ejercicio y/o recuperación de una ergometría a los que posteriormente se les realizó una coronariografía se distribuyeron en dos grupos: Grupo I (GI): 118 pacientes que mostraron prolongación del intervalo $QTc_{máx}$ y Grupo II (GII): 48 pacientes que acortaron normalmente el $QTc_{máx}$. Se analizaron parámetros clínicos, ergométricos y electrocardiográficos y la angiografía coronaria para comprobar la presencia de enfermedad arterial coronaria significativa.
Resultados: En 102 de los 166 pacientes incluidos (61,4%) se diagnosticó enfermedad arterial coronaria significativa, todos ellos pertenecientes al GI. El GI mostró alta prevalencia de pacientes con enfermedad arterial coronaria significativa (86,4%

REV ARGENT CARDIOL 2014;82:487-493. http://dx.doi.org/10.7775/rac.v82.i6.4298

Received: 04/06/2014 *Accepted:* 09/26/2014

Address for reprints: Dra. Norma Crudo - Av.. Alte. Brown 240 - 2° piso - (C1155ADP) Buenos Aires, Argentina - Tel.-Fax: 011 4121-0873 - e-mail: normacrudogianni@yahoo.com.ar

[MTSAC] Hospital General de Agudos "Dr. Cosme Argerich" - Department of Cardiology. Buenos Aires, Argentina
[MTSAC] Full Member of the Argentine Society of Cardiology

vs. 0%; p < 0,001), bajo umbral isquémico, recuperación tardía del infra-ST, mayor ensanchamiento del complejo $QRS_{máx}$, incompetencia cronotrópica y baja tolerancia al ejercicio. Durante la prueba ergométrica graduada los pacientes del GII presentaron mayor prevalencia de hipertensión arterial grave y el infra-ST < 1 mm en el segundo minuto del posesfuerzo. El incremento del intervalo $QTc_{máx}$ resultó un predictor independiente de enfermedad coronaria (p < 0,001).

Conclusiones: La prolongación del intervalo QTcmáx sumado al infra-ST ≥ 1 mm incrementó notoriamente la capacidad de la prueba ergométrica graduada para diagnosticar la presencia de enfermedad arterial coronaria significativa, patología que estuvo ausente en todos los pacientes con infra-ST que acortaron normalmente el $QTc_{máx}$.

Palabras clave: Prueba ergométrica graduada - Intervalo QTc - Infradesnivel del ST.

Abbreviations

CAD	Coronary artery disease	**EST**	Exercise stress test
HR	Heart rate	**QTc**	Corrected QT-interval
PMHR	Predicted maximal heart rate	**QTc_{max}**	QTc interval induced by maximal exercise
HT	Hypertension	**BP**	Blood pressure
ST-dep	ST-segment depression		

INTRODUCTION

The ST-segment depression (ST-dep) observed in stress testing, either during exercise or in the immediate recovery period, is considered an electrocardiographic sign of subendocardial ischemia and a predictor of acute coronary events. It has also been shown that the magnitude, the extent in the number of electrocardiographic leads involve d and the ST-dep appearing early during exercise stress test (EST), provide valuable information which can improve the efficiency of risk stratification and the management of patients with coronary artery disease. (1-4)

However, the clinical usefulness of exercise stress testing to indicate the presence and functional severity of coronary artery stenosis is limited by the relatively low sensitivity and specificity of ST-dep. Therefore, the modifications of other electrocardiographic variables during exercise, which may provide additional and complementary information to ST-dep, should be investigated. (5-7)

Previous studies have demonstrated that prolongation of the corrected QT interval (QTc) is the earliest event following the occlusion of an epicardial coronary artery in all patients, occurring before electrocardiographic ST-segment and T-wave changes, ischemia-related left ventricular functional changes and the presence of clinical symptoms as angina or dyspnea. (8, 9)

Considering these observations, the aim of the present study was:

a) To investigate whether modifications of the QTc interval induced by maximal exercise (QTc_{max}) together with ST-dep ≥ 1 mm can increase the capability of EST to detect significant CAD and thus reduce the number of test-related false positive results.

b) To determine if other electrocardiographic and clinical signs observed during peak exercise or immediate exercise recovery may also provide useful information to identify patients with significant coronary artery stenosis and high ischemic risk.

METHODS

This observational and retrospective study enrolled 166 consecutive patients with the following inclusion criteria: a) ST-dep ≥ 1 mm at 80 ms after the J point in two or more consecutive leads during active exercise or in the recovery stage of an EST (10), and, b) a coronary angiography performed within 6 months after EST.

Patients were divided into two groups based on the modifications of QTc interval duration during EST:

Group I (GI): 118 patients (71.7%) with QTc interval prolongation induced by maximal exercise (QTc_{max}).

Group II (GII): 48 patients (28.3%) with normal QTc_{max} shortening during active exercise.

Patients with history of myocardial infarction within one month before the study, QRS ≥ 0.11 s, baseline QTc interval ≥ 0.44 s, valvular heart disease or cardiomyopathies, Wolf-Parkinson-White syndrome, atrial fibrillation, frequent and complex ventricular arrhythmias, those receiving medication or with conditions affecting automatism, conduction and/or ventricular repolarization, or inability to interpret or perform measurements in the electrocardiogram during EST were excluded from the study.

The main reasons to perform EST were: regular monitoring of patients with history of acute coronary events or who had previously undergone invasive procedures; evaluation of functional capacity before joining a gym or performing competitive sports; evaluation of chest pain under study and of the ischemic threshold in patients with coronary artery disease and symptoms of angina or dyspnea.

The EST was performed using a cycle ergometer connected to a computer-based system with capability of continuous monitoring and 12-lead electrocardiogram recording at a speed of 25 mm/s at the end of each stage, in addition to heart rate (HR) and blood pressure (BP) measurements. A continuous and progressive two-phase protocol was used, consisting in: the active exercise phase, with 3-minute stages with progressive loads of 150 kgm, and the recovery phase, with three stages of 1 minute followed by two stages of 3 minutes.

During EST, it was assumed that patients presented: a) hypertension (HT), when maximal BP was > 220/115 mm Hg; b) abnormal BP response, when BP did not increase in two or more successive stages; c) low ischemic threshold, when ST-dep was present with or without angina at a workload < 300 kgm/min; d) low functional capacity with exercise intolerance when maximum workload was < 300 kgm/min; and e) late recovery of ST-dep when it persisted ≥ 6 minutes in the recovery phase. (11, 12)

In each group, the presence of ST-dep < 2 mm and ST-

dep ≥ 2 mm at 80 ms after the J point, greater ST-dep at the second minute of the recovery period and ST-dep < 1 mm at the second minute of repolarization was evaluated. (1, 7, 11) The number of patients that: a) reached 85% of the predicted maximal heart rate (MHR) calculated with the Robinson formula; (13); b) did not reach 62% of the predicted MHR because of beta blocker treatment; (14) and, c) presented angina and/or ventricular arrhythmias during EST, was established in each group.

Using the computer-based system, which stores the electrocardiographic records of each EST stage, two independent observers calculated average values, expressed in milliseconds, of the following electrocardiographic parameters, during three consecutive cycles, in leads V4, V5 and V6 at baseline, at the end of the maximal workload achieved and at the second minute of the recovery period: RR interval (RR), PR interval (PR); (15) QRS-complex (QRS) duration; (16) QT interval (QT) measured from the beginning of the QRS to the end of the T-wave defined as the intersection of the tangent between the apex of the curve between the T and U waves and the downslope of the T wave; QTc calculated according to Bazzet's formula (QT/√RR); (17) the presence of QTc_{max} ≥ 458 ms and ≥ 470 ms (18, 19) and the magnitude of the ST-dep at 80 ms after the J point.

In the coronary angiography, significant coronary artery stenosis was defined as ≥ 70% for the coronary arteries and ≥ 50% for the left main coronary artery.

Statistical analysis

Categorical variables are presented as frequencies with the corresponding percentage. Continuous variables are expressed as mean ± standard deviation (SD) and median (interquartile range), as applicable.

Discrete variables were analyzed with the chi square test.

For continuous variables, the t test for two independent samples or the Kruskal-Wallis test were used, depending on their distribution. A paired t test was used to compare intragroup differences of continuous variables. Stepwise multivariate logistic regression was used to determine the independent value of QTc_{max} prolongation for the diagnosis of coronary artery disease. A p value < 0.05 was considered statistically significant.

Sensitivity, specificity, positive predictive value and negative predictive value provided by QTc prolongation at maximal exercise or at the second minute of the recovery period were evaluated for the diagnosis of significant CAD.

RESULTS

Patients were divided into two groups according to QTc_{max} at peak exercise and/or at the second minute of the recovery period: GI, which included 118 patients with QTc_{max} prolongation and GII, with 48 patients with QTc_{max} normal shortening.

Table 1 summarizes the clinical characteristics of both groups. There was no age difference between both groups. In GI, the prevalence of male gender was higher; the presence of angina or dyspnea as a reason to perform the study was significantly more common, and the prevalence of obesity was greater, but that of smoking was lower. There were no significant differences in the rest of the coronary risk factors considered.

A history of acute coronary syndrome was more common in GI and thus these patients were receiving more antiischemic drugs.

The angiography showed significant coronary artery stenosis in 61.4% of patients (n = 102). Although the prevalence of significant CAD was lower in women (14.4% vs. 72%; p = 0.002), the extent and severity of coronary artery stenosis was greater, with significant 3-vessel disease (47.1% vs. 12.9%; p = 0.001).

Table 2 shows data of the exercise stress tests and electrocardiograms in both groups. Patients in GI presented more frequently ST-dep ≥ 2 mm (p < 0.001), ischemic threshold < 300 kgm/min (p < 0.0001); late recovery of ST-dep (p < 0.001); greater ST-dep in the recovery period (p = 0.008); prolonged QRS_{max} (p = 0.01) and maximal stress test workload ≤ 300 kgm/min (p = 0.01). Also, 53 patients in GI (44.9%) presented significant QTc_{max} prolongation ≥ 458 ms and in 25 patients (21.2%) QTc_{max} was ≥ 470 ms.

Patients in GII had greater prevalence of severe HT during peak exercise associated with greater ST-dep (p < 0.0001). In this group, there was a greater proportion of patients who had normal ST or ST-dep < 1 mm in the second minute of the recovery period (p < 0.001) and of those with 1 to 9 mm ST-dep (p < 0.001).

Table 3 summarizes the distribution of significant CAD findings according to QTc response during active exercise. Coronary angiography showed significant CAD in 86.4% of GI patients while none of the patients in GII had significant coronary artery stenosis (p < 0.001). Therefore, QTc prolongation during peak exercise or at the second minute of the recovery period, associated with ST-dep ≥ 1 mm presents a sensitivity of 86.4% (95% CI 80.3-92.6), a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 75% (95% CI 64.4-85.6) for the diagnosis of significant CAD. Maximal QTc interval resulted as an independent and statistically significant predictor of CAD (p < 0.001) (Table 4).

DISCUSSION

Previous studies and meta analyses (6, 20, 21) have established that the sensitivity of ST-dep to diagnose significant CAD during the active phase or the recovery period of EST ranges between 60% and 70%, and may reach 80% in patients with 3-vessel disease or left main coronary artery stenosis, as the sensitivity of ST-dep would be directly related with the magnitude and extent of subendocardial ischemia. (22)

In our population, only 102 (61.4%) of 166 patients that presented ST-dep ≥ 1 mm during active exercise or during the recovery period of an EST had evidence of significant CAD in the coronary angiography. This result is near the lower limit of the values reported by previous studies and would be due to the fact that our catheterization laboratory protocol is more selective, as it considers that ≥70% stenosis is significant instead of ≥50% as has been reported in most of the cited studies. This relatively low percentage of pa-

	Group I (n = 118)		Group II (n = 48)		p
Age, years	56.9 ± 7.1		58.1 ± 7.2		0.32
	n	%	n	%	
Male	93	83.8	18	37.5	< 0.001
Female	25	21.2	30	62.5	
Reasons for ordering the study					
Control	56	47.4	6	12.5	< 0.001
Functional capacity	5	4.3	7	14.6	
Chest pain under study	41	34.7	31	64.6	
Angina/dyspnea	16	13.6	4	8.3	
Risk factors					
Hypertension	75	63.6	33	68.7	0.52
Diabetes	15	12.7	8	16.6	0.5
Dyslipidemia	83	70.3	29	60.4	0.21
Current smoking	61	51.6	33	68.7	0.05
Family history	34	28.8	21	43.7	0.06
Obesity	50	42.3	11	22.9	0.01
≥ 3 risk factors	61	51.6	18	37.5	0.09
Normal treatment					
Antiischemic drugs	69	58.5	16	33.3	0.003
Antiplatelet and/or anticoagulation agents	71	60.1	23	47.9	0.14
History of acute coronary syndrome	63	53.3	13	27.1	0.002
Significant coronary artery disease	102	86.4	0	0	< 0.001

Table 1. Clinical characteristics of patients according to corrected QT interval during exercise stress test

tients with significant coronary artery stenosis significantly increased (from 61.4% to 86.4%) when QTc_{max} prolongation was added to ST-dep ≥ 1 mm. This result is similar to that of a previous study, (23) which correlated the increase in the duration of the QTc interval induced by exercise with the presence of ischemic areas in exercise myocardial perfusion scintigraphy.

In addition, ST-dep ≥ 2 mm at 80 ms after the J point demonstrated higher capability to diagnose significant CAD when ST-dep recovered ≥ 6 minutes after exercise, it occurred in patients who reached a workload < 300 kgm/min (low ischemic threshold), (11, 12) it was associated with longer duration of the QRSmax (16) and when ST depression was greater during the recovery period of the EST.

On the contrary, a marked statistical difference in the absence of significant CAD was observed in patients with normal ST or ST-dep < 1 mm in the second minute of the recovery period, and in those with greater ST-dep during active exercise associated with severe BP increase. (24)

The high prevalence of low ischemic threshold, low exercise capacity and chronotropic incompetence in GI patients (11-14) is coincidental with that of previous studies which have demonstrated that these parameters are markers of extensive coronary artery disease and are independent predictors of high ischemic risk and greater mortality.

Thus, QTc_{max} prolongation plus ST-dep ≥ 1 mm improved the diagnostic capacity of EST, with a sensitivity of 86.4% and a specificity of 100%. The positive predictive value of QTc_{max} is 100%, with no false positive results, but it does not detect all the patients with CAD because its sensitivity is 86%. The negative predictive value was 75% (64% to 85.6%) due to the presence of a few false negative results.

Previous studies have demonstrated that acute myocardial ischemia prolongs the duration of the QTc interval because it increases the heterogeneity of ventricular repolarization by producing dispersion in the duration of the action potentials stimulated by the adrenergic stimulus, increased extracellular potassium and focal myocardial fiber hypopolarization. It was also demonstrated that during percutaneous coronary intervention, the QT interval presented significant prolongation immediately after balloon inflation that persisted for minutes or even hours. (25) The longer QTc_{max} duration during EST is produced by a similar mechanism. (8, 26) Based on these findings, we assume that QTc_{max} prolongation induced by exercise during EST could be considered an early indicator of transient acute myocardial ischemia, and that longer duration of the QTc_{max} would be related with more extensive and significant coronary artery steno-

Table 2. Exercise stress test and electrocardiographic results in both groups

	Group I (n = 118) ms		Group II (n = 48) ms		p
Baseline PR	166.4 ± 13.1		162.7 ± 16.3		0.12
PR max	151.9 ± 27.2		143.1 ± 21.1		0.07
Baseline QRS	82.9 ± 10.8		80.3 ± 10.4		0.16
QRS max	87.1 ± 12.3		78.4 ± 13.6		< 0.001
Baseline QTc	408.5 ± 19.0		430.4 ± 11.7		< 0.001
QTc max	451.9 ± 18.8		405.8 ± 15.0		< 0.001
	n	%	n	%	
ST-dep 1 to 9 mm	50	42.3	37	77.1	< 0.001
ST-dep ≥ 2 mm	68	57.7	11	22.9	< 0.001
Greater ST-dep in recovery period	32	27.1	4	8.3	0.008
Reached ≥ 85% predicted MHR	41	34.7	28	58.3	0.005
Reached ≤ 62% predicted MHR	19	16.1	2	4.1	0.03
Maximum workload ≤ 300 kgm/min	18	15.2	1	2.1	0.01
Ischemic threshold < 300 kgm/min	26	22.03	0	0	< 0.001
HT	51	43.2	38	79.2	< 0.001
PR max / baseline PR > 1	39	33.1	9	18.7	0.06
↑ QRS	68	57.7	18	37.5	0.01
ST-dep < 1 mm at 2nd minute of recovery period	20	16.9	36	72.9	< 0.001
Abnormal BP response	4	3.4	1	2.1	0.66
Late recovery of ST-dep	27	22.8	0	0	< 0.001
QTc max ≥ 458 ms	53	44.9	0	0	< 0.001
QTc max ≥ 470 ms	25	21.2	0	0	0.001
Angina and/or dyspnea	37	31.3	17	35.4	0.61
Ventricular arrhythmia	29	24.5	9	18.7	0.42

QTc: Corrected QT-interval. ST-dep: ST-segment depression. MHR: Maximal heart rate. HT: Hypertension. BP: Blood pressure

Table 3. Distribution of significant coronary artery disease according to corrected QT response during exercise stress test associated with ST-segment depression ≥ 1 mm

	ST-dep ≥ 1 mm + ↑ QTc (n = 118)	ST-dep ≥ 1 mm + ↓ QTc (n = 48)
Significant CAD 102 (61.4%)	102 (86.4%)	0 (0%)
Non-significant CAD 64 (38.6%)	16 (13.6%)	48 (100%)

QTc: Corrected QT-interval. ST-dep: ST-segment depression. CAD: Coronary artery disease

sis. This would explain why a longer QTc_{max} ≥458 ms, and particularly ≥470 ms demonstrated to be an independent predictor of high ischemic and arrhythmogenic risk. (18, 19)

In the 16 patients with prolonged QTc_{max} during EST associated with ST-dep but with no angiographic evidence of significant CAD, we consider that the pathophysiological mechanism could be attributed to the endothelial dysfunction related with the X syndrome (27) that affects myocardial microcirculation and produces different degrees of myocardial ischemic involvement. This ischemia delays ventricular repolarization and alters its regional homogeneity, but is not associated with the presence of severe stenosis of the coronary arteries.

The low number of patients and of women included is a limitation of the study; yet, the differences between the groups are very clear. Due to the retrospective nature of this study these findings should be confirmed by larger prospective investigations.

CONCLUSIONS

QTc_{max} prolongation plus ST-dep ≥ 1-mm produced a significant increase in the capability of EST to detect significant coronary artery disease. ST-segment depression ≥1 mm, regardless of its magnitude, that is associated with normal QTc_{max} shortening, would not be related with the presence of significant CAD.

ST-dep ≥ 1 mm at maximal workload coincidental with severe increase in BP (severe HT) and rapid ST-dep normalization at the second minute of the recovery

Table 4. Exercise stress test predictors of coronary artery disease. Univariate and multivariate analyses

A. Univariate analysis

	Coronary artery disease (n = 102)		Without coronary stenosis (n = 64)				
	n	%	n	%	p	OR	95% CI
ST-dep (1 to 9 mm)	50	49.0	48	75.0	**0.001**	0.32	0.15-0.67
ST-dep ≥ 2 mm	68	66.7	16	25.0	**< 0.0001**	4.64	2.23-9.73
Greater ST-dep in recovery period	32	31.4	7	10.9	**0.004**	3.72	1.43-
Reached ≥ 85% predicted MHR	41	40.2	37	57.8	**0.04**	0.49	10.04
Reached ≤ 62% predicted MHR≤	19	18.6	5	7.8	0.08	2.70	0.25-0.97
Maximum workload ≤ 300 kgm/min	18	17.6	2	3.1	**0.01**	6.64	0.88-8.80
HT	52	51.0	39	60.9	0.27	0.67	1.40-43.0
PR max / baseline PR > 1	39	38.2	15	23.4	0.15	1.75	0.34-1.32
↑ QRS	68	66.7	28	43.8	**0.005**	2.57	0.83-3.72
ST-dep < 1 mm at 2nd minute of recovery period	20	19.6	47	73.4	**< 0.0001**	0.09	1.29-5.16 0.04-0.20
Angina or dyspnea	37	36.3	23	35.9	0.9	1.01	0.50-2.05
Ventricular arrhythmia	29	28.4	14	21.9	0.4	1.46	0.66-3.24

B. Multivariate analysis

	OR	95% CI	95% CI
ST > 2 mm	2.48	2.16 a 3.8	0.001
QTc prolongation	2.27	1.16 a 3.37	< 0.001

QTc: Corrected QT-interval ST-dep: ST-segment depression MHR: Maximal heart rate HT: Hypertension.

period was highly prevalent in patients without significant coronary artery stenosis.

Conflicts of interest

None declared.
(See authors' conflicts of interest forms in the web / Supplementary Material).

REFERENCES

1. Prakash M, Myers J, Froelicher VF, Marcus R, Do D, Kalisetti D, et al. Clinical and exercise test predictors of all-cause mortality: results from > 6,000 consecutive referred male patients. Chest 2001;120:1003-13. http://doi.org/ddtz9k

2. Morrow K, Morris CK, Froelicher VF, Hideg A, Hunter D, Johnson E, et al. Prediction of cardiovascular death in men undergoing noninvasive evaluation for coronary artery disease. Ann Intern Med 1993;118:689-95. http://doi.org/v3q

3. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation 2004;110:1920-5. http://doi.org/d2p647

4. Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. JAMA 2004;292:1462-8. http://doi.org/cv925s

5. Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. Ann Intern Med 1976;85:277-86. http://doi.org/v3r

6. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989;80:87-98. http://doi.org/d3xthf

7. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. Circulation 2006;114:2070-82. http://doi.org/d95hv9

8. Kenigsberg DN, Khanal S, Kowalski M, Krishnan SC. Prolongation of the QTc interval is seen uniformly during early transmural ischemia. J Am Coll Cardiol 2007;49:1299-305. http://doi.org/brfzrn

9. Lee E, Michaels AD, Selvester RH, Drew BJ. Ischemic Cascade: Sequence of ECG, acoustic cardiographic changes, and angina during coronary occlusion. Circulation 2008;118:S760-S761.

10. Rywik TM, O'Connor FC, Gittings NS, Wright JG, Khan AA, Fleg JL. Role of nondiagnostic exercise-induced ST-segment abnormalities in predicting future coronary events in asymptomatic volunteers. Circulation 2002;106:2787-92. http://doi.org/b8jg83

11. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 2001;104:1694-740. http://doi.org/dg9bt7

12. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801. http://doi.org/d2kb82

13. Elhendy A, Mahoney DW, Khandheria BK, Burger K, Pellikka PA. Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia. J Am Coll Cardiol 2003;42:823-30. http://doi.org/d74ptw

14. Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). Am J Cardiol 2005;96:1328-33. http://doi.org/fm84kp

15. Chan YH, Siu CW, Yiu KH, Yiu YF, Lau KK, Lam TH, et al. Prolongation of PR interval is associated with endothelial dysfunction and activation of vascular repair in high-risk cardiovascular patients. J Interv Card Electrophysiol 2013;37:55-61. http://doi.org/v3s

16. Efrati S, Cantor A, Goldfarb B, Ilia R. The predictive value of exercise QRS duration changes for post-PTCA coronary events. Ann Noninvasive Electrocardiol 2003;8:60-7. http://doi.org/cjznv9

17. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standard-

ization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:982-91. http://doi.org/c7vp73

18. Jimenez-Candil J, Diego M, Cruz González I, González Matas JM, Martin F, Pabon P, et al. Relationship between the QTc interval at hospital admission and the severity of the underlying ischaemia in low and intermediate risk people studied for acute chest pain. Int J Cardiol 2008;126:84-91. http://doi.org/ch9tf6

19. Gadaleta FL, Llois SC, Lapuente AR, Batchvarov VN, Kaski JC. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. Am J Cardiol 2003;92:203-5. http://doi.org/bg98qj

20. Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis 1989;32:173-206. http://doi.org/bg6zmc

21. Detrano R, Gianrossi R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al. Exercise-induced ST segment depression in the diagnosis of multivessel coronary disease: a meta-analysis. J Am Coll Cardiol 1989;14:1501-8. http://doi.org/dtfpdv

22. Tavel ME, Shaar C. Relation between the electrocardiographic stress test and degree and location of myocardial ischemia. Am J Cardiol 1999;84:119-24. http://doi.org/cbvvsq

23. Arab D, Valeti V, Schunemann HJ, Lopez-Candales A. Usefulness of the QTc interval in predicting myocardial ischemia in patients undergoing exercise stress testing. Am J Cardiol 2000;85:764-6. http://doi.org/czwhcp

24. Lauer MS, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD. Angiographic and prognostic implications of an exaggerated exercise systolic blood pressure response and rest systolic blood pressure in adults undergoing evaluation for suspected coronary artery disease. J Am Coll Cardiol 1995;26:1630-6. http://doi.org/bgnq58

25. Nowinski K, Jensen S, Lundahl G, Bergfeldt L. Changes in ventricular repolarization during percutaneous transluminal coronary angioplasty in humans assessed by QT interval, QT dispersion and T vector loop morphology. J Intern Med 2000;248:126-36. http://doi.org/ff7dhc

26. Dresing TJ, Blackstone EH, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. Am J Cardiol 2000;86:602-9. http://doi.org/c9b7z3

27. Mammana C, Salomone OA, Kautzner J, Schwartzman RA, Kaski JC. Heart rate-independent prolongation of QTc interval in women with syndrome X. Clin Cardiol 1997;20:357-60. http://doi.org/bfsxdx