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***Prognostic value of SPECT myocardial perfusion imaging and
exercise test***

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Abstract

Introduction: Although emphasis has been placed on the diagnostic value of traditional parameters, like ST-depression, the exercise electrocardiogram stress testing (ExECG) provides other valuable diagnostic and prognostic variables that are not considered in the standard report of this test. Our purpose was to evaluate the long-term prognostic value of exercise test over clinical assessment and myocardial perfusion imaging (MPI) result in patients referred to MPI.

Methods: This was a retrospective study that included 352 patients with suspected or known coronary heart disease (CHD) who, between January 1st and December 31st of 2002, underwent ExECG during the performance of MPI through gated-single photon emission computed tomography (SPECT). All patients underwent exercise treadmill test using standard Bruce Protocol. Rest heart rate (HR), maximal HR during exercise, rest and stress systolic and diastolic blood pressure (BP), the amplitude of the ST depression, the occurrence of angina and exercise duration were recorded throughout the test. An abnormal MPI test was considered in the presence of perfusion abnormalities in stress and/or rest images and/or a left ventricular ejection fraction (LVEF) under 50%. During follow-up, cardiac death and nonfatal myocardial infarction were defined as major cardiac events.

Results: The mean follow-up time was $125 \pm 85,6$ months. During this period, there were 58 events, including 17 cardiac deaths and 41 nonfatal myocardial infarctions. Using Cox survival analysis, diabetes (HR = 2,5; CI = 1,3 – 4,7; p = 0,003), previous history of CHD (HR = 3,4; CI = 1,9 – 6,1; p = <0,0001), male gender (HR = 4,6; CI = 1,97 – 10,74 ; p = 0,0004), difference HR (HR = 1; CI = 1-1 ; p = 0,01) and systolic BP (HR = 0,9; CI = 0,9 - 1; p = 0,025) were related with cardiac events. In a multivariate analysis, the clinical model was predictive of cardiac events ($X^2 = 34,6$; p = <0,0001) and its prognostic power increased when

the difference of heart rate and systolic blood pressure at rest and exercise were forced into the model ($X^2 = 45,8$; $p = <0,0001$). The inclusion of the information related with MPI did not increase significantly the predictive power of the model ($X^2 = 48,7$; $p = <0,0001$).

Conclusion: In our study population, exercise MPI failed to add incremental significant risk-stratification beyond ExECG variables in a long-term follow-up period. Difference of heart rate and systolic blood pressure at rest and exercise seem to neutralize the impact of MPI results on cardiac events.

Keywords: Exercise Test, Myocardial Perfusion Imaging, Prognosis, Coronary Disease

Glossary

BP – Blood Pressure

CHD – Coronary Heart Disease

CI – Chronotropic Incompetence

CVD – Cardiovascular Disease

DP – Double Product

DTS – Duke Treadmill Score

ECG – Electrocardiography

ESC – European Society of Cardiology

ExECG – Exercise Electrocardiogram Stress Testing

HR – Heart Rate

HUC – Hospital da Universidade de Coimbra

LVEF – Left Ventricular Ejection Fraction

MPI – Myocardial Perfusion Imaging

PTP – Pre-Test Probability

SPECT – Single-photon Emission Computed Tomography

Introduction

Cardiovascular disease (CVD) is the most common, life-threatening disease in Europe, responsible for 45% of all non-communicable disease deaths. Stroke and ischemic heart disease account for almost all deaths due to CVD¹.

In Europe and considering gender, CVD is responsible for 49% and 40% of all deaths in women and men, respectively, and coronary heart disease accounts for 20% of deaths in women and 19% in men.¹

Obesity, insulin resistance and type 2 diabetes mellitus are increasing and are powerful risk factors². These conventional risk factors for the development of coronary heart disease (CHD) are occurring in the general context of population growth and as a consequence of the increase in the average age of the world population. These factors, as well as hypertension, hypercholesterolemia, smoking and sedentary life² have an effect on the progression of the atherosclerotic heart disease.

From a pathophysiological point of view, CHD is a condition in which there is an inadequate blood supply to the myocardium. Typically, ischemia corresponds to a mismatch between oxygen supply and demand which is inducible by exercise, emotion or other stress and reproducible, but could also occur spontaneously. The most common cause of myocardial ischemia is the atherosclerotic disease of coronary arteries³. Other causes are focal or diffuse epicardial coronary spasm and microvascular dysfunction⁴.

CHD has several clinical manifestations including, acute coronary syndromes, sudden death, heart failure and in its stable form, angina. Angina is a chest discomfort, described as heaviness, pressure, choking or, rarely, a frank pain, that arises with exercise or emotions and reliefs with rest or vasodilators.

The European Society of Cardiology (ESC) guidelines on stable coronary artery disease⁵ recommend a stepwise management of these patients, namely, in what respects diagnosis and risk stratification. According with the pre-test probability (PTP) of disease, non-invasive diagnostic tests may be required and depending on their results, treatment will be decided.⁵

Two important tools in the diagnosis and prognosis of CHD are exercise electrocardiogram stress test (ExECG) and myocardial perfusion imaging (MPI) through gated-single-photon emission computed tomography (SPECT), offering the latter higher sensitivity on the identification of CHD than the former. ExECG remains a useful option due to its simplicity and widespread availability, presenting a low sensitivity and a high specificity in CHD diagnosis.(45-50% and 85-90%, respectively)⁶. Meanwhile, MPI has a sensitivity of 73-92% and a specificity between 63-87%⁷.

In the most recent guidelines, ExECG is recommended as the initial test for establishing the diagnosis of stable CHD in patients with symptoms of angina and intermediate PTP of CHD, free of anti-ischaemic drugs, unless they cannot exercise or display electrocardiographic (ECG) changes which make ECG non-evaluable (Class I, Level B). An imaging stress test is recommended as the initial test for diagnosing stable CHD if the PTP is between 66-85% or if left ventricular ejection fraction (LVEF) is less than 50% without typical angina (Class I, B). For risk stratification, MPI is preferred, if there is local expertise and availability in patients with CHD after significant change in symptom level (Class I, B).⁵

Although emphasis has been placed on the diagnostic value of traditional parameters, like ST-depression, the ExECG provides other precious diagnostic and prognostic variables that are not considered in the standard report of this test.^{8,9} Several studies have reported short-term prognostic implications of these variables¹⁰⁻¹⁵, but there is insufficient data of its long-term prognostic value.

Our aim was to evaluate the long-term prognostic value of exercise test over clinical assessment and MPI result in a group of patients referred for MPI.

Material and Methods

Type of study

This is a retrospective cohort study, where patients with suspected or known CHD underwent ExECG during the performance of MPI through gated-SPECT between January 1st and December 31st of 2002. Both tests were performed in Hospitais da Universidade de Coimbra (HUC). The total study population consisted of 352 patients, with no exclusion criteria. Nine patients were lost for follow-up, with our analysis focusing on the remaining 343 subjects.

Exercise ECG stress testing Protocol

All patients underwent exercise treadmill test using standard Bruce Protocol⁶.

Rest heart rate (HR), maximal HR during exercise, rest and stress systolic and diastolic blood pressure (BP), the amplitude of the ST depression, the occurrence of angina and exercise duration were recorded during the test.

The main diagnostic electrocardiographic abnormality during ECG exercise testing consists of a horizontal or down-sloping ST-segment depression $\geq 0.1\text{mV}$, prevailing for at least 0,06 – 0,08 seconds after J-point, in one or more ECG leads. When the patient had this finding during the ExECG, the test was considered “positive”.

When at least 85% of the maximum predicted heart rate is not achieved in the absence of signs of ischaemia or when ECG changes are equivocal¹⁶, we considered the test “non-conclusive”.

The stress testing, was considered “submaximal” when the ExECG ended with less than 85% of the patient maximal HR, independently of symptoms of ischaemia. The maximal HR was estimated using age-predicted equation of $HR_{max} = 220 - \text{age}$.

Duke treadmill score (DTS) was also estimated and patients were distributed according to the low, intermediate and high risk class levels.

The double product, HR reserve and chronotropic response to exercise were also calculated for each patient.

$$\text{DTS} = \text{Exercise Time} - (5 \times \text{Max ST}) - (4 \times \text{Angina Index})$$

- 1) Low risk: $\geq +5$
- 2) Moderate risk: +4 to -10
- 3) High risk: ≤ -11

$$HR_{reserve} = HR_{max} - HR_{rest}$$

Chronotropic incompetence (CI)¹⁷ is defined as an abnormal HR response to exercise. In our study, using the values assessed during the ExECG, we calculated this percentage and a value under 80% was considered abnormal¹⁸.

$$\text{Percent HR reserve} = (\text{peak HR} - \text{rest HR}) / (220 - \text{age} - \text{rest HR}) \times 100$$

The double product (DP), is defined as the product between systolic blood pressure and HR¹⁹. In our study, we determined the double product at rest (DPrest), during exercise (DPexercise) and the difference between these two values (DPdifference).

$$\text{Double Product} = \text{HR} \times \text{systolicBP}$$

Myocardial Perfusion Imaging and Acquisition Protocol

All patients were injected with 370 -555 MBq (according to their weight) of Tc-99m tetrofosmin during peak exercise. The images were performed using a dual-head camera (*VentriTM* gamma camera), step and shoot acquisition, with 64 stops and a 180° arc from right anterior oblique to left anterior oblique. Non-attenuation corrected and ECG-gated transverse images were reconstructed with filtered back-projection. The images were assessed by specialists that ranked the tests as “normal” or “abnormal”. An abnormal test includes perfusion abnormalities in stress and/or rest images and/or a left ventricular ejection fraction under 50%.

Follow-up

Follow-up data was obtained by reviewing patient’s records. The follow-up was completed in December 31st of 2015 or until the occurrence of a major cardiac event. Cardiac death and nonfatal myocardial infarction were considered major cardiac events.

Statistical Analysis

All data was presented as mean \pm standard deviation for continuous variables and relative frequency for categorical variables. Continuous variables were compared through Student-t test and categorical variables were compared using Pearson chi-squared test. Univariate and multivariate Cox proportional hazard models identified and assessed predictors of “Cardiac Events”.

Results

Study population

The study population consisted of 343 patients undergoing MPI with ExECG, 241 men (68,2%) and 112 women (31,8%), with a mean age of $59 \pm 10,6$ years (range 25 – 81 years) and an average follow-up period of $125 \pm 85,6$ months (range 1-167 months).

Table 1 – Population Summary

Variables	
Age	$59 \pm 10,6$ years
Male Gender	68,4% (n=241)
	43,5% (n=153)
CHD	<ul style="list-style-type: none"> • <i>males 54,3% (n=131)</i> • <i>females 14,4% (n=22)</i>
Diabetes	15,3% (n=54)
	<ul style="list-style-type: none"> • <i>males 16,2% (n=39)</i> • <i>females 13,4% (n=15)</i>
Chronic Kidney Disease	11,4% (n=40)
	<ul style="list-style-type: none"> • <i>males 12,4% (n=30)</i> • <i>females 11,2% (n=10)</i>
Positive ExECG	43,2% (n=152)
	<ul style="list-style-type: none"> • <i>males 43,9% (n=106)</i> • <i>females 41,1% (n=46)</i>
Abnormal MPI	61,1% (n=215)
	<ul style="list-style-type: none"> • <i>males 75,9% (n=183)</i> • <i>females 28,6% (n=32)</i>

A summary of demographic and clinical information of all 343 patients analyzed in this study is shown on **Table 1**. A predominance of male gender (241/112) was reported, with a mean age of $59 \pm 10,8$ (range 25 – 81 years). Fifty-four patents had diabetes (15,3%), 153 (43,5%) had known CHD and 40 patients had kidney disease (11,4%) under dialysis.

A positive ExECG was noticed in 152 patients (43.2%) and 61.1% of MPI were abnormal.

Considering DTS, 161 (45,2%) patients were considered of low-risk, 170 (48,3%) had a moderate-risk and 21 (6%) were classified as high-risk patients (**Table 3**).

In the study population, 17 cardiac deaths (4,8%), 41 nonfatal myocardial infarctions (11,6%) and 79 non-cardiac deaths (22,4%) were observed. In total, we reported 58 cardiac events (16.4%).

Differences between patients with and without cardiac events

Comparing patients with cardiac events versus those with no events, we found significant differences in gender (male), reported diabetes, and previous CHD. An abnormal MPI was seen more often in patients with events (**Table 2**)

In what refers to the ExECG, no significant differences were seen in the number of positive tests, in the amplitude of the ST depression, in the occurrence of angina and in exercise duration. Those patients with higher rest HR and diastolic BP, and those with lower differences in HR and systolic BP during exercise had more events. Lower DP variation was also related with events. High-risk patients, according to DTS, did not have a significant higher rate of events (**Table 2**).

Univariate analysis

The results of Cox univariate analysis are shown in **Table 4**. Male gender, a history of diabetes or CHD were event predictors. As expected, an abnormal MPI was also related to the occurrence of cardiac events.

As for ExECG variables, the difference between HR, systolic BP and DP at rest and exercise, were associated with events (**Table 4**).

Multivariate analysis

The variables identified in the univariate analysis were forced into multivariate models. A clinical model, a clinical and ExECG model and a clinical, ExECG and MPI model are shown in **Tables 5, 6 and 7**, respectively. Graphical comparison between models can be seen in **Figure 1**.

The clinical model (**Table 5**) was predictive of cardiac events and its prognostic power increased when ExECG variables were forced into the model (**Table 6**). The inclusion of the

information related with MPI did not increase significantly the predictive power of the model (Table 7).

Table 2 – Differences between patients with and without events

Variables	Cardiac Events (58)	No Events (285)	p
Gender (male)	52 (89,7%)	182 (63,9%)	<0,0001
Age	59,1±10,6	59,2±10,7	0,9
Diabetes	14 (24,1%)	39 (13,7%)	0,04
CHD	39(67,1%)	110(38,6%)	<0,0001
ExECG positive	29 (50%)	121(42,4%)	0,3
ExECG submaximal	21 (36,2%)	77 (27,8%)	0,2
HR rest	72,6±12,3	68,5±12,9	0,03
HR exercise	136,8±21,0	138,8±12,9	0,46
Difference HR	64,2±20,0	70,3±18,6	0,03
Systolic BP rest	155,4±23,8	152,5±22,4	0,4
Systolic BP exercise	187,3±26,0	190,8±28,3	0,4
Difference Systolic BP	31,9±20,0	38,3±20,8	0,03
Diastolic BP rest	89,5±12,3	85,7±10,9	0,03
Diastolic BP exercise	82,1±16,9	81,8±15,9	0,9
Difference Diastolic BP	-7,4±14,0	- 3,9±13,4	0,07
InfraST	0,9±1,1	0,8±1,2	0,7
Pain during ExECG	11 (17,5%)	50 (17,5%)	0,8
Exercise time (s)	439,4±159,9	451,6±143,2	0,6
MPI abnormal	50 (86,9%)	160 (56,8%)	<0,0001
HR reserve	73,5±20,7	76,7±18,1	0,3
Hear Rate reserve <80%	37 (63,8%)	158 (55,4%)	0,3
DP rest	11309±2987	10463±2478	0,07
DP max	25657±5280	26487±5222	0,3
DP Difference	14347±4503	16024±4741	0,01
DTS High risk	5 (9,3%)	14 (4,9%)	0,2

Table 3 – Duke Treadmill Score and class distribution

DTS	Cardiac Events (58)	No Events (285)	Total (343)	p
Low	24 (41,4%)	130 (45,6%)	154 (44,8%)	0,84
Moderate	29 (50%)	141 (49,5%)	170 (49,6%)	0,7
High	5 (9,3%)	14 (4,9%)	19 (4,9%)	0,2

Table 4 – Univariate Cox proportional hazard analysis for Cardiac Events

Variable	Hazard Ratio	IC	p
Gender Male	4,6	1,97-10,74	0,0004
Diabetes	2,5	1,3-4,7	0,003
CHD	3,4	1,9-6,1	<0,0001
Resting HR	1	1-1	0,44
Difference HR	1	1-1	0,01
Diastolic BP Rest	1	1-1	0,022
Difference Systolic BP	0,9	0,9-1	0,025
DP Difference	1	1-1	0,04
Abnormal MPI	4,3	2,0-9,1	<0,0001

Table 5 - Multivariate clinical model

Variable	Hazard Ratio	IC	p	X ²	p
Gender Male	3	1,97-10,74	0,006		
Diabetes	2,5	1,3-4,6	0,003	34,6	<0,0001
CHD	2,5	1,4-4,5	0,002		

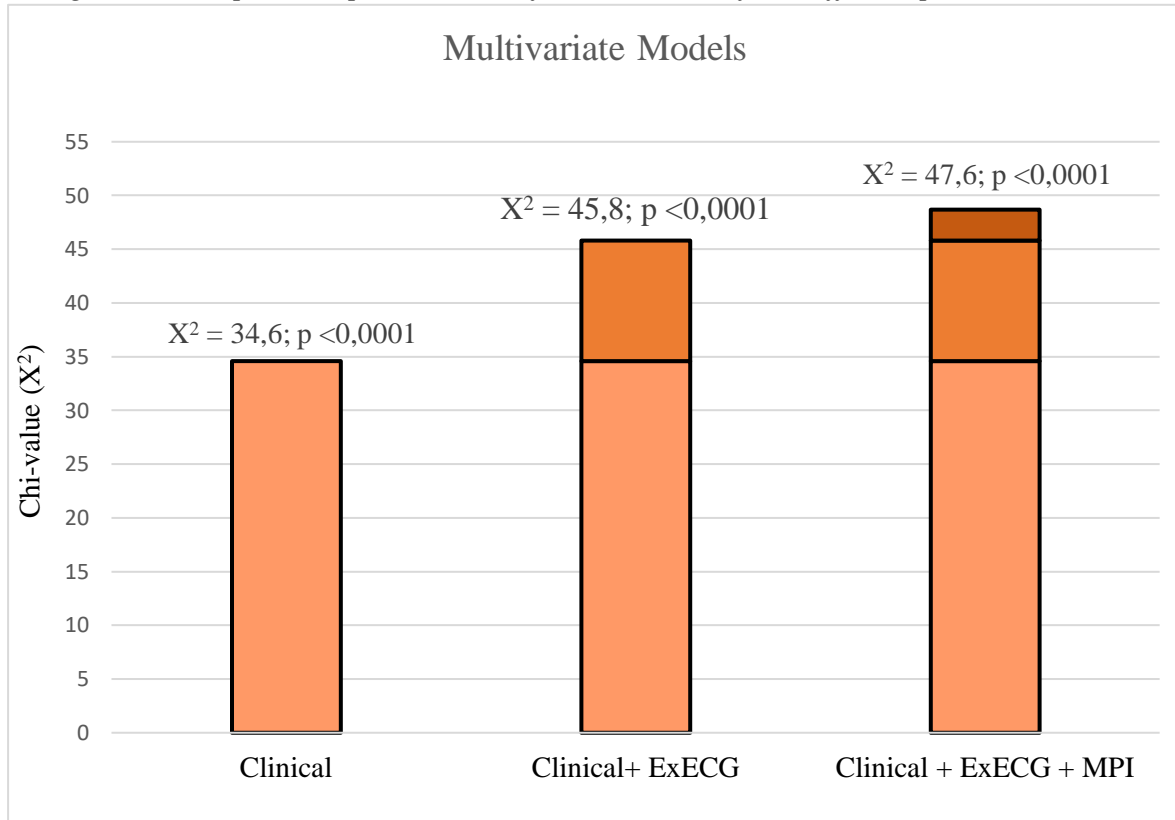
Table 6 – Multivariate clinical and exercise model

Variable	Hazard Ratio	IC	p	X ²	p
Gender Male	3	1,6-8,7	0,003		
Diabetes	2,5	1,09-3,85	0,026		
CHD	2,5	1,4-4,5	0,002	45,8	<0,0001
Difference HR	0,9	0,9-1	0,07		
Difference Systolic BP	0,9	0,9-1	0,01		

Table 7 – Multivariate, clinical, ExECG and MPI model

Variable	Hazard Ratio	IC	p	X ²	p
Gender Male	3,1	1,2-7,6	0,02		
Diabetes	2,2	1,2-4,0	0,01		
CHD	1,7	0,9-3,1	0,08		
Difference HR	0,9	0,9-1	0,06	48,7	<0,0001
Difference Systolic BP	0,9	0,9-1	0,02		
MPI abnormal	2,1	0,9-4,8	0,07		

Figure 1 – Graphical representation of the chi-value of the different predictive models



Discussion

The importance of ExECG on the diagnosis and risk stratification of CHD seems to be underestimated. In the present study, a group of patients referred for MPI were followed and clinical, ExECG and MPI variables were compared as predictors of cardiac events.

According to our results, men had more events than women and the male gender was predictor of cardiac events. This is probably related with the fact that in the studied group, previous CHD, diabetes, a positive ExECG and an abnormal MPI were more prevalent in men.

Our data suggests that diabetic patients, regardless of previous CHD, have a higher risk of nonfatal myocardial infarction and cardiac death. According to what Haffner et al.²⁰ and Juutiainen et al.²¹ reported, diabetes was a CHD clinical surrogate.

Previous published studies had shown that a subject with diabetes had abnormal heart rate responses. Banthia et al.²² showed a delayed heart rate recovery at 1 minute after exercise completion and Georgoulis et al.²³ found that diabetes is associated with abnormal heart rate recovery.

Cheng et al.²⁴ found that heart rate recovery was an independent prognostic indicator for cardiovascular death and all-cause mortality in 2333 men with documented diabetes. In a smaller sample, a recent study concluded that chronotropic incompetence in male patients with Type 2 DM was independently related to exercise tolerance and adipose tissue, providing a further insight of the etiology of CI in diabetics²⁵. Consequently, some authors are highlighting the possible impact of therapeutic interventions for partial restoration of the chronotropic response in type 2 diabetics²⁶

Arbit et al. published a study evaluating the prognostic contribution of exercise capacity, heart rate recovery and chronotropic incompetence in the prediction of cardiac death in a total of 11,218 patients without valvular disease and not on β blockers¹³. For a mean follow-up period of 3.2 ± 2.5 years, these exercise variables proved to be independent predictors of all-cause mortality and cardiac death¹³. A study published in 2014, with a mean follow-up of 719 ± 252 days, also concluded %HR Reserve to be an important predictor of cardiac death²⁷. In the FIT project, higher resting heart was also associated with increased mortality risk. On the contrary, higher peak heart rate was associated with decreased risk. In a recently published meta-analysis, involving 848320 patients and 25800 CV deaths, Dongfeng et al. supports this evidence, reporting a relative risk with 10 beats/min increment of resting heart rate of 1.08 (95% CI 1.06–1.10)¹².

According to our results, there was a statistically significant difference in the resting heart rate between the group with cardiac events and those with no events, with the former having a higher resting heart rate. Nevertheless, the univariate analysis did not confirm this variable as a predictor of cardiac events. This could be explained by the smaller sample of our study population in comparison to the studies mentioned above.

Our results support the fact that the heart rate response during the exercise testing could have a prognostic value. Leeper et al. in his series, with a mean follow-up 5.4 ± 2.1 years, reported an association between initial heart rate and improved survival. However, heart rate increase at peak exercise and DTS were shown to be more powerful predictors of prognosis¹⁰. In our study, the cardiac events group was associated with a lower peak heart rate ($136,8 \pm 21,0$ vs. $138,8 \pm 12,9$) and a higher percentage of high-risk DTS (9,3% vs. 4,9%) in a trend level.

Moreover, patients with cardiac events had a lower difference systolic BP. Gupta et al¹⁵ reported systolic BP response to maximal exercise stress testing to add prognostic

information to CV mortality independent of age. Despite these results, it was surprising that there was no significant difference in peak systolic BP, considering its association with severe CHD, reduced ejection fraction, or both^{11,14}. This could probably be explained by the diverse demographic characteristics of our study population.

In the original cohort, in which the Duke Treadmill Score was created, angina, whether test-limiting or not, was a predictive variable of cardiac prognosis in CHD²⁸. Nevertheless, a number of other cohort studies have failed to find an independent predictive value of exercise-related angina once other variables were considered^{29,30}. Our results support the fact that angina was not related with events, despite being a common symptom between patients with CHD.

Additionally, our results show no predictive value of ST-depression response to exercise. This result is not unexpected considering that many conditions, such as the anatomic distribution of ischemia, can confound the sensitivity and specificity of the ECG for detection of coronary disease^{31,32}.

Although widely used for risk stratification, DTS has some limitations. A recent study found DTS is not a significant predictor of hard events in patients aged ≥ 80 years³³. In the present study, DTS did not present a significant difference between both groups.

Previously, Hachamovitch et al had also reported added prognostic value of MPI for hard cardiac events³⁴. Nevertheless, a recent Cleveland Clinic³⁵ study concluded that for a median follow-up time of 2.4 years, exercise MPI perfusion failed to provide incremental significant risk stratification beyond exercise capacity, existing no difference in mortality with an abnormal MPI in comparison with those with normal MPI. Similar conclusions were reported by other short-term studies^{36,37}. Our data supports this same evidence, but for a long-

term follow-up period. In our study, MPI also did not increment ExECG variables prognostic capacity when compared to ExECG alone.

ECG has well-known limitations for diagnosing obstructive coronary disease. Nevertheless, this study suggests that ExECG could benefit with the assessment of other variables. Instead of only evaluating ST-segment changes, the report should include other major prognostic variables, such as the existence of chronotropic incompetence⁸ or blood pressure response to exercise. Another possible approach can be the integration of multiple exercise test parameters and conventional risk factors for improved CHD risk assessment³⁸.

Limitations

The main limitation of our study was its retrospective character. In this type of study, hospital registries are not always clear about the cause of death causing sometimes constraints in dealing of data. Additionally, all subjects of our study population had indication to perform a MPI, which could be due to previous ExECG results. This could explain the under value of DTS in our patients. The lack of difference in exercise test duration could be explained by the homogeneity of our study population's exercise capacity, which should, in turn, also be regarded as a study limitation.

In our study, we could not guarantee the suspension of β -blockers before ExECG, which could undermine the results of Bruce Protocol. In some clinical settings, there is an interest to evaluate the exercise capacity under medication. Likewise, after exercise test, the patients received diverse therapeutic strategies, which were adjusted individually for each patient.

Heart rate recovery, according to the literature, seems to be an important prognostic variable. It was not included in our analysis.

It is important to take into account that there are more complex and precise scores with the use of MPI, and that a quantitative evaluation may be characterized by even higher

effectiveness³⁹. In our study, MPI results were classified as “abnormal” or “normal”, which undervalues this test. It would be interesting to have information about risk factors to have a better categorization of our population (i.e. smoking)⁴⁰.

Conclusion

In our study population, exercise MPI failed to add incremental significant risk-stratification beyond ExECG variables in a long-term follow-up period. Difference of heart rate and systolic blood pressure at rest and exercise seem to neutralize the impact of MPI results on cardiac events. Likewise, male patients, patients with a history of CHD or diabetes should be followed carefully looking for signs of progression of disease or instability.

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