

Is Cold Pressor Test Useful to Predict Cardiovascular Events in Patients with Not Documented Coronary Artery Disease?

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SUMMARY

Background

The endothelial dysfunction is the first known alteration that takes part in the development of ischemic heart disease. The lack of well-developed methodologies to recognize patients that could have a cardiovascular event in the preclinical stage of the disease alert us about the need of taking additional methods of diagnosis for its early identification. The endothelial function in the coronary arteries was evaluated with myocardial perfusion SPECT imaging and the cold pressor test.

Objective

To determine the prevalence of the cold pressor test in 511 patients with no proved ischemic heart disease, as well as, the associated coronary risk factors in those patients with a positive result and to analyze the incidence of cardiovascular events in a 50-month monitoring.

Material and Methods

A tomographic study of myocardial perfusion SPECT imaging was performed in 511 patients in a department of nuclear medicine, whose result versus the exercise showed uniform radiotracer uptake. No patient had history of myocardial revascularization or previous myocardial infarction. The cold pressor test was performed within 5 days after the admission protocol. The test is positive when radioisotope hypo-uptake is observed at any segment that was not present in the cardiac stress test and it is negative when there are no changes in the uptake between both studies.

The average monitoring was 24 ± 13 months, which could be completed in 95% of the patients. Cardiac mortality, myocardial infarction, cerebrovascular accident and revascularization procedures were analyzed.

Results

The mean age was 58.7 years with a prevalence of 52.6% in men. Prevalence of risk factors: diabetes 10.3%, dyslipidemia 69.3%, hypertension 63.4%, obesity 25.2%, and tobacco smoking 22.3%.

The test was positive in 32.4% of the patients. 3.9% of the patients did not tolerate a cold stimulus and 5.3% had vasovagal response.

During 50 months, the event-free survival was 95.6% and 86.6% in patients with negative and positive test, respectively ($p < 0.01$).

Conclusions

The prevalence of the positive cold pressor test in patients with no proved ischemic heart disease was 32.4%. Men and high body mass index were associated with a positive test. The positive cold pressor test would identify patients who could suffer from cardiovascular events.

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Key words

> Ischemic heart disease - Endothelial dysfunction - Cold pressor test - Prognosis

Abbreviations

> CPK Atrioventricular | LDL Low-density lipoproteins

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BACKGROUND

At present, there are no well-developed methodologies to recognize patients that could have a cardiovascular event in the preclinical stage of the cardiovascular disease. These data alert us about the need of taking additional methods of diagnosis for the early identification of the disease and the research of more efficient therapeutics to reduce cardiovascular morbimortality.

Furchgott and Zawadzki (1) showed that the endothelium regulates the vascular tone. Subsequent studies (2) showed other functions, for example the intervention in coagulation, inhibition of cell proliferation, etc.

Oxidation of LDL cholesterol allows the formation of superoxide anions and other free radicals which generate oxidative stress and stimulate the synthesis of proinflammatory factors that attract monocytes which are adhered to the endothelial cells. (3) Diabetes, hypertension and tobacco smoking cause the increase of free radicals that change the endothelial function. This alteration is called endothelial dysfunction, the first known step in the process of atherosclerotic cardiovascular disease. (4-6)

Nabel et al. observed vasodilation in normal arteries and vasoconstriction in sick arteries with the cold pressor test. (7) Schächinger et al. showed that the vasomotor response of the coronary tree versus the presence of acetylcholine and the sympathetic stimulation due to the cold pressor test predicted the progression of the coronary disease and cardiovascular events. (8)

The present study was carried out with the following objectives:

1. To determine the prevalence of the positive cold pressor test in patients with no proved ischemic heart disease.
2. To observe the prevalence of coronary risk factors in patients with positive cold pressor test.
3. To stratify the predictive power of coronary events that has a positive response to the cold pressor test.

MATERIAL AND METHODS

Between October, 2003 and December, 2007, 511 patients (58.7 ± 10 years, with a prevalence of 52.6% of men) with myocardial perfusion studies in rest and normal effort were included. This population was steered by its general practitioners to a nuclear medicine center for the execution of this study with diagnostic purposes. The population was > 21 years of age and with an ejection fraction $\geq 50\%$ with normal ventricular volumes. None of these patients had history of myocardial infarction, revascularization surgery, coronary angioplasty, cerebrovascular accident, intermittent claudication, valvular heart disease or Raynaud's phenomenon. Patients did not have left bundle branch block or atrial fibrillation.

A medical record was done for every patient. It included cardiovascular symptoms, coronary risk factors and the result of previous complementary studies (Table 1).

Myocardial perfusion

The used protocol was continuous and scalariform, in cycle ergometer with blood pressure control and continuous monitoring. The effort stops when the person reaches the desirable heart rate according to Robinson table (9, 10) or when there are clinical or electrocardiographic criteria to interrupt the exercise. (11) A minute before ending

the maximum effort, 25 mCi of ^{99m}Tc -mibi are injected intravenously. After thirty minutes cardiac images in a gamma camera with gated SPECT are acquired, which are processed and interpreted following the classical criteria. (12)

The rest study is performed between 24 and 72 hrs after the effort, with the administration of the same radiopharmaceutical dose and the acquisition of images in the same conditions and with the same parameters as in the effort stage.

Besides, a program, which allows the quantification of the size in altered myocardial areas with a method developed by O' Connor et al. in 1989, is available. (13)

Cold pressor test

511 patients accepted to participate in the study and between the third and fifth day, a myocardial perfusion study with the cold pressor test was performed. It was done by introducing a hand in cold water (4°C) during four minutes with blood pressure and heart rate monitoring. Then 25 mCi of ^{99m}Tc -mibi were injected intravenously and after 30 minutes cardiac images in the same way and with the same parameters as in the effort study were acquired.

The cold pressor test was performed in 90.8% of the population. The test was not performed in 27 patients (5.3%) who had vasovagal reaction and 20 patients (3.9%) with cold intolerance.

The images from the cold pressor test and the post-effort were compared. The results are listed below:

Positive test: when there is hypo-uptake in some segment of the perfusion images which were done with the cold pressor test. This hypo-uptake was not present in post-effort images.

Negative test: when there are no changes in radiotracer uptake in none of the myocardial perfusion images which were obtained after effort and cold pressor test.

The quantification of the hypo-uptake area was analyzed with O'Connor technique, in post-effort and cold pressor test images. When the difference of the compromised area between the two images was $\leq 3\%$ the cold pressor test was considered negative and $> 3\%$ was positive.

Demographic features

The prevalence of coronary risk factors, symptoms and the medication indicated in this population which arose from the first interview are shown in table 1.

Monitoring

A monitoring during 50 months was performed and the following events were analyzed: a) cardiovascular mortality, b) myocardial infarction, c) procedures of myocardial revascularization which included myocardial revascularization surgery and angioplasty, d) cerebrovascular accident.

Cardiovascular death is defined as any death due to myocardial or cerebral infarction or sudden death from documented cardiac origin. The myocardial infarction is defined as an elevation of CPK enzyme, twice the superior limit accompanied by a ST-T elevation > 0.1 mV in at least two electrocardiographic derivations. The procedures of myocardial revascularization in those patients who were admitted due to unstable angina pectoris and who needed a revascularization treatment, either due to angioplasty or revascularization surgery were considered as an event. In asymptomatic patients who were studied and then revascularized, the revascularization procedure was not considered as an event.

A list of patients, with their symptoms, admissions, event date and the last contact with the doctor, was sent to all the general practitioners by e-mail. The professionals

Table 1. Characteristics of the studied patients

Variables	n = 511 patients
Age (years)	58,7 ± 10
Body mass index	27,2 ± 4
Male, n (%)	269 (52,6)
Family history of heart disease, n (%)	246 (53,8)
Diabetes, n (%)	50 (10,3)
Dyslipidemia n (%)	341 (69,3)
Tobacco smoking, n (%)	102 (22,3)
Hipertensión, n (%)	313 (63,4)
Obesity, n (%)	129 (25,2)
Angina pectoris, n (%)	27 (5,3%)
Arrhythmia, n (%)	69 (13,5)
Asymptomatic patients, n (%)	113 (22,1)
Dyspnea, n (%)	59 (11,5)
Precordialgia, n (%)	273 (53,4)
AIIRA, n (%)	66 (13,0)
Aspirin, n (%)	145 (28,5)
Betablockers, n (%)	164 (32,3)
Statins, n (%)	148 (29,1)
ACE inhibitors, n (%)	96 (18,9)

Quantitative variable: Mean ± standard deviation. Qualitative variable: n (%).

AIIRA: Angiotensin II receptor antagonist. ACE inhibitors: Angiotensin-converting enzyme inhibitors.

knew the work protocol and the study result. Our medical team was communicated with all the general practitioners that had had patients with events in the monitoring in order to obtain all the information and the necessary information of the event. 95% of the patients were located. The average time of monitoring of these patients was 24 ± 13 months, with a range between 3 and 50 months.

Statistical analysis

Student's t-test was performed for the quantitative variables when two independent samples were compared, evaluating the homogeneity assumptions of the variances with Fisher's test.

The results are expressed as mean ± standard deviation. The confidence intervals (CI 95%) were also included.

The proportions with the Chi-square test were compared for the qualitative data. The strength of association was evaluated with *odds ratio*.

An association was considered statistically significant when the null hypothesis was rejected when the p level was < 0.05 . The prevalence of the cold pressor test result, as response variable, was associated with independent or predicted variables as coronary risk factors, sex (gender) and medication.

The event-free survival curve was analyzed with the Kaplan-Meier method and the statistical significance between the positive and negative results of the cold pressor test with the Mantel-Cox test.

The time of cardiovascular event-free survival as dependent variable was associated with one or several independent or predicted variables. For this purpose, the proportional hazard model or Cox model was used, where

the *hazard ratio* was interpreted as the factor by which the risk to suffer from a cardiovascular event in individuals with positive or negative results in the cold pressor test is multiplied.

This model presumes that there are no interactions among the independent variables. It also presumes that the *hazard ratio* of the predicted variable is the same for any time t. To visualize if this supposition is carried out, we have represented the estimates graphics of the risk and survival functions where the two curves are approximately parallel. As it may be observed in the survival curves, they never cross each other.

Likewise, with the result of the cold pressor test, a univariate and multivariate analysis of different variables, as risk factors, age, sex (gender) was done.

RESULTS

Prevalence of the cold pressor test

The cold pressor test was positive in 166 cases (32.4%). The correlation of the prevalence of the cold pressor test result with different variables is shown in table 2. The coronary risk factors in patients with positive cold pressor test were similar to those with negative result. People with high body mass index had more probability of having positive results. Men showed more probabilities (two and half times) of having positive cold pressor test than women.

Cardiovascular events

From 464 patients who carried out the cold pressor test 441 were located (95%). In the analysis of Kaplan Meier's curve (Event-free survival) only the first cardiovascular event was taken into account. During monitoring, 12 patients suffered some cardiovascular event, 2 of them had two events.

The incidence of cardiovascular events is shown in table 3. The most frequent was unstable angina, which required angioplasty in 5 patients and myocardial revascularization surgery in 4. The incidence of acute myocardial infarction was observed in 3 patients, while cerebrovascular accident happened in one and sudden death also in one. In this monitoring period, there were 3 non-cardiac deaths that were not considered as events in the present analysis.

*The coronary risk factors and their association with cardiovascular events are shown in table 4. Dyslipidemia, hypertension, tobacco smoking and family history were not significantly linked with these events.

However, in diabetic patients the possibility to suffer from cardiac events was almost eight times greater than in non-diabetic patients and in those patients who had a positive cold pressor test, the probability to suffer from an event was four times greater than in those patients with negative result.

The received medication (See Table 4) did not have any influence on the events due to, probably, the low utilization rate.

The predictive value of cardiovascular events is shown in table 5, evaluating the coronary risk factors and the result of the cold pressor test according to Cox model. The two only independent predictor variables of events were diabetes and the positive cold pressor test. The risk to suffer from cardiovascular events was almost seven times greater in diabetic patients and two times greater in individuals with positive cold pressor test.

Variables	Positive cold pressor test (n = 166)	Negative cold pressor test (n = 298)	p	OR	CI 95%
Age, years (mean ± SD)	58,6 ± 10,2	59 ± 10,7	0,74		-1,67, 2,33
BMI (kg / m ² ± SD)	27,8 ± 4,20	26,9 ± 4,1	0,02		-1,73, -0,14
Male, n (%)	95 (57,2)	133 (44,6)	0,0001	2,57	1,73, 3,83
Diabetes, n (%)	20 (12,0)	29 (9,7)	0,43	-	-
Dyslipidemia, n (%)	110 (66,3)	209 (70,1)	0,40	-	-
Family history, n (%)	88 (53,0)	158 (53,0)	0,97	-	-
HTN n (%)	116 (69,8)	184 (61,7)	0,07	-	-
Tobacco smoking, n (%)	41 (24,7)	63 (21,1)	0,37	-	-
Betablockers, n (%)	59 (35,5)	94 (31,5)	0,43	-	-
ACE inhibitors, n (%)	32 (19,3)	60 (20,1)	0,82	-	-
AIIRA, n (%)	23 (13,8)	38 (12,7)	0,73	-	-
Statins n (%)	51 (30,7)	83 (27,8)	0,51	-	-
Aspirin, n (%)	51 (30,7)	78 (26,1)	0,29	-	-

SD: Standard deviation. BMI: Body mass index. OR: Odds ratio. CI: Confidence interval. HTN: Hypertension. ACE inhibitors: Angiotensin-converting enzyme inhibitors. AIIRA: Angiotensin II receptor antagonist.

Table 2. Analysis of coronary risk factors and suitable medication with the prevalence of the cold pressor test result.

Analysis of the event-free survival

The cumulative proportion of patients with no cardiovascular events according to the result of the cold pressor test is shown in figure 1. Individuals with negative cold pressor test had an event-free survival of 95.6%, while in those with positive result was 86.6%. The difference between both populations is statistically significant (p = 0.01). It is interesting to mention that the cardiovascular events in the group with negative results happened only in the second half of the curve, that is, after 24 months.

DISCUSSION

This work shows that patients with no proved ischemic heart disease through radioisotope studies but with an increase in the coronary vascular tone in response to the cold pressor test have a greater incidence of cardiovascular events.

Experimental and clinical studies showed that the normal endothelial function keeps antithrombotic and anti-atherosclerotic effects. (12-14) On the other hand, several publications have shown that the alteration of the endothelial function is the first known disorder in the development and progression of the atherosclerotic disease. (14-16) Therefore, the detection of the endothelial dysfunction is a possible alternative to identify patients in the preclinical stage of this entity.

Ludmer et al. (17) were the first in injecting intracoronary acetylcholine to observe the vasomotor effect in the coronary arteries. Acetylcholine produced vasodilation in normal coronary arteries and, paradoxically, vasoconstriction in arteries with atherosclerosis.

Masoli et al. (18) have observed perfusion defects in those zones where vasoconstriction of sick coronary arteries through the administration of intracoronary

Table 3. Incidence of cardiovascular events in patients with positive and negative cold pressor test

Cardiovascular events	Patients with positive cold pressor test (n = 166 (32.4%))	Patients with negative cold pressor test (n = 298 (58.3%))
Myocardial revascularization surgery	3	1
Angioplasty	2	3
Myocardial infarction	3	0
Ischemic cerebrovascular accident	1	0
Sudden death	1	0
Total events	10	4

Note: Fourteen cardiac events happened in twelve patients

acetylcholine and the intravenous injection of 99mTc-mibi at the moment of maximum action of acetylcholine is produced. This publication suggests that myocardial perfusion studies could identify coronary artery territories with abnormal response to acetylcholine, as it was observed in the coronary angiography.

Nabel et al. (7) investigated the endothelial function with the cold pressor test. The hypothesis was based on the greater sensitivity for the observed vasoconstriction in vascular segments with atheromatous plaques. Previous studies (19-20) showed that the predominant response of the sympathetic stimulation produced by the cold pressor test in these segments is vasoconstriction.

The cold pressor test represents a useful method to investigate the presence of endothelial dysfunction. Its value in the clinic lies in its non-invasive character and its good reproducibility. (21-22)

Table 4. Analysis of coronary risk factors, received medication and incidence of cardiac events

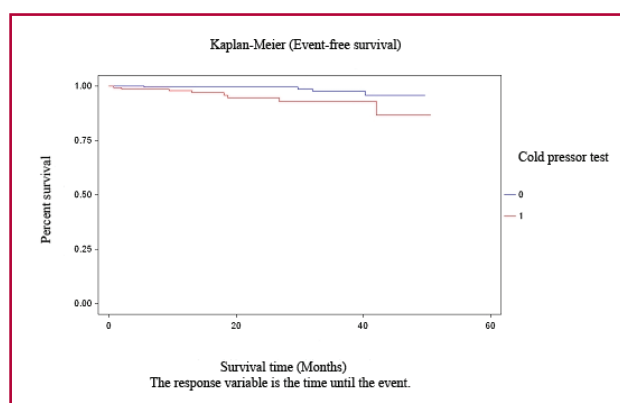
Qualitative variables	With events (12 patients)	With no events (452 patients)	Test of proportional risk p	HR	CI 95%
Male, n (%)	10 (83,3)	232 (51,3)	0,06	4,21	
Dyslipidemia, n (%)	9 (75)	313 (69,2)	0,66	1,34	
Diabetes, n (%)	5 (41,6)	43 (9,5)	0,003	7,20	1,93-26,81
Family history, n (%)	8 (66,6)	238 (52,6)	0,34	1,26	
HTN, n (%)	9 (75)	292 (64,6)	0,62	1,39	
Tobacco smoking, n (%)	4 (33,3)	98 (21,6)	0,61	1,42	
Cold pressor test, n (%)	8 (66,6)	158 (34,9)	0,02	4,10	1,23-13,66
Betablockers, n (%)	4 (33,3)	226 (50)	0,17		
ACE inhibitors, n (%)	3 (25)	86 (19,0)	0,48		
AIIRA, n (%)	2 (16,6)	61 (13,5)	0,56		
Statins, n (%)	5 (41,6)	133 (29,4)	0,28		
Aspirin, n (%)	6 (50)	128 (28,3)	0,09		

HTN: Hypertension. HR: Hazard ratio. ACE inhibitors: Angiotensin-converting enzyme inhibitors. AIIRA: Angiotensin II receptor antagonist.

Table 5. Cox proportional hazards model.

Predictor variable	Coefficient	Standard Error	Z	p	Relative risk	p
Diabetes	1,89687	0,76140	2,49	0,0127	6,66	1,50-29,64
Cold pressor test	1,76634	0,89160	1,98	0,0476	1,85	0,02-3,51
Family history	0,09677	0,28883	0,34	0,7376	1,10	
Dyslipidemia	1,05639	1,10102	0,96	0,3373	2,88	
HTN	0,74336	1,09110	0,68	0,4957	2,10	
Obesity	1,12104	1,13712	0,99	0,3242	3,07	
Sex (gender)	1,12438	1,11582	1,01	0,3136	3,08	
Tobacco smoking	0,48840	0,87910	0,56	0,5785	1,63	

Here, the time until an event is taken into account as a response variable and there are several analyzed predictor variables.

**Table 1.** Event-free survival in patients with negative (light blue) and positive (red curve) cold pressor test.

Interpretation of the cold pressor test results

As Nabel et al. checked, (7) the sympathetic activation generated by the cold pressor test increased a 64% the coronary flow in normal coronary arteries due to vasodilation. Consequently, the cold pressor test response and the exercise in individuals with normal

coronary arteries are similar; that is, myocardial perfusion images obtained after both procedures do not show differences in the radiotracer uptake. Moreover, this uptake is uniform in all analyzed segments since an increase in the coronary flow is produced in both situations. This result would correspond to a negative cold pressor test, which would indicate that the patient does not present significant obstructions or endothelial dysfunction.

Whereas, a positive result suggests that there exists a difference of radioisotope uptake in some segment between the images acquired in the post-effort and the cold pressor test. If the individual has a uniform uptake in the immediate post-effort, as it happened in all patients in this study, and there is a hypo-uptake induced by the cold pressor test in some zone that was normally perfused in the post-effort stage, the study would identify individuals that do not have significant obstruction in the coronary tree, but that suffer from endothelial dysfunction. Vasoconstriction causes the sympathetic activation generated by the cold pressor test in the sick coronary artery. It produces a decrease of the coronary flow.

In our population, the lack of correlation between conventional risk factors and the prevalence of

the positive cold pressor test calls the attention. A population with a low risk to suffer from a coronary disease, since all patients had a myocardial perfusion study with normal effort leads to a lack of association. The mean age of our population was 58 years, so we expect to find a greater prevalence of endothelial dysfunction in male population, since there is a late onset of cardiovascular disease in women.

Relationship between the cold pressor test result and the evolution

Schächinger et al. (8) have evaluated the impact of the endothelial dysfunction in the long-term and they conclude that the endothelial dysfunction could predict in the long-term the progression of atherosclerotic disease and the frequency of cardiac events. If this population is compared with the present study, we may mention that the characteristics of both as regards age, sex (gender) and coronary risk factors are similar. However, the prevalence of the positive cold pressor test in Schächinger's study was double, due to different inclusion and exclusion criteria which were used in both studies. This reason also explains a less incidence of cardiac events shown in our study, although the most frequent event in both populations was unstable angina, which required revascularization procedures.

In both studies, a multivariate analysis by Cox regression, adjusted by classical coronary risk factors, age, sex (gender) and tests of vascular reactivity, revealed that the cold pressor test was an independent predictor of event-free survival. However, for Schächinger, hypertension was another independent predictor of worst prognosis of cardiovascular disease, while diabetes was the most powerful coronary risk factor in our population.

On the other hand, Suwaide et al. (23) designed a study to evaluate, in the short-term, the patients' behavior with mild coronary disease that was diagnosed on the alterations of the endothelial function. Authors concluded that in individuals with no significant obstruction of the coronary tree but with severe endothelial dysfunction, the probability to suffer from a cardiovascular event is greater.

Limitations of the studied population

The prevalence of endothelial dysfunction in this study was 32.4%, inferior figure to the one observed in other studies, (8, 23, 24) despite the high prevalence of hypertension and dyslipidemia.

Beller and Zaret (25) have performed a meta-analysis of 14 studies, whose objective was to determine the prognostic value of the myocardial perfusion images acquired after exercise in more than 12000 patients. The incidence of events in this group with normal perfusion study was 0.6% per year. This would indicate that patients with normal perfusion study incorporate a population of low risk.

The incorporation of individuals with normal perfusion studies shows a high probability to suffer from a mild coronary disease or not. If patients with myocardial perfusion defects are not included during exercise, the individuals with significant coronary disease and those with severe endothelial dysfunction would be excluded, as it was shown in other publications. (7, 28, 29) These reasons could explain

the low prevalence of individuals with endothelial dysfunction in the studied population if it is compared with other studies. (8, 26, 27)

CONCLUSIONS

1. The prevalence of the positive cold pressor test in patients with normal perfusion studies was 32.4%.
2. In male patients with high body mass index, the probability of a positive result in the cold pressor test was greater.
3. The most frequent event was unstable angina which requires some revascularization procedure.
4. In patients with positive cold pressor test, the probability to suffer from an event was four times greater than in those with a negative result.

RESUMEN

¿La prueba del frío podría predecir la aparición de eventos cardiovasculares en pacientes sin enfermedad coronaria demostrada?

Introducción

La disfunción endotelial es la primera alteración conocida que interviene en el desarrollo de la cardiopatía isquémica. La falta de metodologías adecuadamente desarrolladas que permitan reconocer en la etapa preclínica de la enfermedad a los pacientes en riesgo de padecer un evento cardiovascular alertan sobre la necesidad de adoptar métodos adicionales de diagnóstico para su identificación precoz. La función endotelial en las arterias coronarias fue evaluada con perfusión miocárdica SPECT y la prueba del frío.

Objetivo

Determinar la prevalencia de la prueba del frío en 511 pacientes sin cardiopatía isquémica demostrada, como también de los factores de riesgo coronario asociados en aquellos con resultado positivo y analizar la incidencia de eventos cardiovasculares en un seguimiento de cincuenta meses.

Material y métodos

En un servicio de medicina nuclear se realizó en 511 pacientes un estudio tomográfico de perfusión miocárdica (SPECT), cuyo resultado ante el ejercicio reveló una captación uniforme del radiotrazador. Ningún paciente tenía antecedentes de revascularización miocárdica ni de infarto previo. Entre los dos y los cinco días posteriores al ingreso en el protocolo se efectuó la prueba del frío. Se considera que ésta es positiva cuando se observa hipocaptación del ra⁻dioisótopo en algún segmento que no existía en el estudio del esfuerzo y negativo cuando no hay cambios en la captación entre ambos estudios.

El seguimiento promedio fue de 24 ± 13 meses, el cual pudo completarse en el 95% de los participantes. Se analizaron los eventos mortalidad cardíaca, infarto de miocardio, accidente cerebrovascular y procedimientos de revascularización.

Resultados

La edad media fue de 58,7 años con una prevalencia del sexo masculino del 52,6%. Prevalencia de factores de riesgo: diabetes 10,3%, dislipidemia

69,3%, hipertensión arterial 63,4%, obesidad 25,2% y tabaquismo 22,3%.

En el 32,4% de los pacientes la prueba fue positiva. El 3,9% no toleró el frío y el 5,3% tuvo reacción vagal. Durante cincuenta meses, la sobrevida libre de eventos fue del 95,6% y del 86,6% en los grupos con prueba del frío negativa y positiva, respectivamente ($p < 0,01$).

Conclusiones

La prevalencia de la prueba del frío positiva en pacientes sin cardiopatía isquémica demostrada fue del 32,4%. El sexo masculino y el índice de masa corporal elevado se asociaron con un resultado positivo de la prueba. La prueba del frío positiva identificaría a pacientes que podrían padecer eventos cardiovasculares.

Palabras clave > Cardiopatía isquémica - Disfunción endotelial - Prueba del frío - Pronóstico

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