Electrocardiographic Score: Application in Exercise Test for the Assessment of Ischemic Preconditioning

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Abstract

Background: The time for 1.0 mm ST-segment depression (T-1.0 mm) adopted to characterize ischemic preconditioning (IPC) in sequential exercise tests is consistent and reproducible; however, it has several limitations.

Objective: To apply an electrocardiographic score of myocardial ischemia in sequential exercise tests, comparing it to the conventional T-1.0 mm index.

Methods: Sixty one patients with mean age of 62.2 ± 7.5 years were evaluated; 86.9% were males. A total of 151 tests were analyzed, 116 of which were from patients who completed two assessment phases. The first phase comprised two sequential exercise tests for the documentation of IPC; the second phase, initiated one week later, comprised two more tests carried out under the effect of repaglinide. Two observers who were blind to the tests applied the score.

Results: Perfect inter and intraobserver agreement was found (Kendall tau-b = 0.96, p < 0.0001, and Kendall tau-b = 0.98, p < 0.0001, respectively). Values of sensitivity and specificity, negative predictive value, positive predictive value and accuracy were 72.41%, 89.29%, 75.8%, 87.5% and 81.0%, respectively.

Conclusion: The ischemic score is a consistent and reproducible method for the documentation of IPC, and is a feasible alternative to T-1.0 mm. (Arq Bras Cardiol 2010; 95(4): 486-492)

Key words: Ischemic preconditioning myocardial; angina *pectoris*; myocardial infarction; ergometry.

Introduction

Ischemic preconditioning (IPC) is a phenomenon in which brief episodes of ischemia with intermittent periods of reperfusion determine less myocardial cell necrosis when these cells undergo subsequent longer ischemic episodes[1].

Evidences of IPC in the human myocardium have been reported during coronary angioplasty[2,3], coronary artery bypass surgery[4], and in clinical trials[5,6]. The clinical expression of IPC is the occurrence of angina *pectoris* preceding acute myocardial infarction. Individuals presenting with angina *pectoris* preceding myocardial infarction show reduced myocardial infarct size, independent of the presence of collateral circulation or previous use of medication[5].

IPC is known to be directly independent of hemodynamic factors and is primarily related to metabolic mechanisms of the myocardium. The discovery of ATP-sensitive K channels led to a series of investigations whose objective was to confirm their role as endogenous mediators in myocardial protection, including the correlation with IPC[7,8].

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The phenomenon of IPC is transient and, once triggered, lasts approximately two hours[9]. Nevertheless, a second window of protection or delayed IPC has been shown to occur 24 hours after the same preconditioning stimulus, and could last up to 48 hours[10].

The human model of IPC documentation is based on the assessment of the warm-up phenomenon which, in clinical practice, is based on the performance of sequential exercise tests (SET)[11]. The improvement of ischemic parameters in patients with coronary artery disease undergoing SET permits a better understanding of the IPC phenomenon and is consistent with the mechanisms of myocardial adaptation to ischemia[12].

Demonstration of IPC using SET has important clinical implications. Some studies adopting the SET model demonstrated that sulfonylureas[13-15] and glinides[16] block IPC in diabetic patients with coronary insufficiency. This IPC blockade was considered to be the explanation for the increased cardiovascular mortality seen in diabetic patients being treated with sulfonylureas in the UGDP study[17]. It could also explain the poorer prognosis observed in patients who were receiving sulfonylureas at the moment of myocardial infarction[18].

The parameters used for the characterization of IPC in SET are[13-16, 19-22]:

- Improved time to 1.0 mm ST-segment depression (T-1.0 mm);

- Improved double product or heart rate at T-1.0 mm;
- Improved time to angina *pectoris*;
- Improved double product or heart rate at the moment of angina *pectoris*.

These parameters, commonly adopted for the characterization of IPC in SET, are considered consistent and reproducible; however, they have some limitations[23].

Indexes based on angina are limited because it occurs in less than 50.0% of the cases; also, it is a symptom that is subject to very different interpretations due to its subjective nature[16].

Improvement in T-1.0 mm is classically adopted for the characterization of IPC. T-1.0 mm is an index of myocardial tolerance to ischemia and is considered only for horizontal and downsloping ST-segment depression at the moment that 1.0-mm ST-segment depression is achieved.

Limitations of T-1.0 mm:

- It is subject to inter and intraobserver disagreement;
- It may be influenced by the effect of training or treadmill adaptation;
- It does not consider either the maximum magnitude of the ST-segment depression or the worst morphology documented in the test;
- It may go unnoticed during the test;
- It may be misinterpreted due to the presence of artifacts;
- There is no differential value defined in the literature to confirm IPC documentation.
- It does not permit documentation of the maximum IPC expression when the second exercise test is negative.
- It does not permit IPC documentation when the exercise test is positive due to an exclusive ST-segment alteration in the recovery phase.

The double product or heart rate at T-1.0 mm are considered objective indexes of ischemic threshold, reflecting the myocardial oxygen consumption at the beginning of ischemia. Since these parameters derive from T-1.0 mm, they are also subject to the same limitations, in addition to being directly influenced by baseline blood pressure and heart rate values.

The limitations previously described coupled with the lack of standardization and a proper codification of the ischemic response while SET is performed encouraged the elaboration of an electrocardiographic score of myocardial ischemia[24].

Objective

To apply an electrocardiographic score of myocardial ischemia in SET used for the assessment of IPC in diabetic patients, comparing it to conventional T-1.0 mm.

Patients

The study population comprised non-insulin dependent diabetic patients with angiographically proven two or three-vessel coronary artery disease and normal ventricular function. Only those with a positive exercise test were selected for the study. The inclusion criteria comprised patients with stable angina, preserved left ventricular function and controlled type-2 diabetes mellitus.

A total of 61 patients were included in the study to undergo SET. Their mean age was 62.2 ± 7.5 years, and 86.9% were males. Approximately 41.0% of the patients had already suffered a myocardial infarction more than six months before, and 4.9% showed a two-vessel occlusive pattern. A total of 151 tests were analyzed; 116 of them were from patients who had completed two assessment phases and 35 were from patients who were excluded due to failure to show IPC. The exclusion criteria were: unstable angina, myocardial infarction in the past six months, dilated or hypertrophic cardiomyopathy, aortic stenosis, motor limitations for the performance of the exercise and electrocardiographic findings that limited the morphological analysis for the definition of myocardial ischemia.

Methods

This study was approved by the Research Ethics Committee (CAPPesq 0701/05) and all patients gave written informed consent.

The patients underwent symptom-limited exercise tests using the Bruce protocol. Standardized Mason-Likar 12-lead electrocardiographic studies were performed before exertion, at the moment of T-1.0 mm, at peak exercise, at the moment of the worst electrocardiographic change, and at every minute of recovery, which lasted for 6 minutes. Improvement by at least 30 seconds in the second test arbitrarily defined the presence of IPC.

The criteria for interruption of the test and for the definition of a positive test were based on the recommendations of the Guidelines of the Brazilian Society of Cardiology[25] and of the American College of Cardiology/American Heart Association[26].

Electrocardiographic interpretation

During exercise, T-1.0 mm was confirmed by the consensus between two experienced cardiologists. The myocardial ischemia score was independently applied by two other experienced cardiologists (observer 1 and observer 2) one month after the end of the two study phases. Both observers were blind to the final interpretation of IPC. All tests were reevaluated by observer 1, 30 days after the end of the study, for assessment of the intraobserver variation.

The score

The score classifies the different patterns of the electrocardiographic response based on three aspects: magnitude, morphology and timing of the ST-segment deviations. Each aspect is graded from 0 to 4 points (Tables 1, 2, and 3), thus resulting in a scale ranging from 0 to 12 points.

Morphological analysis

Four morphological patterns of ST-segment depression and one of elevation were considered.

1. Upsloping ST-segment depression. The rapid or slow

Table 1 - Classification of the magnitude of ST-segment deviations

Magnitude	Score
0 mm	0
< 1.0 mm	1
1 to 1.5 mm	2
1.6 to 2.0 mm	3
> 2.0 mm	4

Table 2 - Morphological classification of the ST-segment deviations

Morphology	Score
Upsloping (slow or rapid)	0
Convex	1
Horizontal	2
Downsloping	3
Elevation	4

Table 3 - Timing of ST-segment deviations

Timing	Score
Transient peak. ST-segment deviation after 12 minutes. Recovery within up to one minute.	0
Peak and/or recovery. ST-segment deviation between 9 and 12 minutes or exclusive post-exercise change.	1
Early with rapid recovery. ST-segment deviation between 3 and 9 minutes. Recovery within up to three minutes in the post-exercise period.	2
Early with slow recovery. ST-segment deviation between 3 and 9 minutes. Recovery after three minutes in the post-exercise period.	3
Very early. ST-segment deviation in the first phase (up to three minutes).	4

upsloping patterns are categorized in this item. The reference point for the measurement of upsloping ST-segment depression was the Y point, 80 ms apart from the J point.

2. Convex-type ST-segment depression. The presence of a convexity in the ST-segment characterizes this morphological pattern. It was measured at the Y point, 80ms apart from the J point.

3. Horizontal ST-segment depression. This morphological pattern was measured at the Y point, 80 ms apart from the J point.

4. Downsloping ST-segment depression. This morphological pattern was measured at the J point.

5. ST-segment elevation. This morphological pattern should be measured at the Y point, 40 ms apart from the J point.

Definition of the magnitude of the ST-segment deviations

The measurement was taken according to the morphological pattern of the ST-segment deviations, considering the lead with the greatest change for scoring. In order to build the score, the magnitude of the deviations was classified into 5 categories:

1. Absence of ST-segment deviations. The reference point is located in the PQ baseline or maintains the same magnitude of the baseline.

2. Slight ST-segment deviation. ST-segment depression or elevation smaller than 1.0 mm.

3. ST-segment deviation from 1.0 to 1.5 mm. ST-segment depression or elevation between 1.0 mm and 1.5 mm.

4. ST-segment deviation from 1.6 to 2.0 mm. ST-segment depression or elevation greater than 1.5 mm and lower than or equal to 2.0 mm.

5. ST-segment deviation greater than 2.0 mm. Significant ST-segment depression or elevation.

Timing and duration of changes

In order to score this component, 5 patterns were considered:

1. Transient peak: when the ST-segment deviation occurs exclusively in the exercise phase, starting after 12 minutes of the Bruce protocol. Total resolution of the ST-segment deviation should occur before the first minute of recovery.

2. Peak and/or recovery: corresponds to the test where the ST-segment deviation occurs between the 9th and 12th minute of the Bruce protocol. ST-segment deviations occurring exclusively in the recovery phase were also considered in this pattern.

3. Early with rapid resolution: when the ST-segment deviation occurs between the 3rd and 9th minute of the Bruce protocol, with total resolution occurring before the 3rd minute of recovery.

4. Early with slow resolution: when the ST-segment deviation occurs between the 3rd and 9th minute of the Bruce protocol, with total resolution occurring after the 3rd minute of recovery.

5. Very early: when the ST-segment deviation occurs up to the third minute of exercise, with up to 5 MET, corresponding to the alteration that occurs in the first stage of the Bruce protocol.

Specific situations

When worsening of the morphological pattern occurred in the recovery phase, the worst morphology and its corresponding magnitude were considered, and changes in the exercise phases were disregarded. In order to score the moment of deviation, the beginning of the ST-segment deviation during exercise was maintained.

Study design

After one week of discontinuation of the negative chronotropic medications and oral hypoglycemic agents, the patients were referred for the study in two phases:

Phase I. The patients underwent two SET (T1 and T2), with a 30-minute interval between them. Those showing IPC were referred for the second phase.

Phase II. The patients were started on repaglinide at a daily dose of 2 mg, tid, for 7 days. Then, the patients underwent two more tests (T3 and T4) also with a 30-minute interval between them.

Statistical analysis

The weighted kappa statistic with respective 95% confidence interval was used as a measurement for the assessment of inter and intraobserver agreement for each of the three components of the score[27]. The following classification was used for the interpretation of the results of the analyses based on kappa statistic and/or intraclass correlation coefficient (ICC):

a) almost perfect agreement, for values from 0.81 to 1.00;

b) substantial agreement, for values from 0.61 to 0.80;

c) moderate agreement, for values from 0.41 to 0.60;

d) fair agreement, for values from 0.21 to 0.40;

e) mild agreement, for values from 0 to 0.20; and

f) poor agreement, for negative values.

Kendall-tau and ICC were used to evaluate the inter and intraobserver agreement in the total score, defined as the sum of the three components of the score of myocardial ischemia. The values of Kendall-tau, kappa statistic, and ICC vary from -1 to +1, where -1 means complete disagreement and +1 means perfect agreement[28].

Given the number of categories observed in the total score, the Lin agreement coefficient was also adopted to evaluate the degree of agreement between the two observers. For this coefficient, excellent agreement was defined for values higher than 0.90; satisfactory agreement for values between 0.6 and 0.9; and unsatisfactory agreement for values lower than 0.6[29].

The linear correlation analyses were carried out using the Pearson's correlation coefficient (r) and the Spearman's rank correlation coefficient (rho), when the conditions for the application of the Pearson's correlation were not met[30]. A strong linear correlation was defined for $|r| > 0.7$. Moderate correlation was defined for $0.4 < |r| \leq 0.7$. Weak correlation was defined for $0.2 < |r| \leq 0.4$, and very weak correlation for $|r| \leq 0.2$.

Sensitivity and specificity values, positive predictive value, and negative predictive value were calculated considering IPC documentation, when an improvement by at least 30 seconds in T-1.0 mm was observed. When equal values or increase in the score occurred, IPC was considered absent.

Results

Interobserver variability

Perfect agreement between the two observers (Kendall tau-b = 0.96, $p < 0.0001$ and Lin's agreement coefficient = 0.9767 with 95% CI of 0.968 to 0.9831) was observed in the analysis of the total ischemia score for all sequential exercise tests assessed (n = 151 tests). The intraclass correlation coefficient showed almost perfect agreement between the observers (ICC = 0.98).

Excellent interobserver agreement was found for the interpretation of the score of ischemia when the tests of patients undergoing the two protocol phases exclusively (n = 116 tests) were evaluated. The calculated Lin's agreement coefficient was 0.97 (95% CI 0.96 to 0.98).

When only the tests of patients who had been excluded in the first protocol phase were evaluated, i.e., those not showing improved IPC indexes (n = 35 tests), excellent agreement between observers 1 and 2 was once again demonstrated. The calculated Lin's agreement coefficient was 0.99 (95% CI 0.98 to 0.99).

The following coefficients were obtained between the two observers, considering each component of the score of myocardial ischemia:

- for the magnitude parameter, almost perfect concordance (Kappa = 0.99; 95% CI 0.97 to 1.0);
- for the morphology parameter, almost perfect agreement (Kappa = 0.88; 95% CI 0.77 to 0.94); and
- for the timing parameter, perfect agreement (Kappa = 1; 95% CI 1.0 to 1.0).

Intraobserver variability

Considering the total score for all 151 tests, perfect agreement was observed between the two analyses (Kendal tau-b = 0.98, $p < 0.0001$ and Lin's agreement coefficient = 0.995 with 95% CI 0.994 to 0.997). The intraclass correlation coefficient showed almost perfect agreement between the two analyses (ICC = 0.99).

When the three score components were assessed separately, the weighted Kappa statistic showed almost perfect agreement between the two analyses, as shown in Table 4.

Accuracy

Sensitivity and specificity values, negative predictive value, positive predictive value and accuracy were 72.41%, 89.29%, 75.8%, 87.5% and 81.0%, respectively. These calculations were based on contingency Table 5.

Table 4 - Analysis of intraobserver agreement

Parameters	Weighted Kappa
Magnitude	0.95 (I95% CI 0.91 - 0.98)
Morphology	1.0 (95% CI 1.0 - 1.0)
Timing	1.0 (95% CI 1.0 - 1.0)

Table 5 - Contingency table considering increases by at least 30 seconds in T-1.0 mm for the characterization of IPC

		T-1.0 mm	
		Positive	Negative
Score of ischemia	Positive	21	3
	Negative	8	25

T-1.0 mm index

The kappa statistic was also adopted to evaluate the agreement between the score of myocardial ischemia and T-1.0 mm for the characterization of IPC. The calculated value was 0.615 (substantial agreement).

Considering the sample of individuals who completed both phases (n = 116), the correlation coefficient between T-1.0 mm and the double product at the moment of T-1.0 mm was r = 0.1024, p = 0.27 (95% CI, -0.08 to 0.27). Therefore, no significant linear correlation was observed between the indexes classically used for the definition of IPC (Figure 1).

Discussion

In the assessment of IPC using SET, no consensus exists on how to characterize the presence or absence of this phenomenon by means of the conventional T-1.0 mm. Although many authors consider that improvement of T-1.0 mm in the second test is an expression of IPC[13-16,19,20,21,31], the minimum improvement difference is yet to be defined.

Since the morphological interpretation of the electrocardiogram is subjective and there is much information that needs to be weighted, the application of the score of ischemia meets the demand for the use of more intelligent, simplified and organized systems for a better definition of positive exercise tests. All aspects of the score are easily assessed, thus facilitating the integration of information among clinicians and specialists.

The score of myocardial ischemia was conceived in a way analogous to the score of myocardial perfusion, which defined parameters and points empirically[32,33].

The magnitude ranges of the electrocardiographic scale of ischemia were based on the classical Diamond-Forrester's study[34], where the correlation between the degrees of ST-segment depression and the probability of coronary artery disease was demonstrated.

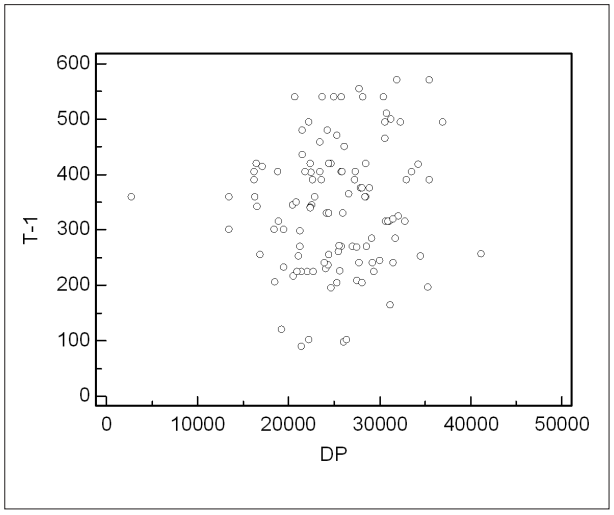

Figure 1 - Correlation analysis between the T-1.0 mm (index of tolerance to myocardial ischemia) and the double product (DP), at the moment of T-1.0 mm (threshold index for myocardial ischemia).

The sum of the ST-segment deviations was not used as a parameter within the scale of ischemia because it is known for not having a good correlation with the extent of ischemia or coronary artery disease[35].

The different morphological patterns of ST-segment depression of the electrocardiographic score of ischemia were classified based on data of the literature[25,26].

The timing component of the score of ischemia was idealized based on the proven fact that the early onset of ST-segment deviations defines more severe cases of myocardial ischemia[36].

In our sample, despite the severity of the pattern of coronary obstruction, no case of intra-exercise inotropic deficit was observed, which suggests that the interpretation of the electrocardiographic response per se has a greater practical value only for the assessment of the severity of ischemia.

The validity and reproducibility of the score of myocardial ischemia was supported by the different analyses that demonstrated excellent intra and interobserver agreement, in addition to consistent sensitivity and specificity values, positive predictive value and negative predictive value.

Since there is no gold standard of reference for the definition of IPC in exercise tests, the following parameters were used for the calculation of sensitivity, specificity, positive and negative predictive values:

- T-1.0 mm was the reference standard for the analysis, and improvement by at least 30 seconds in the second test characterized the presence of IPC;
- Improvement in the score of ischemia, with reduction by at least one point in the total score defined the presence of IPC;
- Unchanged score of ischemia or an increase by at least one point in the total score defined absence of IPC.

Even when each component of the score of myocardial ischemia was evaluated separately, perfect to almost perfect agreement was observed between the two observers.

Also, the agreement between the score of myocardial ischemia and the T-1.0 mm for the characterization of IPC was considered substantial.

When the correlation coefficient between T-1.0 mm and the double product of the moment of T-1.0 mm - which are the indexes classically used for the definition of IPC, was evaluated, no significant linear correlation was observed.

The population of diabetic patients with coronary artery disease derived from the MASS II study[37]; it included patients with artery disease confirmed by angiographic studies excluding false-positive results.

In the present study, repaglinide brought about negative modifications not only in the warm-up phenomenon, but also in the exercise tolerance indexes and the post-exercise electrocardiographic response[16]. By blocking K-ATP channels of beta-pancreatic cells, sulfonylureas and glinides can also act in myocardial K-ATP channels suppressing IPC[3,13-18]. For suppressing this phenomenon of myocardial protection, the repaglinide action is assumed as deleterious, with a potential harmful effect on the myocardium in face of ischemic events.

The lack of a means for characterizing positive exercise

tests ultimately generates poorly structured reports which commonly result in ambiguities and misunderstandings between the professional administering the exercise test and the clinician, in addition to determining an inappropriate comparison of results from different studies.

Conclusion

From the electrocardiographic point of view, the score of ischemia is consistent and reproducible, and may be considered a feasible alternative to the conventional index of time to 1.0 mm of ST-segment depression for the assessment of ischemic preconditioning.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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