English 48

Articles

(Some of these were translated from Portuguese to English and some corrected ONLY)
(alguns destes resumos foram traduzidos do português para o inglês e outros somente corrigidos)

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Article 1

From: Former Student Andrea Kayo, undated, untitled, corrected ONLY

ABSTRACT

Background

An up-to-date overview of the effectiveness and safety of dynamic exercise therapy (exercise therapy with a sufficient intensity, duration, and frequency to establish improvement in aerobic capacity and/or muscle strength), is lacking.

Objective

To assess the effectiveness and safety of short-term (< three months) and long-term (> three months) dynamic exercise therapy programs (aerobic capacity and/or muscle strength training), either land- or water-based, for people with Rheumatoid Arthritis (RA). To do this, we updated a previous Cochrane review (van den Ende, 1998) and made categories for the different forms of dynamic exercise programs.

Criteria for considering studies for this review

A literature search (as of December 2008) within various databases was performed in order to identify randomised controlled trials (RCTs).

Selection criteria

RCTs that included an exercise program fulfilling the following criteria were selected: a) frequency at least twice weekly for >20 minutes; b) duration >6 weeks; c) aerobic exercise intensity >55% of the maximum heart rate and/or muscle strengthening exercises starting at 30% to 50% of one repetition maximum; and d) performed under supervision. Moreover, the RCT included one or more of the following outcome measures: functional ability, aerobic capacity, muscle strength, pain, disease activity or radiological damage.

Data collection and analysis

Two review authors independently selected eligible studies, rated the methodology quality, and extracted data. A qualitative analysis (best-evidence synthesis) was performed and, where appropriate, also a quantitative data analysis (pooled effect sizes).

Main results

In total, eight studies were included in this updated review (two additional studies). Four of the eight studies fulfilled at least 8/10 methodology criteria. In this updated review, four different

dynamic exercise programs were found: (1) short-term, land-based aerobic capacity training, which results show moderate evidence for a positive effect on aerobic capacity - pooled effect size 0.99 (95% CI 0.29 to 1.68); (2) short-term, land-based aerobic capacity and muscle strength training, which results show moderate evidence for a positive effect on aerobic capacity and muscle strength - pooled effect size 0.47 (95% CI 0.01 to 0.93); (3) short-term, water-based aerobic capacity training, which results show limited evidence for a positive effect on functional ability and aerobic capacity; and (4) long-term, land-based aerobic capacity and muscle strength training, which results show moderate evidence for a positive effect on aerobic capacity and muscle strength. With respect to safety, no deleterious effects were found in any of the included studies.

Authors' conclusions

Based on the evidence found, aerobic capacity training combined with muscle strength training is recommended as routine practice in patients with RA.

PLAIN LANGUAGE SUMMARY

This summary of a Cochrane review presents what we know from research about the effect of exercise on Rheumatoid Arthritis (RA).

The review shows that, in people with rheumatoid arthritis:

- Aerobic exercise and muscle strength training on land probably improve pain and physical function slightly in the short term.

- There were no harmful side effects, such as increased pain or damage to your joints, of exercise found in this review. This was true for exercising on land or in water, although most of the studies were not long enough to tell if exercise might cause joint damage.

What is dynamic exercise and what is rheumatoid arthritis?

Dynamic exercise therapy programs mean activities with enough intensity, duration, and frequency to improve stamina or muscle strength. Exercise can be any activity that enhances physical fitness. Exercise which gives you more energy, endurance or stamina is often called aerobic exercise. People exercise for many different reasons including weight loss, strengthening muscles and for general fitness.

When you have rheumatoid arthritis, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff and painful. The small joints of your hands and feet are usually affected first. There is no cure for RA at present, so treatments such as exercises aim to relieve pain and stiffness and improve your ability to move.

Best estimates of what happens to people with rheumatoid arthritis who take part in a short-term land-based dynamic exercise program:

Pain (higher scores mean worse or more severe pain)

- People who took part rated their pain to be about half a point lower on a scale of 0 to 10 after 12 weeks (6% absolute improvement).
- People who took part in a dynamic exercise program rated their pain to be about half a point on a scale of 0 to 10.
- People who did not exercise rated their pain to be 1 on a scale of 0 to 10.

Physical Function (higher score means worse physical function)

- People who took part rated their physical function to be about half a point lower on a scale of 0 to 3 after 12 weeks (6% absolute improvement).

- People who took part in a dynamic exercise program rated their physical function to be about 1.5 on a scale of 0 to 3.
- People who did not exercise rated their physical function to be 1 on a scale of 0 to 3.

W H A T ' S N E W

What's new
Last assessed as up-to-date: 16 June 2009.

Date	Event	Description
22 April 2009	New citation required but conclusions have not changed	Change in authors
22 April 2009	New search has been performed	Update of a withdrawn review (See published notes for details on update).
26 May 2008	Amended	CMSG ID: C119-R

B A C K G R O U N D

Exercise therapy is a regular component in the physical therapy treatment of patients with rheumatoid arthritis (RA) since it has various health benefits. Apart from general effects including a reduced risk of coronary heart disease, diabetes, hypertension, and colon cancer, a number of specific health benefits have been described for RA, such as improved functional ability (De Jong 2003 ; Macera 2003 ; Pate 1995 ; Van den Ende 1996).

Exercise is recommended in various multidisciplinary guidelines, such as the Canadian Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercises in the management of RA, and in multidisciplinary guidelines such as the EULAR recommendations and the ACR guideline for the management of (early) RA (ACR 2002 ; Combe 2007 ; Ottawa 2004).

Exercise therapy can be performed at different intensity levels. Dynamic exercise therapy can be defined as exercise therapy with a sufficient intensity, duration, and frequency to establish improvement in aerobic capacity or muscle strength, or both (Pollock 1998).

In a Cochrane review by Van den Ende et al 1998 it was concluded that, for individuals with RA, dynamic exercise therapy had a positive effect on aerobic capacity, muscle strength, and joint mobility with no detrimental effects on disease activity or pain (van den Ende 1998). Since then, a number of reviews on exercise therapy in RA have been published (Gaudin 2007 ; Hakkinen 2004 ; Stenström 2003). In these reviews, no explicit inclusion criteria were used regarding the characteristics of the exercise programs, for example intensity, duration, frequency, and supervision of exercises (Hakkinen 2004 ; Stenström 2003). Moreover, radiological damage was not considered as a safety parameter (Hakkinen 2004 ; Stenström 2003). In addition, the methodological quality of the studies was not taken into account (Hakkinen 2004 ; Stenström 2003), no systematic quantitative or qualitative data analysis was applied (Gaudin 2007 ; Hakkinen 2004 ; Stenström 2003), and the heterogeneity of the interventions was not addressed in the analyses (Gaudin 2007 ; Hakkinen 2004 ; Stenström 2003).

Our objective was, therefore, to update the review by van den Ende et al 1998 (van den Ende 1998) by assessing and summarizing the available evidence as of 2009 on the effectiveness and

safety of dynamic exercise therapy for people with RA using the Cochrane Collaboration methodologies (Higgins 2008).

To address the heterogeneity of the interventions, a distinction was made between (a) short-term and long-term exercise therapy programs, (b) land-based and water-based exercise therapy programs, and (c) exercises aimed to improve aerobic capacity, muscle strength, or both.

OBJECTIVES

The primary aim was to determine the effectiveness (regarding functional ability, aerobic capacity, and muscle strength) and the safety (regarding self-reported pain, disease activity, and radiological damage) of dynamic exercise therapy (land-based and water-based) in people with RA.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

RCTs comparing exercise therapy in people with RA with another form of exercise therapy or with a non-exercising control group, were selected. Studies were identified as randomised if the treatment assignment was described with words such as randomly, at random, or randomisation.

English 48

Article 2

From: Former Student Conceição, undated, titled, corrected ONLY

A Workshop on Breast Self-Exam: A Strategy for Self-Awareness in Adolescents

ABSTRACT

Objectives: to verify the repercussion of the know-how transmitted by the workshops on Breast Self-Examination (BSE) for Adolescents in their daily-living, as well as to identify in this population if there were a spread of information by these adolescents during social relations. **Methods:** it is a quantitative study answered by 474 adolescents from secondary and high schools in Embu das Artes, who were enrolled in 2006 and 2007. **Results:** data were collected from structured and semi-structured questions, answered by participants, having an estimate frequency of over 50% of questions on "the repercussion of the workshop content" and under 50% on "the multiplying action." **Conclusion:** the workshop helps the formation of the self-concept by adolescents, of their bodies; it informs them on breast cancer and the benefits from the practices and healthy attitudes in their daily-living, using the breast self-examination technique as a pedagogical instrument.

Key Words: Adolescents, Health of Adolescents, Self-Examination, Education on Health

Introduction:

The workshop on Breast Self-Exam (BSE) for adolescents is a systematic activity that is part of the workshop program on Sexual Orientation, developed at public secondary and high schools in the district of Santo Eduardo, in the "Escola Promotora da Saúde" Project, linked to the Faculty-Assisted Integration Program of Embu (FAIP – Embu), sponsored by UNIFESP, in the Estância Turística de Embu das Artes County.

The elaboration of the pedagogical strategy was for the self-awareness of the body, having as a reference the fact that the body changes during puberty favor the self-awareness to participants, using the Breast Self-Exam (BSE) technique as a pedagogical instrument that, through recreational activities, it favors the perception of parameters of normal breast development so that they can identify, be aware of and be able to recognize the breast and its abnormality, going for a self-care through the learning of habits and behaviors related to breast cancer risk factors and preventive approaches to health aggravation.

Based on the connection of the Self-Care and Self-Awareness theory, it can be said that self-awareness is a consequence of introspection, thoughts-over and self-interpretation. The adolescent, when he becomes aware of himself, permits himself to know his inner part, his truths by choice that satisfy him in his necessities, for his own personal desire before turning

himself to the outer world. Self-care is not only a momentaneous thing, from adolescence to adulthood, but, a time when the person starts to take care of himself throughout his existence.

Self-care can be understood as an active social behavior within a public health perspective in which a set of approaches for self-care encompasses the practices of daily living activities in that the individual starts and performs for her own benefit in all stages of life, in the maintenance of life, health and well-being. This behavior once settled offers the individual a self-awareness pathway, a support to a change of attitude which implies in a constant learning for people beyond their daily living. In this way, learning does not mean to acquire more information but to expand the capacity to produce the results that it really wants to get. It is a learning process that helps people, especially children, adolescents and young adults to construct their own projects of future life.

The man is not a product of his body, but it is he who produces the body in interaction with the others through his immersion in the symbolic and visual, individual, social and cultural universe. The social and cultural structure in which the individual is inserted explains the origin of his social representations and of the imaginary and the use of his body; that is, the body is socially constructed.

The workshop on BSE offers the adolescents an instrument of corporal perception that presents to them a new approach to look at their corporal scheme. According to the concept that the social construction of the body intervenes and or makes the well-being of a population difficult, the pedagogical activity understands and interferes, in their daily living, preventive actions and promoters of health to develop a useful behavior for a social living and the citizenship practices.

In the period of development of this study, the National Cancer Control Institute (NCCI) reported in the estimates for 2008 that the number of new breast cancer cases would be 49,400 with an estimate risk of 51 cases in every 100,000 women; and it is estimated that, in 2020, the breast tumor cases will reach one million. Cancer becomes a problem to nurses from the moment that it becomes a public health concern regarding its magnitude (high morbidity) and transcedence (high social and economy cost). In the same document, it is highlighted that the role of the nurse at work in the primary prevention is education on health. Besides that, it reinforces the thesis that BSE does not diagnose breast cancer making evident that the use of this technique should be beyond the morphological alteration detection; it should teach the woman to know her body better and to have a greater health control participation.

At the same time, a bimonthly magazine of The Nursing Regional Agency, São Paulo, highlighted the importance for the professional to develop and implement his role as a health educator so that he can orient the individual, the family and the community on cancer risk factors as well as ways to prevent and, also, to promote education programs on health as a propagation of his action and intervention.

Based on all of this background and being the community the structural context of our protocol, the workshops on BSE were directed to the school grounds, highlighting to adolescents that the Breast Self- Exam techniques can be an instrument of awareness of their own body, capable of creating to them the importance of its shapes from them identified so that it helps in the acceptance or the exclusion of new values on self-care.

Methodology

This is a quantitative survey whose objectives were to verify the repercussion of awareness transmitted through the Breast Self-Exam Workshops in the participants' daily living as well as to identify in this population if there were a spread of information in their social contact. The emphasis of this study was to make it possible to compare and contrast it how a person, group or thing acts or functions at the presence of realistic dominant conditions.

The population in this study was adolescents of ages 10–24 years, female, and those who took part of the workshops in 2006 and 2007, attending public secondary and high schools in the morning or afternoon: E.E. Alexandrina Bassiti; E.E. Jardim da Luz; and E.E. Odete Maria de Freitas, located in the neighborhood of Santo Eduardo in the Embu County, São Paulo.

We performed a pilot study in 2005 in which we defined the social demographic profile of population so we could work with a safer concept of adolescence and puberty as OMS premises, in which adolescence is represented by individuals of ages 10-19 years, and the young between 15-24, whereas the Statute of Child and Adolescent defines it as 12-18.

The instrument for data collection was structured and semi-structured questions, 15 of which were open and multiple-choice questions, answered by 474 girls out of 571 participants between 2006 and 2007. It encompasses variables as age and schooling – Q1 and Q2 – to categorize the population by the variables in study: the practice of BSE – Q3 to Q6; risk factors – Q7 to Q11; Multiplying action – Q8 to Q12; self-awareness of body – Q1; and the description of the being aware of the body acquired – Q16. Regarding the open questions, the data were presented in category tables.

The data were analyzed as the variables in the study and were presented in tables using the SPSS program of statistics, version 13.0 and Excel 2000.

The expectation set by this study was to find 50% of answers positive to the adhesion of the Self-Exam as an instrument of self-awareness, to the spread of information received based on the similar previous work in which the author had average positive responses of 23%, in a population of 127 adolescents from three suburban schools in Ohio, USA.

It is also worth highlighting that the study was evaluated and approved by the Ethics Committee of Universidade Federal de São Paulo, under the protocol number 1530/07. From there, we can confirm that all methodological procedures follow standards from Resolução 196/96 which is on Norms for Research Involving Human Beings.

RESULTS

The prevalence of the frequency of positive responses of over 50% of estimates established previously, was found in the following questions (Q3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15) in the questionnaire and below 50% are the positive results on "spread of information" (Q12), "Why didn't you teach others?" (Q12.1), and "Who did you teach?" (Q13).

The average age (Q1) was 14 years and, regarding schooling (Q2), 82.3% of participants were students in 6°, 7°, and 8° grades and 17.8% were elementary and high school students.

Schooling scored 82.3% of participants in 6°, 7°, and 8° grades being this the best period of life to offer workshops for the adolescents stay longer at the school grounds. On the other hand, 17.8% of participants were in 1° and 2° grades of high school. This datum shows that above 8° grade the number of students in high school grows smaller.

The variables offering positive answers to the practice of BSE were: in "Have you been looking at yourself in the mirror?," the rate was 90.1%; in "Before the shower/bath, have you been looking at your breasts?," the rate was 77.8% and in "Have you been examining or touching your breast more often?," the rate was 69.6%. Breast touching was seen in having a positive response of 69.6% indicating that adolescents perform breast touching on a daily basis, opposite to 30.4% of "no" or "did not respond."

Regarding risk factors related to breast cancer, we verified that as far as food habit changes after workshops is concerned, there was an adhesion to food care. The question "it changed," corresponding to a positive response of 69.4% to "it did not change."

Other risk factors like smoking and drinking habits show significant frequency of no adhesion to smoking as 95.6% and of no consumption or adhesion of drinking in 83.1%. The question "I cut down on smoking" and "I quit smoking" add at 3.4%, a rate much below the expected, meaning that the adolescents do not have a close relationship with the habit of smoking. But, the same questions on drinking shows another reality; the question "I continue drinking" corresponds to 8.2%; "I cut down on drinking" and "I quit drinking" correspond to 15.2% of adolescents who have a close relationship with alcohol drinking.

Regarding "the practice of physical exercises," it showed good results in 94.3% of the responses indicating that adolescents adhere to the practice of physical exercises as a prevention of health aggravation and the commitment with the quality of life. Concerning "the visit to a gynecologist," we found 69% of responses as "I never went," and 17.1% as "I started doing it," and 12.4% as "I still do it." This latter rate represents 59 adolescents out of 474 expressing that this interest in medical control is occurring now.

The repercussion of the multiplying spread of information by adolescents was measured in "You taught another person the BSE?" and showed 71.9% of negative responses over the expectation that at least half of participants could become a multiplier.

As shown in Table 1, the distribution of responses by adolescents on schooling, we used the Pearson K-square test to check the association between responses and the level of education. There is a statistically significant association between the question "Have you been looking at yourself in the mirror?," ($p=0.015$), and answers from those who changed their diets after the workshop, ($p=0.047$) and in relation to alcohol drinking consumption ($p=0.002$).

Regarding the questions "Did you teach another person to do the Breast Self-Exam?" (Q12) and "Taking part in the Breast Self-Exam Workshop helped me to know my body better," (Q15) considering their association with schooling, the sample evidences permit to reject the null hypothesis of no association between the reasons for not teaching others the Breast Self-Exam technique.

In "Why didn't you teach others?" (Q12.1) and schooling, there was an association between these two variables ($p=0.012$). Still in it, we highlight the alternative "I don't feel at home," as having 24.7%, being a rate much lower than expected. This estimate shows the fragility of

adolescents to speak out pertaining subjects on body. For the adolescents who reported to have spread the information obtained in the workshop, 65.2% responded to have found it “easy” to speak about BSE and 25.7% responded to have found it “difficult”. The adolescents answered questions about themselves going against the results in the latter question in which they exposed the fragility to discuss their bodies with others.

The approach of repercussion of the workshop in the self-awareness in adolescents was measured when asked “Taking part in the workshop helped me to know my body better?.” The result, 87.8% related to 12.2% as a negative response, gives substance and validates, in our understanding, the strategy of self-awareness and self-care in the prevention of breast cancer and the promotion of healthy habits for a good quality of life in adolescents.

The other questions do not present statistically significant associations with schooling, the know-how and practice of BSE in the prevention of breast cancer.

DISCUSSION

For the analysis of the collected data, we found it difficult to establish the study expectation due to the lack of theoretical reference. Most of studies had as a focus the awareness of breast cancer and there were very few national studies. With this, we established after a pre-test an estimate of over 50% of positive answers, that is, 30% superior to the one reached in the study done in Ohio, USA.

The workshop identified that the number of adolescents is greater for those in secondary school which is ideal for the development of a strategy during high school period; this number drops, justified by the pedagogical coordinators for since 8th grade some start to work, needing to be transferred to night schools, which makes it difficult and does not encourage them to move on with the course as well as activities regarding education on health.

The practice of the BSE technique had as a goal to verify the importance that the adolescents gave to “looking” at their own breasts after the workshop, arising physical and functional self-awareness and affective meaning, as later revealed by the positive results obtained of over 50%. The systematic technique of BSE makes breast touch and body contour for adolescents familiar, and it works with feelings of inhibition, fear and shame, as mentioned in similar studies performed young students of nursing.

The growth of breasts is the only hint of the start of sexual maturation, their readiness for adult life. We know that adolescents suffer a feeling of weakness, fear and anxiety with the loss of the body of a child, having still a childish mind for a body of an adult. The positive answers of over 50% by adolescents regarding their body show the importance to know the functioning of their organs, of their body and how they will be useful further in their sexual intercourse.

Regarding the relation of risk factors on breast cancer, the results obtained show us the acceptance to the change of healthy food habits. Among the negative answers, the adolescents who did not change their food habits, they recognize they need to change. For us to reach this food change awareness, we used the on the representation of the link between a healthy body and what is imposed as a mass model of an ideal body by the media, the Internet and other communication means today in which we all live and grow up.

We found in another study, evident results that the prevalence of food disorder associated to corporal unsatisfaction may be reported ever since the age of 7 years. This is concerning to the influence of our contemporary world, our technology, the media and to the strategy for the consumption on body issues for financial purposes. It generates influences and social and physical modifications to which we are subject.

The workshop contemplated practices so that the adolescents could identify the adequate way for a healthy diet, making easy the development and the elaboration of their self-image, thus, their self-awareness and then self-care. It is fundamental that the society be flexible regarding adolescent values in their synthesis of healthy self-image for having as a whole their integrity and their own subjectification.

Regarding the practice of physical activities, many adolescents during workshops stated they practice sports, walk to school and also are positive to physical exercises done at school; moreover, claiming changes in these activities: being practiced apart from the boys, and, exercises for the woman's body aesthetics.

Among different schools, reports about alcohol drinking were expressed as "the usual" even by the younger ones and interpreted naturally by them due to the fact of drinking reports by close family members, parents, and friends, characterizing it as a habit in the daily living. Regarding smoking habits, there was a fall in the percentage of consumption. We found two studies which describe the use of alcohol due to school friend's pressure or by a family member, besides the easy access to alcohol purchase favoring a predisposition to the risk factor. The authors identified that, among students in secondary or high schools, about 80.5% have already consumed alcohol, at least once before, and 28% have smoked, at least once before, and 5% often smoke; a frequent relationship found in our study.

A visit to a gynecologist has obtained negative answers as expected. It would be unreal if we thought that after the first menstruation every adolescent should see a gynecologist for this involves cultural family standards which we should respect. From the family values standard, the workshop achieved its goal when informing and orienting the importance of seeing a gynecologist as a procedure or resource for the diagnosis of an anomaly found in the breast and in the body of the adolescent, making them aware to the necessity of self-care, and, demystifying that seeing a gynecologist is permitted not only to married women but also for those who have an active sexual life, for childbearing problems, pregnancy, but also, for the prevention and provision of health for adolescents.

Through the multiplying action, we obtained a percentage lower than expected. In that, 71.9% of adolescents reported their conflicts and immaturity when dealing with the issue "their own body," which causes them embarrassment being around other women.

From the positive results of over 50% obtained by the BSE workshop, we highlighted the obtained healthy practices as well as the benefits to adopt them and also we set them in different social conditions of each adolescent, making the adolescent notice something through experiences related to her corporal scheme, which leads her responses to embarrassment, several different situations and her own choices from her social group requests.

CONCLUSION

The repercussion of the workshops in the daily living of adolescents brought us optimistic results both by the receptivity of information obtained and by the changes registered in their daily living. With positive answers of over 50%, we report that the participants regarding previous knowledge of their body and after the workshops, they started to examine them better, they found what they did not know and learned important things about them.

Breast touching through Self-Exam was recognized as an instrument of corporal perception, bringing meditations, elaborations, comprehension and awareness of corporal scheme, still in the maturation process and modifications as affective, physical, and social. Worried with the usual body contour, the adolescents had the opportunity to live a pedagogical activity on Health Education in which they acquired new body awareness, reporting their anxieties to corporal changes and to the real and ideal body.

Curiously, during this workshop, we found adolescents having breast nodules as well as servers and teachers having breast nodules or a history of breast cancer. These adolescents, besides taking part, also they enriched the activity with the report of the finding, treatment, follow-up, and prognosis that interested a lot the colleagues. This justifies the viability of the workshops for, for adult women, the feeling and the esteem of the work was visible and when they examine themselves and report their experience highlighting the importance of knowing the body earlier the better the promotion and prevention of health aggravation.

The role of the nurse on Health Education, in this study, brought us a rich experience because, besides their participation in the workshops, the sharing during relationships and extra doubt clarifying of adolescents, there was a deep integration with teachers and school boards. Despite the multiplication of information have had results lower than 50% of positive answers, having been invited by a board of one of the schools, we took part of lectures on BSE with students, parents and guests in one of school celebrations where we could make this workshop incorporated to the school syllabus during the period of research.

The workshops tried to find in the daily living reality of the community to which they belong the adaptation to the new costumes and habits to enroot the information and prevention awareness in the social conditions so that the adversities do not discourage them in the personal and social assimilation reflected in their healthy corporal perception and development.

When using the self-exam approach as a pedagogical instrument for self-awareness, we put into practice a prevention action on Health Education, we offered to these adolescents a subjective approach between the concept construction action in itself and the promotion of self-care in their daily living, contextualizing the information regarding breast cancer and, thus, to be able to understand the benefits to develop, incorporate healthy habits for the improvement of the quality of adult life. We are prone to believe that this work will be the start for the multiplication of Breast Self-Exam Workshops regarding Health projects.

Table 1- Distribution of Adolescents Regarding Schooling

	degree:	elementary				high school				
	6°grade		7°grade		8°grade		1º grade		2º grade		P value
variables	N	%	N	%	N	%	N	%	N	%	
Have you been looking at yourself in the mirror?											
no	10	7.9	11	6.2	14	16.3	9	17.3	1	3.1	0.015
yes	115	91.3	166	93.3	72	83.7	43	82.7	31	96.9	
did not respond	1	0.8	1	0.6	0	0	0	0	0	0	
Before shower/bath, have you been looking at your breasts in the mirror?											
no	21	16.7	35	19.7	22	25.6	17	32.7	8	25.0	0.148
yes	104	82.5	142	79.8	64	74.4	35	67.3	24	75.0	
did not respond	1	0.8	1	0.6	0	0	0	0	0	0	
Have you been examining or touching your breasts more often?											
no	36	28.6	53	29.8	30	34.9	17	32.7	6	18.8	0.531
yes	89	70.6	124	69.7	56	65.1	35	67.3	26	81.3	
did not respond	1	0.8	1	0.6	0	0	0	0	0	0	
Have you been doing the Breast Self-Exam technique?											
no	61	48.4	74	41.6	45	52.3	25	48.1	13	40.6	0.494
yes	65	51.6	103	57.9	41	47.7	27	51.9	19	59.4	
did not respond	0	0	1	0.6	0	0	0	0	0	0	
Have you changed your diet after the workshop?											
I did not change	30	23.8	58	32.6	27	31.4	22	42.3	5	15.6	0.047
I changed it	96	76.2	119	66.9	58	67.4	30	57.7	26	81.3	
did not respond	0	0	1	0.6	1	1.2	0	0	1	3.1	
Regarding smoking habits:											
I never smoked	121	96.0	170	95.5	83	96.5	48	92.3	31	96.9	0.799
I still smoke	1	0.8	3	1.7	1	1.2	0	0	0	0	
I cut down on smoking	1	0.8	2	1.1	0	0	2	3,8	0	0	
I quit smoking	3	2.4	3	1.7	2	2.3	2	3.8	1	3.1	

Regarding the intake of alcohol drinking:											
I never drank	111	88.1	148	83.1	69	80.2	40	76.9	26	81.3	0.002
I still drink	4	3.2	16	9.0	5	5.8	11	21.2	3	9.4	
I cut down on drinking	9	7.1	10	5.6	12	14.0	1	1.9	1	3.1	
I quit drinking	2	1.6	4	2.2	0	0	0	0	2	6.3	
Regarding physical exercise practices:											
I don't do it	3	2.4	10	5.6	5	5.8	7	13.5	2	6.3	0.177
I do it	111	88.1	156	87.6	77	89.5	42	80.8	26	81.3	
I started doing it	12	9.5	12	6.7	4	4.7	3	5.8	4	12.5	
Regarding visits to a gynecologist:											
I never went	86	68.3	123	69.1	68	79.1	33	63.5	17	53.1	0.132
I still do it	19	15.1	23	12.9	8	9.3	7	13.5	2	6.3	
I started doing it	21	16.7	29	16.3	9	10.5	12	23.1	10	31.3	
did not respond	0	0	3	1.7	1	1.2	0	0	3	9.4	

❖ *Pearson K-square Test*, Test of Association

Table 2- Distribution of Adolescents Regarding Schooling (continuation)

	Degree:	elementary					high school				
	6° grade		7° grade		8° grade		1º grade		2º grade		P Value
	N	%	N	%	N	%	N	%	N	%	
Did you teach someone else to do the Breast Self-Exam?											
yes	27	21.4	56	31.5	18	20.9	16	30.8	9	28.1	0.204
no	99	78.6	121	68.0	68	79.1	36	69.2	23	71.9	
did not respond	0	0	1	0.6	0	0	0	0	0	0	
Who did you teach the Breast Self-Exam?											
friends	6	22.2	7	12.5	7	38.9	8	50.0	1	11.1	0.074
female family members	20	74.1	41	73.2	10	55.6	6	37.5	8	88.9	
neighbors	0	0	3	5.4	0	0	0	0	0	0	
female friends and family members	1	3.7	5	8.9	1	5.6	2	12.5	0	0	
How was it to do the Breast Self-Exam Workshop?											
easy	82	65.1	121	68.0	48	55.8	36	69.2	22	68.8	0.452
difficult	35	27.8	39	21.9	27	31.4	13	25.0	8	25.0	
did not respond	9	7.1	18	10.1	11	12.8	3	5.8	2	6.3	
Why didn’t you teach others?											
I did not find it necessary	7	7.2	16	13.2	6	8.8	6	17.1	3	13.0	0.012
afraid of misteaching	23	23.7	29	24.0	10	14.7	2	5.7	2	8.7	
I had no opportunity	16	16.5	19	15.7	19	27.9	14	40.0	9	39.1	
I didn’t feel at home	32	33.0	31	25.6	16	23.5	6	17.1	2	8.7	
because they already knew it	18	18.6	23	19.0	17	25.0	7	20.0	7	30.4	
did not respond	1	1.0	3	2.5	0	0	0	0	0	0	

Taking part in the workshop helped you to know your body better?											
yes	114	90.5	153	86.0	75	87.2	47	90.4	27	84.4	0.713
no	12	9.5	23	12.9	10	11.6	4	7.7	5	15.6	
did not respond	0	0	2	1.1	1	1.2	1	1.9	0	0	

❖ *Pearson K-square Test*, Test of Association

English 48

Article 3

From: Current Student Henrique Ferraz, undated, titled, corrected ONLY

NEUROIMAGING ASSESSMENT OF NIGROSOME-1 WITH A MULTIECHO GRE MAGNETIC RESONANCE SEQUENCE INTHE DIFFERENTIATION BETWEEN PARKINSON'S DISEASE FROM ESSENTIAL TREMOR AND HEALTHY INDIVIDUALS

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ABSTRACT

Background and purpose:

Parkinsonism is commonly seen in many clinical conditions and the establishment of its etiology may take many years. The possible development of neuroprotective treatments for Parkinson's disease (PD) in the near future will require correct and early diagnosis. This study aims to analyze the accuracy of a low-cost MRI sequence to differentiate PD from patients with essential tremor (ET) and healthy control (HC) individuals.

Material and methods: We recruited 70 individuals with clinical diagnoses of PD (38 patients), ET (11 patients) and healthy volunteers (21 individuals), all of whom underwent 3T MRI multiecho (MECHO) GRE sequence. Two blinded neuroradiologists independently evaluated the presence or absence of nigrosome-1 (N1). We considered the unilateral or bilateral absence of N1 signal as indicative of PD.

Results: The absence of at least 1 N1 could differentiate with 98% accuracy patients with clinical established PD from healthy controls. The presence of both nigrosomes was 96% accurate as a sign to differentiate PD from ET patients.

Conclusion: The 3T MRI with multiecho GRE is a simple and universally available technique and it can be used as a good auxiliary tool to differentiate PD from ET patients and controls.

Introduction

Parkinsonism is defined as the presence of bradykinesia, as well as at least one of the following: rest tremor, rigidity, or postural instability.[1] Many conditions can present with one or more of these signs and symptoms. Frequently, the etiological diagnosis of tremor disorders and parkinsonism is only made after follow-up since there is no surrogate biological marker for most of these conditions.

Essential tremor (ET) is one of the most common neurological disorders and the most common pathological cause of tremor.[2] Idiopathic Parkinson's disease (PD) underlies most of the cases of parkinsonism, followed by the so-called atypical parkinsonian syndromes (APS), including Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and corticobasal syndrome (CBS). These diseases have different clinical features, responses to treatments and prognoses. The definitive diagnosis of PD requires a neuropathological confirmation, and the

accuracy of clinical diagnosis is suboptimal since clinical overlaps are not infrequent, especially in the early stages of the disease.[3] After a few years of follow-up, many patients with parkinsonism signs will have their diagnosis changed.[4]

With the use of different biomarkers, an increase in accuracy discrimination between different parkinsonian syndromes in vivo has been the objective of several studies. Currently, however, a few of them are clinically validated for the diagnosis of PD and ET. Recently, a new MRI finding distinguishing PD patients from controls has been described in the substantia nigra (SN) on iron-sensitive MRI sequences at high-field strength of 3 Tesla (3T) and ultrahigh-field strength of 7T,[5,6] and this same finding has been studied to differentiate ET from PD[7,8].

The SN is divided into the pars compacta (SNpc), which is densely packed with neuromelanin-containing dopaminergic cells, as well as the pars reticulata (SNpr), which is formed by loose aggregations of GABAergic medium and large neurons. In the SNpc, immunostaining with calbindin D28K was able to distinguish five subgroups of neuromelanin-containing dopaminergic cells in calbindin-negative zones called nigrosomes.[9] Using Perl's staining, the nigrosomes were also proven to be low in iron content compared to the immediate environs.[5,10] The largest of the five nigrosomes is labelled nigrosome-1 (N1) and positioned in the dorsolateral SN.[5]

Postmortem studies in PD have shown that dopaminergic neuronal loss is heterogeneous with the ventrolateral part of the SN being almost destroyed. Meanwhile, its dorsal part is only partially damaged. The neuronal loss is greater in the nigrosomes than other SN subregions with maximal loss (98%) of N1, resulting in the spread to the matrix and other nigrosomes.[9,11] Cellular degeneration in the SN is associated with a 30-35% increase of iron (total and ferric iron) content in the SNpc of patients with PD.[12,13] This iron accumulation may be a nonspecific product of cellular degeneration rather than a cause.

High and ultrahigh MRI with iron-sensitive sequences[5,6] has provided an increase of both spatial resolution and contrast needed to visualize and detect changes in N1, which can be seen in susceptibility-weighted sequences (SWI). The disappearance of N1 on MRI SWI is known to occur in PD over time and it is associated with an increase of iron deposition.[14] T2-weighted GRE images are sensitive to local magnetic field inhomogeneities and modified in the presence of iron.[15] Thus, they may be able to detect the change in iron content in the nigrosome-1 of PD subjects, being a potential biomarker of pathophysiologic changes in these patients.

This study aims to analyze the accuracy of a low-cost MRI sequence to differentiate PD from patients with essential tremor (ET) and healthy control (HC) individuals.

It evaluated the usefulness of this observation to discriminate patients with PD from ET and healthy volunteers.

Material and methods

Subjects

We recruited patients with clinically diagnosed PD, ET, and healthy volunteers between April 2017 and January 2019 at the Federal University of São Paulo movement disorders outpatients' clinic. The inclusion of patients and data collection were carried out following the guidelines of the Declaration of Helsinki. The Institutional Review Board approved the study. All subjects signed an informed consent for inclusion.

The diagnosis of PD was based on the Movement Disorder Society (MDS) PD criteria[16] and all patients had clinically established PD. The diagnosis of ET was based on the MDS Tremor consensus.[17] The exclusion criteria were signs of atypical parkinsonism, history of serious head

trauma, intra-axial brain tumour, psychiatric disorders, the use of medication known to cause parkinsonism, previous cerebrovascular disease (hemorrhagic or ischemic stroke), contraindications to a MRI examination, the presence of severe motion artefacts, and age younger than 40 years.

Healthy controls (HC) were selected from spouses and relatives of PD and ET patients.

The MRI study

All subjects included were submitted to MRI scans acquired on a 3 T Philips Achieva scanner using a 32-channel receiver coil. The presence of the nigrosome-1 area was assessed in all participants in the axial plane perpendicular to the fourth ventricle floor with an AXIAL T2 3D MULTIECHO GRE sequence (Mecho): TR 88 msec / TE range, 11-55 msec; flip angle 10 degrees, 20 slices, matrix 172 x 150, voxel size 0.7 x 0.8 x 2 mm, acquisition time 5:04 minutes. This sequence is known by MULTIECHO FAST FIELD ECHO (mFFE) in Philips's scanners.

All subjects underwent FLAIR, T1 and T2 Grase sequence 3T MR imaging to exclude radiologic signs of atypical parkinsonian syndrome (APS), neoplastic lesions, hydrocephalus, or extensive vascular damage.

Data analysis

The images to determine the presence of N1 following an axial plane perpendicular to the fourth ventricle floor were assessed by two neuroradiologists blinded to the clinical diagnosis. Evaluator 1 had five years of experience in neuroimaging and Evaluator 2 had fifteen in neuroimaging.

The findings were evaluated independently for each side and classified into three categories: normal, probably normal, and absent. They were reclassified as normal nigrosome-1 when the assessment was normal or probably normal for both sides, and abnormal when nigrosome-1 was absent in at least one of the two sides.

Statistical analysis

All statistical analyses were conducted using SPSS software 22.1 for Windows (SPSS, Inc, Chicago, IL), treated by descriptive statistics, with calculations of percentages, means and frequencies, followed by a discussion of the results obtained. The sensitivity, specificity, positive predictive value and negative predictive value for the absence of nigrosome1, were calculated for each evaluator, followed by a combined evaluation. For the sample size calculation, we used the described prevalence of 1680/100,000 to TE[18] (n=11, power of 88.45%), 1250/100,000 to PD[19] (n=38 power of 86.13%) and the formula $N= Z^2*[P*(1-P)] / D^2$ (OPS,1997).[20]

Results

Population

A total of eighty-four subjects were recruited. Eleven patients were excluded for the impossibility of completing MRI because of severe tremor and motion artifacts. Of those, 9 had PD and 2 ET. Three other subjects were excluded due to claustrophobia, one HC and 2 ET patients.

Of the seventy included subjects (50.63% male and 49.35% female), 38 (54.28%) had clinical diagnosis of PD (power of 86.13%), 11 (15.72%) of ET and 21 (30%) were HC. The mean age was 61.35 years.

Nigrosome 1 (N1) analysis

Of the thiry-eight PD patients, evaluator 1 identified absence of at least one N1 in all patients, being unilaterally absent in 8 and bilaterally absent in 30. Evaluator 2 identified absence of at least one N1 in 34 patients, being unilaterally absent in 3 and bilaterally absent in 31. The combined sensitivity for the differentiation between PD and HC was 100%, specificity 95%, positive predictive value (PPV) 97%, negative predictive value (NPV) 100%, and accuracy of 98%. The interrater concordance (kappa) was 0.809.

Concerning the eleven ET patients, evaluator 1 identified the absence of one side of N1 in 2 patients, and the bilateral absence in 1, while evaluator 2 identified the bilateral N1 absence in 4, of whom were the same as for evaluator 1. The combined sensitivity was 82%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 95% and accuracy of 96% for the differentiation between PD and ET. The interrater concordance (kappa) was 0.582.

In the HC group, evaluator 1 identified 2 subjects with a bilateral absence of N1 and evaluator 2 identified a bilateral absence of N1 in 3, being one in common with evaluator 1. For the presence of N1 and the differentiation between TE and HC, sensitivity was 18%, specificity 95%, positive predictive value (PPV) 67%, negative predictive value (NPV) 69% and accuracy of 69%. The interrater concordance (kappa) was 0.452.

Figure 1 - Axial Mecho o 3T, 63-year-old female with essential tremor and 26 years of disease. Bilateral presence of N1 (arrows)

Figure 2 - Axial Mecho 3T, 43-year-old female without neurological disease (healthy control). Bilateral presence of N1 (arrows)

Figure 3 - Axial Mecho 3T MRI, 51-year-old male with Parkinson Disease and 5 years of disease. Bilateral Absence of N1. (arrows)

Table 1 – Clinical and demographic characteristics of patients

Table 2 - Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the nigrosome 1 sign in the diagnosis of idiopathic Parkinson's Disease (PD), Healthy Controls (HC) and Essential Tremor (ET)

Discussion

The loss of nigrosome-1 is a progressive neurodegenerative process and is likely to be more noticeable in patients with a longer and more severe evolution. It is known that, once PD symptoms start, there is already a loss of 60% of dopaminergic neurons in SNpc[21] and the most affected structure is the N1.[11] Notwithstanding, even at early stages of the disease, morphological alterations can be detected by MRI in the N1 region.[22] This makes the high field MRI study of nigrosomes a potential biomarker of neurodegenerative parkinsonism. It is unclear whether the N1 study is a good marker for pre-motor symptomatic patients. Conversely, studies on patients with rapid eye movement sleep behavioural disorder (REM sleep BD) without motor

symptoms have shown that some of them may have an absence of N1 and a lower caption of dopamine transporter 123I-FP-CIT single-photon emission tomography (DAT-SPECT) as compared to healthy individuals.[23] DAT-SPECT can demonstrate striatal dopamine deficit, which is present in PD and absent in ET, differentiating the diseases with high sensitivity and specificity.[24]

Other complementary methods have been studied and have also been shown to be useful to differentiate PD from ET. Transcranial sonography of substantia nigra studies has found hyperechogenicity in the SN area in 90% of PD patients and in only 10-13% of those with ET and HC.[25] In PD, an assessment of alpha-synuclein deposition in skin biopsy is a minimally invasive test with high specificity (to synucleinopathies) but with variable sensibility, according to the methodologies used and the biopsy site.[26]

The cardiac 123 meta-iodobenzylguanidine (MIGB) scintigraphy has demonstrated a reduced MIBG uptake in PD patients due to the cardiac sympathetic denervation observed in this disease. This exam can help to distinguish patients with PD from those with ET and APS.[27]

Comparison with previous studies

In this study, we compared the absence of nigrosome-1 (N1) in PD patients compared to ET patients and healthy individuals using a subjective visual analysis of an iron-sensitive MRI sequence (Mecho) without a processing software or a license requirement. This sequence is an advanced gradient-echo one combining multiple bipolar gradient-echo formations, and its name varies depending on the scanner used. The findings obtained through this technique are similar to previous ones found in publications using other 3T MRI sequences. Schwarz et al[6] found sensitivity of 100%, specificity of 91–93% and accuracy of 91-96% (with the SWI sequence). Noh at al[22] found a sensitivity of 100%, specificity 84.6% and accuracy of 94.6% with a similar sequence, however, referred to by different names (MEDIC; Siemens). Both studies compared PD patients with healthy controls.

Jin et al[7] used quantitative susceptibility mapping (QSM) reconstructed from T2*, from and obtained sensitivity of 79.4% and specificity of 92%. Perez et al[8] evaluated the MRI SWI sequence to differentiate PD from ET and found sensitivity of 93% and specificity of 88% (evaluator with 5 years of experience in neuroimaging) and sensitivity of 93% and specificity of 75% (evaluator with 30 years of experience in neuroimaging).

Comparisons of diagnostic accuracy with other studies should be carefully considered due to the different protocols used, such as the thicknesses of slices and a varying degree of severity. Our sample of PD patients had a mean of MDSUPDRS part III (scale of clinical severity) score of 35.5 (during ‘on’ state) - a little higher than the aforementioned studies.

Practical aspects and considerations

The N1 evaluation was not able to differentiate ET patients from individuals with HC since N1 preservation is expected in both groups. We found two ET patients with a bilateral absence of N1 in both evaluator’s readings and in two other patients with at least one N1 absent. The absence of the nigrosome-1 area in patients with ET could be due to a deficient resolution of the method or the not-fully established relationship between ET and a higher risk of PD. ET patients have a four-times higher risk of developing future PD than matched controls.[28] The four ET patients, aged 50 and over, with abnormal nigrosome-1 imaging had the onset of the disease. None had a substantial response to alcohol and three did not have a positive family history of ET. These characteristics (later onset, non-responsiveness to alcohol, and negative family history) may constitute a subset of ET possibly more prone to develop PD.[29] Also, four healthy individuals had an imaging with the absence of at least one N1. Previous studies have shown

that healthy individuals can present higher susceptibility values of dorsolateral SN[30] and that, with aging,[31] there is an increase in brain iron content, especially in the pallidum, as well as in the SN. Using MRI T2,* Novellino et al[32] demonstrated an increase of iron with similar distribution in 24 ET patients with normal DAT-SPECT.

A recent study by Cheng et al[33] described anatomical variations in N1. These factors combined with the fact that nigrosome assessment is relatively new in the field of neuroimaging and that an upward learning curve is expected, can lead to misinterpretations of nigrosomal imaging.

We believe that N1 imaging may be a useful tool to differentiate degenerative parkinsonism from ET as well as other parkinsonian conditions. However, at this moment, it is not able to replace the careful clinical examination.

Limitations

The study limitations are:

- The absence of a comparative test of dopamine transporter scan
- the small sample size of patients with ET
- the lack of comparison with other MRI iron-sensitive sequence in all patients

Conclusion

Accurate diagnoses of PD in early stages is a matter of concern, especially regarding the treatment and prognosis of the patient. Bearing in mind the future developing therapies with a disease-modifying effect, a correct diagnosis in vivo will be even more important. The results obtained in our study showed high sensitivity, specificity and accuracy of the Mecho technique for the discrimination between PD and healthy controls, as well as good accuracy to discriminate PD from ET. This sequence can be obtained with the standard sequences of MRI and it does not require additional software. The Mecho sequence may be a useful tool to be applied in clinical practice.

English 48

Article 4

From: Former Student Susi Meire, undated, titled, translated

Comparação entre teste ergométrico e cintilografia miocárdica no precondicionamento isquêmico

Descritores: precondicionamento isquêmico; teste de esforço; cintilografia; diagnóstico por imagem

RESUMO

Fundamento: A atenuação do infradesnível do segmento ST provocada pelo precondicionamento precoce está bem documentada, porém sua expressão cintilográfica permanece controversa.

Objetivo: Avaliar se as atenuações eletrocardiográficas do precondicionamento durante testes sequenciais estão associadas a modificações simultâneas das imagens de perfusão miocárdica em indivíduos com doença coronariana.

Métodos: 23 pacientes, idade média 64,5 anos, 19 (82,6%) do sexo masculino e todos com lesão coronária de pelo menos 60%. A medicação foi suspensa por cinco dias. Dois testes sequenciais foram realizados após o exame de seleção, e o terceiro após sete dias. Nos testes de precondicionamento e contraprova o radiofármaco foi administrado no tempo de aparecimento do infradesnível de ST de -2,0 mm e/ou dor precordial anotados no teste de seleção, com posterior aquisição das imagens de perfusão.

Resultados: No teste de precondicionamento houve aumento do tempo para o aparecimento da depressão do segmento ST de 1,0 e 2,0 mm em relação ao teste inicial ($p<0,001$). A redução do valor de ST entre os três testes foi significativa ($3,8\pm0,8$; $2,3\pm0,6$; $3,1\pm1,0$) $p<0,001$. Houve redução nos escores de perfusão de estresse e escore da diferença ($p=0,045$ e $p=0,03$) entre o primeiro e o segundo testes, sem diferença na extensão da área de isquemia entre as três etapas detectadas pela cintilografia.

Conclusão: Houve melhora eletrocardiográfica induzida pelo precondicionamento isquêmico em maior proporção do que a melhora das respectivas imagens de perfusão miocárdica. Não houve associação entre a magnitude da redução da depressão de ST e da redução do escore de perfusão miocárdica.

INTRODUÇÃO

O precondicionamento isquêmico foi reconhecido há cerca de 25 anos. Embora descrito inicialmente no músculo cardíaco em experimentos animais[1], este fenômeno manifesta-se em outros órgãos como cérebro, fígado, rins[2] e musculatura esquelética[3]. O precondicionamento é conceituado como o aumento da tolerância celular à isquemia e lesão de isquemia/reperfusão induzido por curtos episódios de redução do fluxo sanguíneo prévios à ocorrência de isquemia prolongada.

Duas fases de proteção são reconhecidas: fase inicial, designada precondicionamento clássico ou precoce, e fase tardia, o precondicionamento tardio.

A atenuação eletrocardiográfica observada nas salas de cateterismo após momentos de isquemia resultantes da insuflação do balão foi também documentada durante episódios isquêmicos diários provocados por exercício físico[4] e em testes ergométricos sequenciais[5-9]. Dois estudos foram publicados com o objetivo de evidenciar o precondicionamento isquêmico precoce em imagens de cintilografia de perfusão miocárdica, com a utilização de técnicas distintas, isótopos diferentes (Tálio-201 e Tetrofosmin-TC-99m) e resultados divergentes[10,11]. Permanece por esclarecer se as modificações eletrocardiográficas do precondicionamento isquêmico apresentam estreita relação com as alterações perfusionais observadas nos métodos de imagem, com o radiotraçador sestamibi-Tc-99m habitualmente empregado na prática cardiológica brasileira.

OBJETIVO

1) Avaliar se a atenuação eletrocardiográfica associada ao fenômeno do precondicionamento precoce, durante e após a realização de testes ergométricos seqüenciais, corresponde a modificações simultâneas das imagens de cintilografia de perfusão miocárdica com sestamibi-Tc-99m, em indivíduos com doença arterial coronariana documentada.

2) Avaliar a correlação entre a magnitude do infradesnível de ST com o escore de perfusão pela cintilografia miocárdica.

MATERIAL E MÉTODOS

Os pacientes foram provenientes da Seção Médica de Medicina Nuclear e da Seção Médica de Provas Funcionais do Serviço de Reabilitação Cardiovascular do Instituto Dante Pazzanese de Cardiologia. Esta pesquisa foi aprovada pela Comissão de Ética e Pesquisa desta Instituição. Todos os pacientes concordaram em participar e assinaram o Termo de Consentimento Livre e Esclarecido.

Foram selecionados 23 pacientes, de ambos os sexos, entre 18 e 75 anos, que apresentavam testes ergométricos compatíveis com resposta isquêmica do miocárdio por infradesnivelamento do segmento ST $\geq$ 2,0mm (TS- teste de seleção) e imagens cintilográficas com hipoperfusão transitória.

Os critérios de inclusão envolveram pacientes com doença arterial coronáriana (DAC) crônica documentada por cineangiocoronariografia e lesão obstrutiva superior a 60%; clinicamente estáveis; infradesnível do segmento ST de $\geq$ 2,0mm e cintilografia de perfusão miocárdica compatível com isquemia (hipocaptação transitória). Critérios de exclusão: fração de ejeção inferior a 40 %; doença valvar; hipertrofia ventricular esquerda; miocardiopatia hipertrófica; distúrbio de condução intraventricular com complexo QRS igual ou maior a 120 ms; doença de tronco de coronária esquerda; síndrome de pré-excitação ventricular; presença de marcapasso; ou qualquer outra condição que pudesse comprometer a análise eletrocardiográfica.

Os pacientes foram orientados a não se exercitar além de suas atividades habituais no período do estudo. Os medicamentos de ação antiisquêmica, e outras substâncias que pudessem interferir no mecanismo do precondicionamento ou na análise eletrocardiográfica, foram interrompidos por cinco dias.

Testes ergométricos

Os pacientes selecionados foram submetidos a duas etapas de avaliação. A primeira etapa consistiu na realização de dois testes ergométricos sequenciais, sendo o segundo realizado após repouso de quinze a vinte minutos, com o objetivo de acionar o precondicionamento isquêmico. No primeiro teste (T1) foram anotados os tempos (em segundos) para o aparecimento do infradesnível do segmento ST de 1,0 e 2,0 mm, dor precordial (quando presente), frequência cardíaca e pressão arterial correspondente. No segundo teste (T2-precondicionamento), foi administrado o radiofármaco sestamibi-Tc-99m no momento de aparecimento do infradesnivelamento de 2,0 mm. Na segunda etapa, foi realizado novo teste ergométrico (T3-contraprova) e administrado o radiotraçador no mesmo momento do infradesnível do segmento ST de 2,0 mm, anotado no primeiro teste (T1).

O protocolo utilizado nas duas etapas foi o mesmo adotado no teste de seleção, Bruce ou Bruce modificado. Os critérios de interrupção do primeiro teste da primeira etapa (T1) foram os classicamente adotados nas diretrizes brasileiras para teste ergométrico[12]. Foi considerado para registro e análise eletrocardiográfica o maior valor do infradesnível do segmento ST da derivação MC5. Os testes foram realizados no equipamento computadorizado APEX 2000® (TEB – Tecnologia Eletrônica Brasileira, São Paulo, Brasil) que também comandava automaticamente a esteira APEX 200.

Cintilografia de perfusão miocárdica

O equipamento utilizado foi a Câmara Millenium VG (General Electrics Medical Sistems, Milwaukee, EUA) dotada de dois detectores de cintilação angular a 90 graus, com colimadores de furos paralelos de alta resolução e baixa energia. Definiu-se a janela de 10% para o fotopico de energia de 140 KeV característico de Tecnécio-99 metaestável. As imagens foram adquiridas a cada 30 segundos, num total de 30 projeções nos diversos ângulos, sendo 15 para cada cabeça de detecção, de forma intermitente (“Step and Shoot”). As imagens foram captadas pela técnica de tomografia por emissão de fóton único sincronizada com eletrocardiograma, também chamada “gated-SPECT”. As imagens digitais foram obtidas em uma matriz 64 x 64 e todas as informações armazenadas em disco óptico para processamento imediato e posterior gravação em CD.

O rádiofármaco empregado foi o 2-metoxi-isobutil-isonitrila (MIBI), marcado com Tecnécio-99m metaestável (sestamibi-Tc-99m) na dose de 22 ± 2 mCi/paciente/etapa. Para pacientes com peso corpóreo superior a 90Kg, a dose empregada foi 0,31 mCi/Kg de peso. Na etapa de repouso utilizou-se dose semelhante de rádiofármaco empregada na fase de esforço, no protocolo de dois dias; no protocolo de um dia, a dose injetada na fase de repouso correspondeu a um terço da dose de esforço (8 a12 mCi).

As imagens correspondentes aos dois testes do protocolo (T1 e T2) foram comparadas àquelas do teste de seleção (TS) para observar a associação entre as alterações eletrocardiográficas e as imagens cintilográficas.

As imagens de estresse e repouso foram comparadas por análise visual e técnicas habitualmente empregadas na atualidade[13-16]. Para a avaliação da extensão e magnitude das alterações de perfusão foram empregadas análises qualitativa, semi-quantitativa e quantitativa. Para a analise qualitativa foram consideradas perfusão normal, hipocaptação transitória (isquemia), hipocaptação fixa (fibrose) e hipocaptação fixa e transitória (isquemia periinfarto ou coexistência de fibrose e isquemia). Para a análise semiquantitativa foi utilizado o sistema de escores que variou de 0 a 4 para discriminar o grau de perfusão no território afetado, onde 0 é

perfusão normal e 4 é ausência de perfusão[17]. Na análise quantitativa, a extensão do território miocárdico acometido foi avaliada pela análise dos cortes tomográficos do ventrículo esquerdo, dividindo-o em 17 segmentos e comparados entre as diferentes etapas do estudo. Classificou-se a extensão do miocárdio acometido em pequena (1 a 2), moderada (3 a 4) ou extensa (≥5), de acordo com o número de segmentos envolvidos[16]. O somatório das notas atribuídas para cada segmento foi considerado para a imagem de repouso (SRS), esforço (SSS) e a diferença entre elas (SDS) e utilizadas para refletir a área de isquemia[18]. Para análise dos casos deste estudo o SSS foi classificado em menor que quatro, entre quatro e oito e acima de oito (discretamente, moderadamente e francamente anormal, respectivamente). Na análise do escore da diferença (SDS) obtido pela fórmula: SSS – SRS, a diferença igual a 0 não sugeriu isquemia miocárdica transitória, e a diferença de escore maior que 2 foi considerada isquemia transitória[19].

Análise estatística

As características e resultados dos testes da amostra estudada foram descritos por estatística de frequencias, absoluta (n) e relativa (%), quando medida qualitativa, e por estatísticas sumárias de média, desvio padrão (dp) e mediana, quando medida quantitativa.

A avaliação entre as três etapas dos testes foi feita por análise de variância (ANOVA) para medidas repetidas (Neter, 1996), quando a medida quantitativa não rejeitou a distribuição normal, ou ANOVA não paramétrica para dados ordinais quando a medida quantitativa rejeitou distribuição normal ou quando qualitativa ordinal (Brunner e Langer, 2000). Nestes casos, a correção de Bonferroni (Siegel, 1988) foi aplicada no nível descritivo do teste (valor de p) para as comparações entre pares de etapas. Quando as categorias da medida qualitativa não tinham relação de ordem foi aplicado o método Kappa (Fleiss, 1981) para avaliação da concordância entre as respostas.

Para avaliar a associação entre medidas do teste ergométrico e medidas da cintilografia, as diferenças relativas (%) entre as etapas 0 e 1 (□01) e entre 1 e 2 (□12) foram medidas nos dois casos e a correlação entre elas avaliada por método de Pearson (Pereira, 2010).

O nível de significância dos testes foi arbitrado em 5%, ou seja, diferenças foram consideradas significativas quando o nível descritivo do teste (valor de p) foi menor que 5%. A execução dos cálculos estatísticos e a elaboração das tabelas foram realizadas com o auxílio dos softwares: SPSS for Windows versão 19.0 e MS Office Excel.

RESULTADOS

Dos 23 pacientes selecionados, 19 eram do sexo masculino e quatro do feminino, com idade entre 48 e 75 anos, média de 62,04 (dp=6,84). As características clínicas e distribuição dos fatores de risco encontram-se expostos na tabela 1.

O protocolo de Bruce original foi aplicado em oito pacientes (34,8%) e Bruce modificado em 15 pacientes (65,2%). Para a comparação dos resultados dos testes ergométricos utilizamos os valores do teste de seleção (TS), do segundo teste da primeira etapa (teste do precondicionamento isquêmico precoce – T2) e o teste da segunda etapa (teste de contraprova – T3).

Houve redução significativa na média da magnitude do infradesnível do segmento ST no momento de injeção do radiofármaco, bem como no pico do esforço (1,5±0,40; 2,33±0,58) no T1 em comparação ao TS (2,92±0,72; 3,67±0,79) (Tabela 2).

O tempo total de exercício em segundos foi menor nos testes 2 e 3 (486±115; 470±289; p=0,518 e p=0,015) em comparação com o teste de seleção (516±84), sem diferença entre as etapas (p=0,95). O tempo de aparecimento do infradesnivelamento de ST de -1,0 e -2,0 mm foi maior no T2 e menor no T3 (289±125; 374±109), p< 0,001. Também houve redução no tempo de normalização do segmento ST após o exercício no T2, p<0,001. A administração do radiofármaco foi realizada em tempo menor quando comparado com o exame inicial, porém não houve diferença significativa entre as etapas (Tabela 2).

A redução da magnitude do infradesnivelamento do segmento ST pico foi estatisticamente significativa entre as três etapas (3,67 ± 0,79; 2,33 ± 0,58; 3,14 ± 1,05) p < 0,05;

bem como no momento de injeção do sestamibi-Tc-99m, e no sexto minuto da fase de recuperação (Figura 1).

Os valores do produto da frequência cardíaca pela pressão arterial (PFP) entre o teste de seleção e o precondicionamento foram semelhantes no momento correspondente aos infradesnivelamento de -1,0 e -2,0mm; mas diferiram nos momentos de injeção do sestamibi-Tc-99m e pico de esforço.

A média da frequência cardíaca pico não diferiu entre o exame de seleção (145 ± 12) e o teste de precondicionamento (142 ± 13), sendo menor no teste de contraprova (135 ± 11). A frequência cárdica média para a injeção do radiofármaco foi 140 ± 12 no teste de seleção, 134±13 na primeira etapa e 128±10 na segunda etapa. Houve diferença significativa entre as etapas e entre o teste de seleção e de contraprova; contudo esta diferença foi inerente à metodologia empregada.

A dor precordial durante o teste de seleção esteve presente em 11 pacientes (47,8% do total). Durante o segundo teste apenas cinco pacientes apresentaram angina ao esforço, ou seja, redução de 54% em relação ao primeiro teste. No terceiro teste, um paciente não reproduziu o sintoma inicial. Contudo, entre os que apresentaram o sintoma nas três fases, não houve diferença significante entre os tempos de aparecimento e desaparecimento da dor precordial.

O mesmo comportamento pode ser observado quanto à presença de arritmias. Em 12 pacientes houve o aparecimento de arritmias durante o esforço, e em seis a arritmia ocorreu também na segunda etapa (T3). Desta forma, houve redução de 50% na ocorrência de arritmias durante o teste de precondicionamento (Tabela 2).

Os escores de perfusão de esforço (SSS) e a diferença entre o repouso e esforço (SDS) mostraram redução significativa da etapa de seleção para o precondicionamento. Contudo não houve redução no percentual da área isquêmica (Tabela 3).

A magnitude do infradesnível de ST e os valores de SSS não mostrou correlação entre TS e T1 (r=15 e p=0,492), porém houve fraca correlação entre os testes T1 e T2 (r=0,36 e p=0,092).

Dezoito (78,3%) pacientes apresentaram redução igual ou superior a 1,0 mm no teste de precondicionamento, porém apenas sete (38,9%) tiveram melhora concomitante na imagem da perfusão, representada pela redução do SSS e do SDS, sendo que dois deles apresentaram normalização completa da perfusão (Figuras 2 e 3). Onze pacientes tiveram atenuação do infradesnivelamento do segmento ST, sem melhora correspondente nas imagens de perfusão e nos valores dos escores. Assim, cinco pacientes (21,7%) não apresentaram modificação eletrocardiográfica, e três também não apresentaram melhora perfusional.

A análise das variáveis quantitativas das imagens de cintilografia de perfusão não mostrou alterações significativas do percentual de área isquêmica, função ventricular de repouso e após esforço. A redução da área de isquemia entre o teste de seleção e o do precondicionamento foi discreta.

A diminuição do SSS foi observada entre a etapa de seleção e precondicionamento, e entre o teste precondicionamento e contraprova. O mesmo foi observado para o escore da diferença (SDS) entre as três etapas (Tabela 3).

A correlação entre as variáveis: redução do infradesnível de ST igual ou maior que 1,0mm, redução do escore de estresse e redução do escore da diferença maior que dois, foi muito fraca, com coeficiente de correlação r=0,15 (p=0,492) para o infradesnível no momento da injeção do radiofármaco, e r=0,10 (p=0,629) para o infradenível de ST no pico do esforço (figura 4).

DISCUSSÃO

Nossos resultados mostraram redução significativa do infradesnivelamento do segmento ST consequente ao precondicionamento isquêmico, aumento no tempo de aparecimento do infradesnível de -1,0 e -2,0 mm, bem como na normalização mais rápida da depressão do segmento ST. A ocorrência de angina e de arritmias também apresentou redução relevante, 45,4% e 50%, respectivamente. Estes dados são concordantes com os de outras pesquisas[4,5,8,20], e sugerem que os mecanismos envolvidos no precondicionamento interfiram no padrão elétrico celular, tornando o miocárdio menos vulnerável à ação deletéria da isquemia.

A redução dos valores de SSS e SDS nas imagens de perfusão observada neste estudo foi similar aos dados de Koutelou et al[11]. Estes autores observaram redução da extensão da área de isquemia, o que não ocorreu neste estudo. Bogaty et al[10], em investigação semelhante com Tálio-201, também não observaram redução na extensão da área isquêmica. Essas diferenças podem estar relacionadas aos isótopos e protocolos de aplicação utilizados nas três pesquisas.

Bogaty et al. (2001)[10] aplicaram testes ergométricos sequenciais em duas condições distintas e com três semanas de intervalo. Foi utilizado o mesmo valor do duplo produto do primeiro teste como ponto de referência para a administração do radiofármaco (Tálio-201) no segundo teste, no qual haveria o efeito do precondicionamento. Ocorreu evidente atenuação eletrocardiográfica da isquemia, contudo sem modificações significativas nas imagens de perfusão e extensão da isquemia.

Koutelou et al[11] utilizaram a técnica de duplo isótopo de forma não convencional, ou seja, realizaram o primeiro esforço com Tálio-201 e o segundo, após trinta minutos, com tetrosformim-Tc-99m. A fase de repouso foi realizada algumas horas após o segundo teste, com tetrofosmin-Tc-99m. Esta inversão na realização do protocolo de duplo isótopo visou a facilidade logística, porém pode favorecer resultados de imagens normais no segundo teste, por sobreposição de atividade radiológica, mesmo com calibração diferenciada da gama-câmara.

A técnica de realização da cintilografia de perfusão miocárdica com duplo isótopo diminui o tempo total do exame, porém o ^{201}Tálio apresenta maior radioatividade, maior custo e menor disponibilidade no Brasil, motivo pelo qual a técnica de duplo isótopo está em desuso na prática cardiológica. O sestamibi-Tc-99m é o isótopo mais utilizado em nosso país. Apresenta características similares às do tetrofosmin-Tc-99m, porém não havia sido ainda demonstrada a presença do precondicionamento com este radiotraçador exclusivamente; tampouco a correlação entre o grau de atenuação eletrocardiográfica e a melhora das imagens cintilográficas.

A análise do somatório do escore de estresse e do escore da diferença mostrou redução significativa na etapa de precondicionamento em comparação ao teste de seleção. No entanto, não foi observada correlação entre a magnitude do infradesnivelamento de ST no momento da injeção do radiofármaco e a redução do escore de estresse. Tampouco houve correlação com o valor da depressão de ST no pico do exercício.

A comparação entre as etapas de precondicionamento e de contraprova mostrou que houve redução nos valores do somatório dos escores de estresse e da diferença. Houve também associação e concordância "*suave"* (p=0,062; Kappa=0,39) entre o aumento do escore de perfusão e o aumento do infradesnivelamento no pico do exercício (r=0,36 e p=0,08), porém sem associação com o aumento do infradesnível do ST no momento da injeção do radiofármaco (r=0,22 e p=0,30). O pequeno número de pacientes e a menor carga de trabalho realizada no teste de contraprova em relação ao teste de seleção podem ter sido responsáveis por esta fraca correlação (figura 4).

Nossa pesquisa mostrou que as modificações eletrocardiográficas no teste ergométrico induzidas pelo precondicionamento isquêmico foram identificadas com maior frequência do que as alterações das imagens perfusionais. Também observamos que a resposta clínica foi relevante, com redução em torno de 50% na manifestação de angina e de arritmias.

Os resultados discordantes entre os métodos ergométricos e cintilográficos estão relacionados à probabilidade pré-teste de DAC. Mattera et al. (1998)[21] observaram que, em pacientes com alta probabilidade pré-teste, 15% dos que apresentavam teste de esforço normal tinham alterações de perfusão miocárdica, enquanto 41% dos pacientes com resultados ergométricos anormais não apresentavam alterações nas imagens cintilográficas.

De modo semelhante, algumas discrepâncias entre o teste ergométrico e a cintilografia de perfusão miocárdica manifestaram-se também na avaliação do precondicionamento isquêmico. Nesta pesquisa observamos que nem todos os indivíduos apresentam este mecanismo protetor, manifestado por alterações eletrocardiográficas ou cintilográficas. Todavia, até o momento, o teste ergométrico parece ser a melhor ferramenta para detectar a presença do precondicionamento isquêmico. A cintilografia pode ser uma das formas de avaliação eficaz, porém ainda não está claro o porquê da melhora eletrocardiográfica não se traduzir em melhora da perfusão em alguns

pacientes. Estudos com maior número de pacientes poderão elucidar a real utilidade da cintilografia miocárdica na avaliação do precondicionamento isquêmico.

Limitações do estudo

O número pequeno de pacientes e a presença significante de diabetes pode ter influenciado nossos resultados. Igualmente, a inclusão de pacientes com infarto do miocárdio prévio, ainda que o eletrocardiograma de repouso fosse normal ou sem alterações que pudessem influenciar a análise eletrocardiográfica. Contudo, a presença de pequenas áreas de fibrose sem expressão eletrocardiográfica pode ter contribuído para diminuição da sensibilidade das imagens cintilográficas. Outra possível limitação seria a proporção de pacientes com estenose em artéria circunflexa.

CONCLUSÕES

Os resultados deste estudo permitem concluir que:

1) A demonstração do precondicionamento isquêmico precoce pelas atenuações eletrocardiográficas em testes ergométricos sequenciais ocorreu em maior proporção do que a observada nas respectivas imagens de cintilografia de perfusão miocárdica.

2) Não houve correlação entre os valores do infradesnivelamento do segmento ST com o escore de perfusão e com a extensão da área de isquemia detectada pela cintilografia.

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English 48

A Comparison Between Exercise Testing and Myocardial Scintigraphy in Ischemic Preconditioning

Key words: Ischemic preconditioning; Exercise Testing; Scintigraphy; Diagnostic imaging.

ABSTRACT

Background: The attenuation of the ST segment depression caused by early preconditioning is well documented, but its scintigraphy expression remains controversial.

Objective: To evaluate whether the attenuation of electrocardiographic preconditioning during sequential testing is associated with simultaneous changes of myocardial perfusion imaging in patients with coronary disease.

Methods: 23 patients, mean age 64.5 years, of these 19 (82.6%) were male and all had coronary lesion of at least 60%. The medication was suspended for five days. Two sequential tests were performed after the selection phase, and the third after seven days. In the preconditioning and third tests, the radiopharmaceutical was administered at the onset time of ST segment depression of -2.0mm and/or pain, noted in the selection testING, with subsequent acquisition of perfusion imaging.

Results: In preconditioning testing, there was an increase in the onset time of ST segment depression of 1.0 and 2.0 mm regarding the baseline testING ($p<0.001$). Reducing the ST segment value among the three tests was significant (3.8 ± 0.8; 2.3 ± 0.6; 3.1 ± 1.0), $p<0.001$. There was a reduction of exercise testing perfusion and difference scores ($p=0.045$ and $p=0.03$) between the first and second tests, with no difference in the ischemic defect size between the three phases detected by scintigraphy.

Conclusion: There was improvement of the ST segment depression induced by ischemic preconditioning in greater proportion than the improvement of their myocardial perfusion imaging. There was no association between the magnitude of the ST segment depression reduction and the myocardial perfusion score reduction.

English 48

INTRODUCTION

Ischemic preconditioning has been recognized since 25 years ago. Although it was initially described in the cardiac muscle in animal models,[1] this phenomenon occurs in other organs such as brain, liver, kidney[2] and skeletal muscles.[3] This preconditioning has the concept of increased cellular tolerance to ischemia and ischemia/reperfusion lesion induced by short episodes of blood flow reduction prior to the prolonged ischemia occurrence.

Two protection phases are recognized: baseline phase, the so-called early or classic preconditioning, and the late phase, late preconditioning or second window.

The electrocardiographic attenuation observed during the catheterism procedures following ischemia episodes resulting from the balloon inflations was also documented during daily ischemic episodes induced by physical activities and sequential exercise testing.[5-9] Two studies were published aiming to have evidences of early ischemic preconditioning scintigraphic imaging of myocardial perfusion, using distinct techniques, different isotopes (Tl-201 and Tc-99m-terofosmin) and diverging results. It is unclear if electrocardiographic modifications of ischemic preconditioning bear a close relation with perfusion alterations observed in the imaging methods, as usually used the Tc-99m sestamibi radiotracer in the cardiology practices.

OBJECTIVE:

1. To evaluate if the electrocardiographic attenuation associated to the early preconditioning phenomenon during and after the sequential exercise testing, corresponds to simultaneous modifications of myocardial perfusion scintigraphic imaging using Tc-99m-terofosmin, in individuals with reported coronary artery disease.

2. To assess the correlation between the ST segment depression magnitude with the perfusion score through myocardial scintigraphy.

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METHODS

The patients were screened from the Nuclear and Medical Unit and from Cardiovascular Reheabilitation Functional Tests Medical Unit at Dante Pazzanese Cardiology Institute. Informed consent was obtained from all the study's participants.

23 patients, male and female, between ages 18 and 75 years, who presented exercise testing results compatible to myocardial ischemic response by ST segment depression ≥2.0mm (ST, selection test) and transitory hypoperfusion scintigraphy imaging.

The inclusion criteria were: patients with chronic coronary arterial disease (CAD) through coronary angiography and obstructive lesion superior to 60%; clinically stable; ST segment depression ≥ 2.0mm; and myocardial perfusion scintigraphy compatible to ischemia (transitory uptake). The exclusion criteria were: inferior ejection fraction at 40%; valvular disease, left ventricular hypertrophy; hypertrophic myocardiopathy; intraventricular conduction disorder with QRS-complex equal or greater than 120 ms; left main coronary artery disease; ventricular pre-excitement syndrome; the presence of a peacemaker; or any other condition that could put the electrocardiography analysis at risk.

The patients were told not to do more than two of their habitual exercise activities during the study period. The anti-ischemic medications and other substances which could interfere in the preconditioning mechanism or in the electrocardiography analysis, were interrupted for 5 (five) days. This interruption is routinely adopted by the nuclear medicine services for myocardial exams and it was repeated in the protocol phases.

Exercise Testing

The patients enrolled were subjected to 2 assessment phases. The first phase consisted of two sequential exercise tests as for the second performed after a 15-20 min rest aiming to trigger the ischemic preconditioning. In the first test (T1), times in seconds for the onset of ST segment depression of 1.0 and 2.0 mm, precordial pain (when present), heart rate and corresponding blood pressure, were taken. In the second test (T2-preconditioning), the sestamibi-Tc-99m

radiopharmaceutical at the time of onset depression of 2.0 mm. in the second phase, a new exercise testing was performed (T-3 counter-proof testing) and the radiotracer was administered at the same time as of the ST segment depression of 2.0 mm, as taken in the first test (T1).

The protocol used in the two phases was the same as for the ST segment, modified Bruce or Bruce. The interruption criteria in the first test of the first phase (T1) were the ones usually adopted in the Brazilian guidelines[12] for treadmill exercise testing. The greater score of the ST segment depression for the MC5 derivation was considered for electrocardiographic analysis and record. The testing was performed using a computerized device, APEX 2000® (TEB – Tecnologia Eletrônica Brasileira, São Paulo, Brazil), which also controlled the APEX 200 treadmill automatically. The interval between selection testing (Ts) and the first phase of protocol (T1 and T2) ranged between 10-30 days, and, 7-10 days for the second phase (T3) (Figure 1).

Myocardial Perfusion Scintigraphy Imaging

The Millenium VG camera (General Electrics Medical Systems, Milwaukee, USA) was used, featuring two angular scintillation detectors at 90º with high-resolution and low-energy hole collimators . A 10% window was centered on the 140 keV x-ray peak characteristic of Technectium-99m. Imaging was taken every 30 seconds, with a total of 30 projections from different angles, 15 of these for each detection head, intermittently (“Step and Shoot”). Imaging was captured using single-photon emission computed tomography synchronized with electrocardiogram, also called “gate-SPECT.” Digital imaging was obtained using 64 x 64, 16-bit-matrix, and all information was stored in optical disk for immediate process and posterior recording in CD.

The radiopharmaceutical used was 2-metoxi-isobutil-isonitrila-99mTc (Sestamibi- 99mTc) at a dose of 22 ± 2 mCi/patient/phase. For patients with body weight superior to 90Kg, the dose used was 0.31 mCi/Kg. At the rest phase, we used a dose similar to the radiopharmaceutical when used

at the exertion phase, at the 2-day protocol; at the 1-day protocol, the dose injected at the rest phase accounted for one third of the exertion dose (8-12 mCi).

The radiology exposition rate was measured based on the doses administered at rest and during exercise selection testing, added to the doses used in the 2 protocol phases (T2 and T3). Additional rest imaging was performed during the protocol phases not to overcome the recommended maximum exposition rate.

The corresponding images to the two protocol tests (T2 and T3) were compared to those of the selection test (Ts) to observe the correlation between electrocardiographic alterations and the scintigraphy imaging. Rest imaging used for comparison was the same as that of the selection testing.

Rest and stress imaging was compared through visual analysis and techniques frequently used nowadays.[13-16] For the assessment of extent and magnitude of perfusion alterations, semi-quantitative and quantitative analyses were used. For the qualitative analysis, normal perfusion, transitory hypocaptation (ischemia), fixed hypocaptation (fibrosis) and transitory and fixed hypocaptation (periinfarct ischemia or coexistence of fibrosis and ischemia), were considered.

For the semi-quantitative analysis, a score system was used which ranged 0-4 to discriminate (the perfusion defect size), where 0 is normal perfusion and 4 is absence of perfusion.[17] For the quantitative analysis, the affected myocardial defect size was assessed by left ventricle axis tomogram analysis, dividing it into 17 segments and compared to the different study phases. The affected myocardial defect size was ranked as small (1-2), moderate (3-4), or large (≥5), according to the number of segments involved.[16] The summed scores attributed to each segment was considered for the rest score (SRS), summed stress score (SSS) and the summed difference score (SDS) between them, and was used to represent the ischemia size.[18] For analysis of the study cases, the SSS was ranked as follows: lower than 4, between 4 and 8, and greater than 8 (mild, moderate and absolutely normal, respectively). For the difference score (SDS) analysis obtained

by the formula: SSS - SRS, the difference ranked as 0 did not suggest transitory myocardial ischemia, and the difference ranked as greater than 2 was considered transitory ischemia.[19]

Statistical Analysis

The studied sample test characteristics and results were described by absolute (n) and relative (%) frequencies when graded qualitatively, and by average rate, standard deviation (SD) and median statistics, when graded quantitatively. ***T*** **test**

The assessment between the three test phases was made by variant analysis (ANOVA) for repetitive measures, or non-parametric ANOVA for ordinal data when quantitative measures rejected normal distribution or when ordinal qualitative (Brunner and Langer, 2000). In these cases, the Bonferroni correlation (Siegel,1988) was used in the test level described (*p* value) for the comparisons between phase pairs. When qualitative measure categories did not have an order sequence (ordinal scale), the Kappa method (Fleiss, 1981) was used for the assessment of answer agreement.

To assess the association between exercise testing measures and scintigraphic scores, the relative differences (%) between phases 0 and 1 (□01) and between 1 and 2 (□12) were measured in the two cases and the correlation between them was assessed using the Pearson method (Pereira, 2010).

The statistical tests were two-sided with a significant p-value <0.05. Statistical analyses and tables were made using the following softwares: SPSS for Windows version 19.0 and MS Office Excel.

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Results

Of the 23 patients screened, 19 were male and 4 female, ages 48-75 years, with average age of 62.04 (SD=6.84). Clinical characteristics and risk factor distributions are in Table 1.

Bruce protocol was used in 8 patients (34.8%), and modified Bruce in 15 patients (65.2%). For the exercise testing result comparison, we used test scores from the ST segment, from the second test of the first phase (early ischemic preconditioning – T2), and from the second phase (counter-proof – T3).

There was a significant reduction of ST segment depression magnitude score at the moment of radiopharmaceutical infection as well as at the exertion peak (1.5±0.40; 2.33±0.58) during T1 in comparison with ST (2.92±0.72; 3.67±0.79) - Table 2.

The exercise time in seconds was lower during tests 2 and 3 (486±115; 470±289; p=0.518 and p=0.015), respectively, in comparison with selection test (Ts) - 516±84 – with no difference between phases (p=0.95). The onset time for the ST segment depression of -1.0 and -2.0 mm was greater during T2 and lower during T3 (289±125; 374±109), p< 0.001. Also, there was a reduction in the St segment recovery time during T2, p<0.001. The radiopharmaceutical was administered in lower time when compared to the baseline phase; however, there was no significant difference between phases (Table2).

The magnitude reduction of the peak ST segment depression was statistically significant between the three phases - 3.67 ± 0.79; 2.33 ± 0.58; 3.14 ±1.05 – and p < 0.05, as well as at the moment of the sestamibi-Tc-99m injection, and at the sixth minute during recovery phase (Figure 1).

The scores from the product of blood pressure and heart rate – also called double product (DP) – between the selection and preconditioning testing, were similar at the corresponding moment of depression of -1.0 and -2.0; however, they differ at the moment of the sestamibi-Tc-99 injection and exercise peak.

The average peak heart rate did not differ between selection testing (145 ± 12) and preconditioning testing (142 ± 13), being lower during the counter-proof testing (135 ± 11). The average heart rate for the injection of radiopharmaceutical was 140 ± 12 during the selection testing, 134±13during the first phase, and 128±10 during the second. There was a significant

difference between phases and between the selection and counter-proof testing; however, this was inherent to the method applied.

The precordial pain during the selection testing was present in 11 patients (47,8%). During the second test, only 5 patients presented angina during exercise, that is, a reduction of 54% in relation to the first test. During the third test, a patient did not present the baseline symptom. Meanwhile, among those who presented the symptom during the 3 phases, there was no significant difference between the onset time and the precordial pain disappearance.

The same behavior can be observed due to the presence of arrhythmias. There was the occurrence of arrhythmia in 12 patients during the exercise testing, and in 6 (of these???) there was the occurrence of arrhythmia in the second phase (T3). So, there was an arrhythmia occurrence reduction of 50% during the preconditioning testing. (Table 2)

The stress scores (SSS) and the difference scores (SDS) showed a significant reduction during selection testing for preconditioning. However, there was no ischemic defect size reduction (Table 3).

The ST segment depression magnitude and SSS did not show a correlation between ST and T1 (r=15 and p=0.492); however, there was a weak correlation between tests T1 and T2 (r=0.36 and p=0.092).

Eighteen patients (78.3%) had reductions ≥1.0 mm during the preconditioning testing, but only 7 (38.9%) had concomitant perfusion imaging improvement represented by the SSS and SDS reduction, as two of them having complete perfusion recovery (Figures 1 and 2). 11 patients had ST segment depression attenuation, without corresponding improvement in the perfusion imaging and its scores. So, 5 patients (21.7%) did not show electrocardiographic modifications and 3 did not have perfusion improvement.

The quantitative variables analysis of scintigraphic and perfusion imaging did not show significant alterations of the ischemic defect size and of rest and post-stress ventricular functions. The ischemic defect size reduction between the selection and preconditioning testing was small.

The SSS reduction was observed between the selection and preconditioning phases, and between the preconditioning and counter-proof testing. The same was observed for the difference score (SDS) between the 3 phases (Table 3).

The correlation between the variables: ST segment depression reduction ≥1.0 mm, the stress score reduction and the difference score reduction >2, was very weak, with the correlation coefficient r=0.15 (*p*=0.492) for the depression at the moment of radiopharmaceutical injection, and, r=0.10 (*p*=0.629) for the ST segment depression at exertion peak (Figure 4).

Discussion

Our results showed a significant reduction of the ST segment depression as a consequence of ischemic preconditioning, rise of depression onset time of -1.0 and -2.0 mm, as well as the faster ST segment depression recovery. The occurrence of angina and arrhythmias also showed relevant reduction of 45.5% and 50%, respectively. These data are in agreement with those of other studies,[4,5,8,20] and suggest that the mechanisms involved in the preconditioning interfere in the cellular electrical standard, making the myocardium less vulnerable to ischemic deleterious action.

The reduction in the SSS and SDS scores in the perfusion imaging observed in this study were similar to the data from Koutelou et al.[11] These authors observed a reduction of the ischemic area extension, which did not occur in this study. Bogaty et al.,[10] in similar investigation using Talio-201, also did not observe a reduction of the ischemic area extension. These differences may be related to isotopes and different protocols used in the three studies.

Bogaty et al. (2001)[10] applied sequential exercise testing in two distinctive conditions and with a three-week interval. The same value for the double product in the first testing was used as a reference point for the administration of radiopharmaceutical (Talio-201) in the second testing, in which there would be the effect of preconditioning. There was an evident ischemic electrocardiographic attenuation; however, without any significant modifications in the perfusion and ischemic extension imaging.

Koutelou et al.[11] used the double isotope technique unconventionally, that is, they performed the first exertion using Talio-201 and the second, after 30 minutes, using Tc-99m-tetrosformin. This inversion in following the double-isotope protocol was due to the logistics factors, but it could favor normal imaging results in the second testing, through overlying radiologic activity with gamma-chamber calibration.

The myocardial perfusion scintigraphy technique using double isotope lowered the total testing time; but, Talio-201 presents greater radioactivity, higher costs and less availability in Brazil due to the fact that the double-isotope technique is being less and less used in cardiology practices. Tc-99m sestamibi is the mostly used isotope in our country. It presents characteristics similar to Tc-99m tetrofosmin, but the presence of preconditioning had not been demonstrated using exclusively this radiotracer yet; neither, at any rate, was there the correlation between the electrocardiographic attenuation level and the improvement of scintigraphic imaging scores.

The exertion testing and difference summed score analysis showed a significant reduction in the preconditioning phase in comparison with selection testing. However, a correlation between the ST depression magnitude at the moment of radiopharmaceutical injection and the exertion score reduction, was not observed; neither, at any rate, was there a correlation with the ST depression magnitude at exercise peak.

The comparison between the preconditioning phase and counter-proof phase showed that there was a reduction in the exertion exercise testing and difference summed scores. There was also the "mild" association and concordance (p=0.062); Kappa=0.39) between the rise of perfusion score and the rise of depression at exercise peak (r=0.36 and p=0.08); however, without association with the rise of ST depression at the radiopharmaceutical injection moment (r=0.22 and p=0.30). The small number of patients and the lower workload performed during the counter-proof testing regarding selection testing, may have been responsible for this weak correlation (figure 4).

Our study showed that the electrocardiographic modifications during exercise testing induced by ischemic preconditioning were identified with higher frequency than the perfusion imaging alterations. Also, we observed that the clinical response was relevant, with a reduction of about 50% in angina and arrhythmia manifestations.

The adverse results between exercise testing and scintigraphic methods used are related to the pre-testing probability of CAD. Mattera et al. (1998)[21] observed that, in patients with high probability during pre-testing, 15% of those who presented normal exertion testing had myocardial perfusion alterations, whereas 41% of patients with abnormal exercise testing results did not present scintigraphic imaging alterations.

Similarly, some discrepancies between exercise testing and myocardial perfusion scintigraphy appeared during ischemic preconditioning assessment. In this study, we observed that not all individuals present this protective mechanism, triggered by electrocardiographic or scintigraphic alterations. However, to date, exercise testing seems to be a better tool to detect the presence of ischemic preconditioning. Scintigraphy may be one of the ways to have an effective assessment; yet, it is unclear why electrocardiography attenuation does not correspond to a better perfusion imaging in some patients. Studies with a greater number of patients will be able to elucidate the real utility of myocardial scintigraphy for the ischemic preconditioning assessment.

In the ischemic cascade, perfusion alterations precede electrocardiographic alterations in which ischemia stops adequate radiopharmaceuticals capitation from happening, as well as the coronary flow resulting from exercising, favors a greater sensitivity of myocardial perfusion scintigraphy. It should be noted that preconditioning involves intracellular protection mechanisms against cellular death through ATP conservation. There are changes in the sarcolemal and mytocondrial transmembrane ion flow; there are changes in its sarcoplasmatic concentrations which could affect the cellular electrical range without influencing directly the perfusion. The receptor activation in the myocardial cellular membrane that, on the other hand, trigger the ischemic preconditioning cascade, may affect the adequate radiopharmaceutical capitation. Patients with severe coronary disease and a major reduction of coronary reserve, may have their resources for post-stenosis vasodilatation and intracellular protection run out. Thus, the preconditioning activation does not occur.

Study Limitations

The small number of patients and the significant presence of diabetes mellitus may have influenced our results. Equally, the inclusion of patients with previous myocardial infarct even if the electrocardiogram at rest were normal or without alterations which could influence the electrocardiographic analysis. Though, the presence of small areas of fibrosis without eletrocardiographic alterations could have contributed to a lower reading of scintigraphic imaging. Another possible limitation would be the proportion of patients with stenosis in circumflex artery.

Conclusions

We may conclude from the results obtained in this study that:

1. The demonstration of early ischemic preconditioning through electrocardiographic attenuations in sequential exercise testing, occurred in greater proportion than that observed in respective imaging of myocardial perfusion scintigraphy.

2. There was no correlation between the ST segment depression scores with the perfusion score and with the ischemic defect size detected through scintigraphic imaging.

TABLE 1. Demographic and Clinical Characteristics

	n = 23 (%)	Mean ± SD	Mean
Age, yrs		62.04 ± 6.89	64.00
BMI		27.96 ± 3.43	29.31
GENDER			
Male	19 (82.6)		
Female	4 (17.4)		
Risk Factors			
Hypertension	22 (95.7)		
Hypercholesterolemia	20 (87.0)		
Diabetes	14 (60.9)		
Smoking	6 (26.1)		
Previous MI	8 (34.8)		

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Previous CS	7 (30.4)
Angioplasty	7 (30.4)
MEDICAMENTS	
Beta-blocker	17 (73.9)
Aspirin	21 (91.3)
Statin	19 (82.6)
ACE inhibitors	18 (78.3)
Metformin	14 (60.9)
Glibenclamide	2 (8.7)
SIMPTOMS	
Asymptomatic	8 (34.8)
Typical angina	14 (60.9)
Atypical angina	1 (4.3)

SD=standard deviation; BMI=body mass index; MI=myocardial infarction; CS=cardiac surgery; ACE=angiotensin converting enzyme.

Table 2. Exercise Testing Variables

	T0		T2		T3		*P* value	*P* value	*P* value
Variable	**Mean (dp)**	**Med.**	**Mean (dp)**	**Med.**	**Mean (dp)**	**Med.**	**(T0xT2)**	**(T0xT3)**	**(T2xT3)**
Total time (seconds)	516± 83	480	486 ± 115	462	470± 289	480	0.518	0.015	0.95
T -1.0mm (seconds)	245 ± 96	230	339 ± 130	360	289 ± 125	300	**0.000**	0.071	**0.036**
T -2.0mm (seconds)	367 ± 104	360	431 ± 126	420	374 ± 109	360	**0.001**	1.000	**0.010**
MIBI Time (seconds)	450 ± 87	420	408 ± 102	390	412 ± 97	420	**0.020**	0.024	1.000
TN (seg)	569 ± 191	600	353 ± 194	360	507 ± 140	480	**0.000**	0.431	**0.001**
DP -1.0 mm	21,018 ± 4,408	20,800	22,143 ± 5,116	22,400	19,544 ± 3,257	19,720	0.701	0.115	**0.005**
DP -2.0 mm	24,248 ± 4,654	22,800	25,015 ± 4,862	24,160	22,337 ± 3,775	22,610	1.000	0.250	**0.002**
DP MIBI-Tc 99m	27,270 ± 5,097	27,900	24,423 ± 5,557	23,120	23,245 ± 4,198	22,780	**0,016**	0.000	0.192
DP - peak	28,596 ± 5,008	29,000	25,795 ± 5,852	24,600	24,477 ± 4,814	24,300	**0.011**	0.000	0.112
DP - angina	21,476 ± 4,458	20,850	20,868 ± 2,602	21,300	20,865 ± 3,614	20,655	0.296	0.647	**0.062**
ST - peak	3.67 ± 0.79	-3.50	2.33 ± 0.58	-2.00	3.14 ± 1.05	-3.00	**0.000**	0.034	**0.010**
ST - MIBI-Tc 99m	2.96 ± 0.72	-3.00	1.5 ± 0.40	-1.50	2.34 ± 0.80	-2.50	**0.000**	0.016	**0.000**
ST - R6	1.07 ± 0.40	-1.00	0.6 ± 0.40	-0.50	0.9 ± 0.50	-1.00	**0.000**	0.566	**0.003**
Angina time	379 ± 133	360	336 ± 98	300	389 ± 119	412.5	0.624	1.000	0.978
Time for angina off	155 ± 85	120	120 ± 103	60	159 ± 124	120	0.160	1.000	0.422
Estimated MET	7.78 ± 1.46	7.96	7.39 ± 1.44	7.53	7.15 ± 1.49	7.35	0.484	0.015	0.946
Estimated VO_2	27.27 ± 5.12	27.85	25.88 ± 5.04	25.73	25.11 ± 5.20	5.20	0.484	0.015	0.946
	N	**%**	**N**	**%**	**N**	**%**			
Arrhythmia	12	52.2	6	26.1	12	52.2	0.005	1.000	0.043
Angina	11	47.8	5	21.7	10	43.5	0.005	0.569	0.013

SD=standard deviation; T=time; ex=exercise; TN=time for normalization of ST depression; DP=double-product; ST=ST depression; MIBI-Tc99m=radiotracer; R6=six minute recovery of ST depression; MET=metabolic equivalent; VO2=oxygen uptake

Tabela 3. Myocardial Scintigraphy Variables

VARIABLE	T0		T2		T3		*P* value (general)	*P* value (0x2)	*P* value (0x3)	*P* value (2x3)
	Mean (dp)	Med.	Mean (dp)	Med.	Mean (dp)	Med.				
% ischemia[A]	13.8 ± 10.7	10.0	11.4 ± 7.7	10.0	12.5 ± 7.7	15.0	0.6910[A]	NS	NS	NS
EF baseline[A]	58.3 ± 10.0	57.0	58.5 ± 9.6	58.0	58.1± 10.1	58.0	0.7612[A]	NS	NS	NS
EF post-exercise[A]	5.4 ± 8.8	58.0	59.0 ±10.8	56.0	57.3 ± 8.6	56.0	0.3080[A]	NS	NS	NS
SSS	9.35 ± 6.27	8.0	7.00 ± 6.23	6.0	8.13 ± 6.45	6.0	**0.0675[A]**	**0.045[t]**	0.262[t]	**0.056[t]**
SDS	7.43 ± 5.40	6.0	4.91 ± 3.99	5.0	6.22 ± 4.11	6.0	**0.0406[A]**	**0.030[t]**	0.262[t]	**0.039[t]**
	N	**%**	**N**	**%**	**N**	**%**	***P* value**			
Perfusion changes	23	100	21	91.3	23	100	-			
Fibrosis	8	34.7	8	34.7	8	34.7	0.2470[F]			
EF rest (> 50%)	21	91.2	21	91.3	18	78.3	0.7612[A]			
EF post-exercise (> 50%)	20	86.9	20	86.9	17	73.9	0.3080[A]			
Decrease in EF > 5%	3	13.0	4	17.4	4	17.4	0.8231[A-NP]			
Normal TID (< 1.2)	19	82.6	20	87.0	21	91.3	0.192[A-NP]			

SD=standard deviation; A=ANOVA; t=t student test; EF=ejection fraction; NS=not significant (p > 0.05); SSS=*summed stress score*; SDS= *summed diference score*; A-NP=non-parametric ANOVA for repeated measures; F=Friedman test; TID=transient ischemic dilation

Tabela 4. Association of measures categorized between ST segment depression magnitude and SSS

T0 x T2				
Reduction of ST segment depression > 1.0 mm - MIBI		**Reduction of SSS**		**Total**
		NO	**Yes**	
No	n	3	2	5
	%	60.0%	40.0%	21.7%
Yes	n	11	7	18
	%	61.1%	38.9%	78.3%
Total	n	14	9	23
	%	60.9%	39.1%	100.0%
p= 1.000 F				

Reduction ST segment depression > 1.0 mm – Peak		**Reduction of SSS**		**Total**
		NO	**Yes**	
No	n	4	2	6
	%	66.7%	33.3%	26.1%
yes	n	10	7	17
	%	58.8%	41.2%	73.9%
Total	n	14	9	23
	%	60.9%	39.1%	100.0%
p= 1.000 F				

T2 x T3				
Increased ST segment depression > 1.0 mm – MIBI		**Increase in SSS**		**Total**
		No	**Yes**	
No	n	6	4	10
	%	60.0%	40.0%	43.5%
Yes	n	6	7	13
	%	46.2%	53.8%	56.5%
Total	n	12	11	23
	%	52.2%	47.8%	100.0%
p= 0.510P				

Increased ST segment depression > 1.0 mm – Peak		**Increase in SSS**		**Total**
		No	**Yes**	
No	n	9	4	13
	%	69.2%	30.8%	56.5%
Yes	n	3	7	10
	%	30.0%	70.0%	43.5%
Total	n	12	11	23
	%	52.2%	47.8%	100.0%
p= 0.062P (Kappa = 0.388)				

ST=ST segment; MIBI=moment of injection of the radiopharmaceutical Tc-99m-sestamibi; SSS= summed stress score; F=Friedmann test; *p*=p value; P=Pearson correlation

Select Example. Electrocardiographic manifestation of ischemic preconditioning in sequential tests in patients enrolled in the study. Male, 75 yrs, hypertensive, smoker, previous infarction in 2003, Revascularization Surgery in 2003. Stable Angina status.

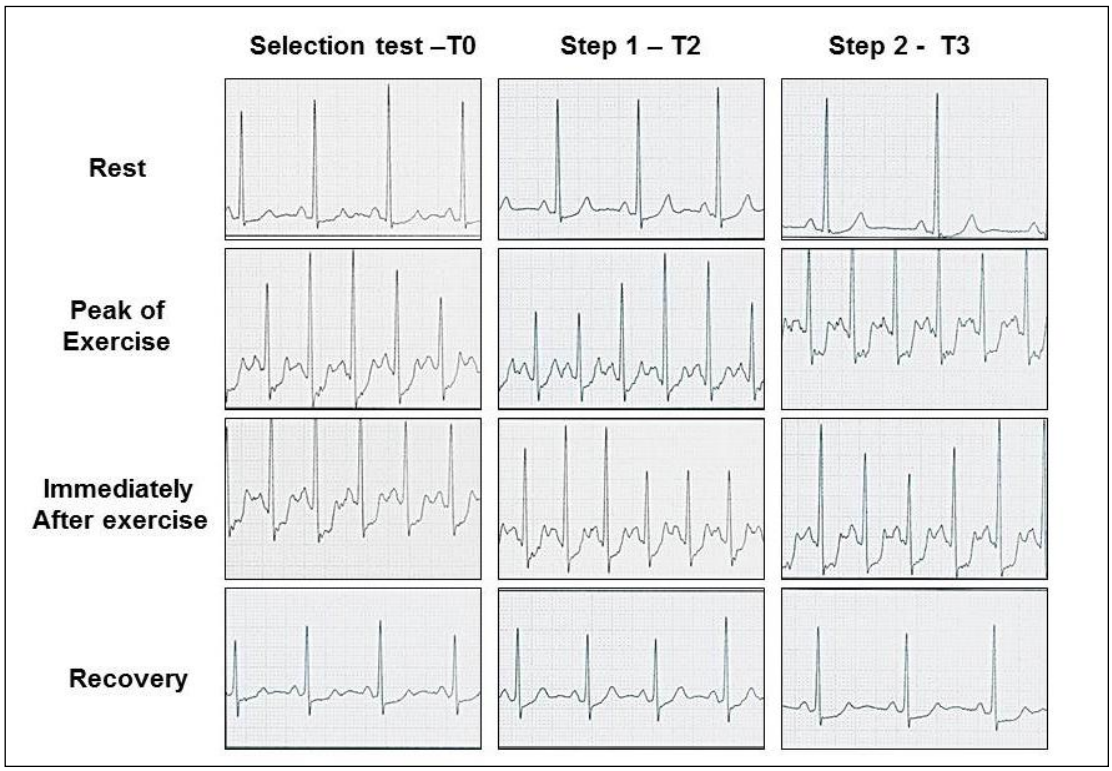

Figura 2. Electrocardiographic changes during the three stages of protocol (Selection, Step 1, Step 2) at different times during test (rest, peak of exercise, immediately after exercise and recovery).

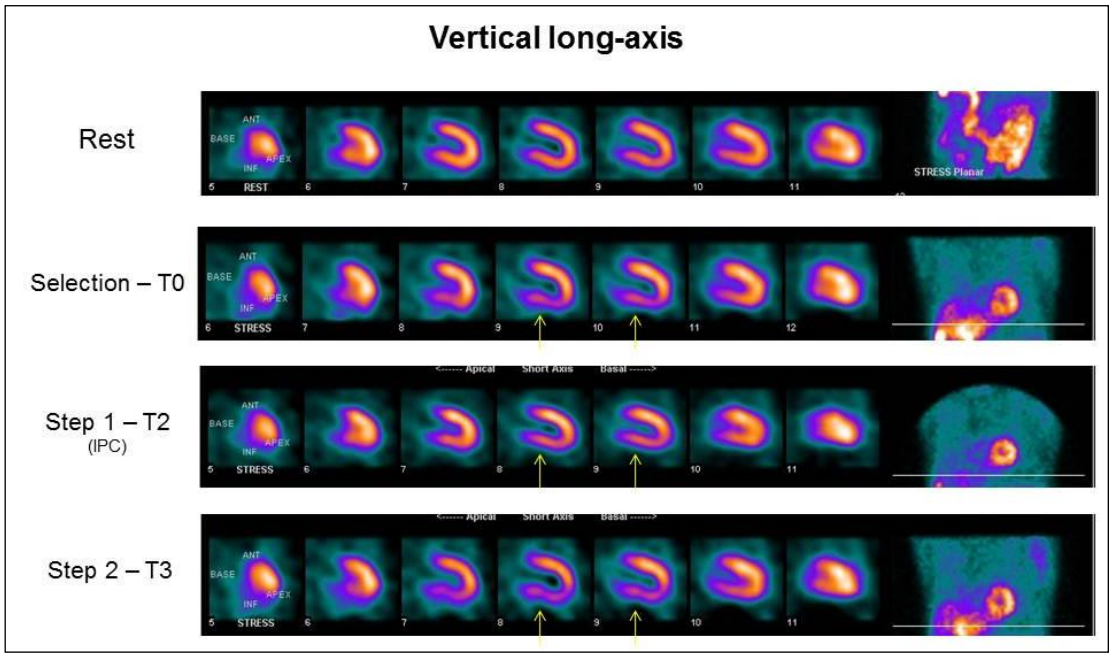

Figura 3. Tomographic long axis vertical showing ischemia in the lower area (T0 and T3) and the effect of preconditioning (T2) compared with the image at rest.

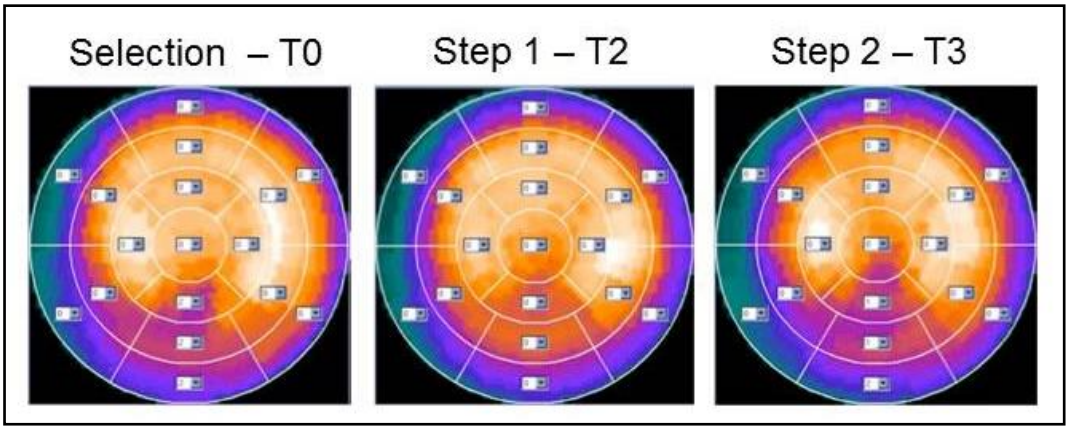

Figura 4. Analysis by polar map segments in times T0, T2 and T3.

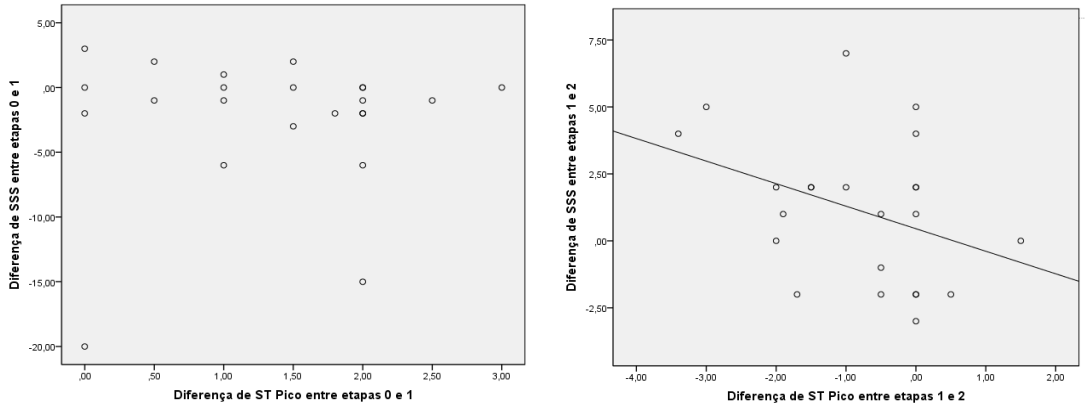

Figura 5. Pearson correlation for the difference in the SSS and the difference of ST depression at peak exercise (A) between stages 0 and 1 (B) between steps 1 and 2