Increased Rate-Pressure Product as Predictor for the Absence of Significant Obstructive Coronary Artery Disease in Patients with Positive Exercise Test

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OBJECTIVE

To correlate values of rate-pressure product (RPP) above 30,000 mmHg.bpm with or without significant obstructive coronary artery disease (CAD) in patients with positive exercise test.

METHODS

A retrospective analysus of 246 patients that had been submitted to Exercise Treadmill Test (ETT) up to 30 days before coronary angiography on suspicion of obstructive disease. The 165 patients in which the ETT was positive were analyzed considering as positive the presence of horizontal or descending depression of the ST segment for at least 1 mm, 0.08 seconds after J point.

RESULTS

Among the 165 appraised patients, 50 (30.3%) reached RPP 30,000 mmHg.bpm, of which 38 (76%) had normal coronary vessel angiography or low degree obstructive coronary artery disease and 12 (24%) had significant. Among the remaining 115 appraised patients with positive ETT and RPP 30,000 mmHg.bpm, 59 (51.3%) were normal or with low significance obstructive coronary artery disease, and 56 (48.7%) had significant disease. (Odds Ratio = 0.3327 CI 95% = 0.1579 to 0.7009; P=0.0034).

CONCLUSION

Based on data collected in the present investigation, it has been demonstrated that RPP above 30,000 mmHg.bpm stands as a relevant variable to predict the absence of significant obstructive coronariopathy in individuals with positive ET and as a useful tool in making clinical decisions.

KEY WORDS

exercise test, rate-pressure product, obstructive coronary artery disease, diagnostic methods

Studies correlating electrocardiographic response to exercise with cinecoronariography (Cine) findings have evidenced normal ECG in up to 30% of patients reporting no evident coronary obstruction[1], with exercise test (ET) sensitivity ranging from 50% to 72% (average 67%), and specificity ranging from 69% to 74% (average 71%)[2-5].

It is important to point out the limitation to such statements, though, since the gold standard for comparion is cinecoronariography – which analyzes coronary artery tree anatomy only, more precisely coronary vessels lumen, rather than the very functional repercussion of obstructions that may occur. Obstructive coronary artery disease (CAD) is not necessarily a synonym for ischemic heart disease; on the other hand, ST-segment depression may or may not express myocardial ischemia, and under no circunstance does it necessarily reflect the anatomic condition related to myocardial perfusion[6]. Initial stages of CAD may determine endothelial dysfunction and trigger abnormal responses from coronary vasculature, even if obstructive disease is not present. Another difficulty is the wide variety of populations studied, not always with superposable characteristics, and the fact that the predictive power of this test is directly related to prevalence in the population studied[7-9]. In individuals with low pre-test disease probability, a positive result has low predictive accuracy, whereas the same positive results in individuals with 50% pre-test probability will determine 88% of post-test disease probability[10].

Rate-pressure product (RPP), which results from multiplying systolic blood pressure (SBP) by heart rate (HR), has been recognized as a relevant parameter in evaluating ventricular function. It has been speculated that high values at peak exertion – thus reflecting cardiac work – are most likely related to good ventricular function and no ischemia condition. The opposite has been reported for very low levels[11-13].

Ergometric National Consensus refers that parameter as the best non-invasive index for myocardial oxygen consumption (MVO_2); the Consensus also refers that its relevance lies in the evaluation of chest pain and of protective therapeutic regimens for myocardial ischemia[14].

In the Exercise Test Guidelines issued by the Brazilian Society of Cardiology[15], high RPP level is referred to as an indication for ET, in association to other methods such as Myocardial Perfusion Cintilography, B_1 recommendation level (recommended; with very good evidence). There is no clear reference to the reason for such indication, although high RPP is known to be associated to false-positive results for the response to ST segment in the ET – due to relative coronary failure - since it demands high consumption of myocardial O_2.

Other methods have been used to try and improve predictive diagnostic value of coronary artery disease. Those methods correlate ET data with myocardial cintilography with Thallium, associated to stress echocardiogram or to other procedures such as Holter and thoracic radiogram, radionuclide ventriculography, fluoroscopy, Thallium and vectorcardiogram increased pulmonary activity[16-23].

Scores have also been developed to correlate ET findings to clinical history in order to predict CAD condition, extension, and prognostics. To that purpose, Kansal et al[24], while studying 608 patients with angina complaints, correlated ET findings in 351 of them through multivariate analysis and proposing a point score to improve CAD diagnosis accuracy. In males, significance variables were: 1) Maximum HR reported was below 80% of expected HR level; 2) depression of ST segment $\geq$ a 1.0mm; 3) age $\geq$ 55 years old; and 4) time exercising on treadmill < 8 minutes. In females, maximum HR reported was < 90% and exercise time < 6 minutes were significant. Maximum HR reduction showed to have the best correlation with CAD, followed by changes in ST segment. However, other variables – such as configuration and magnitude of ST segment depression, RPP < 30,000 mmHg.bpm in males, angina, and exercise time – also showed to be relevant for interpretation. Mark et al[25] conducted a study based on data such as the duration of exercise in association with ST segment depression quantification and the presence or not of angina (Duke Score), therefore identifying patients under low, moderate, or high risk for coronary events, as well as 4-year survival period. They have concluded that the score proposed was valuable in helping decision making on whether to indicate cinecoronariography or not. Morise et al[26] have developed a point score to estimate the probability of CAD in patients with disease suspicion. He considered variables such as gender, age, chest pain condition or not, hormone status, DM, hypertension, smoking habits, hyperlipidemia, family history, and BMI. Variables were selected from a population of normal ECG patients who had been to the hospital for ET, but were submitted to cine. In that study, the authors pointed out the difficulty in using – in clinical practice – the scores as previously proposed by other authors; they also stressed the arbitrary patients are most commonly ranked as under low, intermediate or high probability for CAD. Faris et al[27] have studied the relevance of coronary risk factors and ET finding as significant predictors for CAD in unstable angina females after clinical condition is stabilized. Among other conclusions, the findings on low physical performance in association with low increment RPP have been kept as the only ET parameters shown to be significant predictors of angiographically documented CAD. Raxwal et al[28] have published a study also focusing the development of a new point score, based on clinical history variables and parameters identified in the ET, such as angina severity and quantification of segment ST abnormalities. No difference was reported by the authors for maximum SBP between the 2 groups – with or without CAD. Although RPP differences were found

among patients with and without CAD, the authors have not referred to the statistical significance of those findings. In any case, as for the figures presented, the group with normal coronaries in the population used for score validation showed that RPP was higher when compared to that found in CAD patients, reaching values above 30,000 mmHg.bpm, which emphasized the idea that high RPP presupposes lower probability for CAD, even if changes in the ST segment are present. Ho et al[29], in their purpose to determine whether findings in normal ECG at rest or reporting discreet changes in ST segment or T wave could influence the prognostics of patients submitted to non-invasive investigation of CAD, have calculated a 1 point score for each of the following clinical conditions: Male sex, myocardial infarction history, typical chest angina, DM, insulin use, and every live decade after turning 40. Conclusion fell on score relevance in helping determine prognosis in symptomatic patients – with established or suspicious CAD and normal ECG, or with discreet changes in ST segment and T wave. Morise et al[30] have developed another point score, this time for a population of females, and based on clinical characteristics including age, symptoms, diabetes, smoking habits and serum hormone level in association with ET variables such as depression of ST, HR reached at exercise and angina severity. So, among ET parameters under evaluation, the higher HR level, the lower the number of points to that variable, and therefore, the lower the risk when the other variables are adjusted.

Many of those diagnostic methods described are costly and usually not available. Scores are unquestionably useful; however, either for compliance reasons or because they require the use of computers or calculators, their use in daily cardiological practice is not easy. The ET, though, requires short time, is low cost, and is among the non-invasive procedures with high predictive value[31].

Therefore, the objective of the present study was to correlate RPP values (above 30,000 mmHg.bpm) with or without significant obstructive coronary artery disease at cinecoronariography in patients with positive ET, based on the hypothesis that high values would signal lack of significant coronariopathy.

METHODS

Two hundred, forty-six non-screened patients were included in the study. Age range was 28-79 years of age (mean 58.7±9.4; median 59); 125 (50.8%) were males, with no previously diagnosed CAD (myocardial infarction, myocardial revascularization surgery, or transluminal coronary angioplasty). All had been submitted to cineangiocoronariographic study on the suspicioun of obstructive coronary disease, and to ET in Inbramed (models KT 4000, KT 10200) and standard Imbrasport treadmills less than 30 days before angiographic study. Bruce, Ellestad and Kattus protocols were used, and choice followed pre-test assessment. Heart rate (HR), blood pressures, and electrocardiographic traces measures were obtained at rest, at the end of each stress stage, and at 1, 2, 4 and 6 minutes at recovery, through TEC monitors (Apex 1000, Apex 2000 and Micromed) under continuous follow-up of CM5, D2M and V2M leads. Blood pressure was measured by Tycos aneroid sphygmomanometers, periodically gauged following manufacturer's recommendations. All ET were reviewed by the same observer. This one single criterion for positive results was used retrospectively for the purpose of the present study only, due to the fact it is the easiest to be evaluated and the least prone to subjective interpretation, since in original indication for angiographic exam the clinician requiring it may also have resorted to other criteria, such as pain, arrhythmia, or complementary data on myocardial cintilography. Sones's or Judkins's techniques were used for the cinecoronariographic studies. Digital image equipment were reviewed for the purpose of the present study by the same hemodynamicist. One or more major bundle-branchs with obstructive disease and 50% or higher impairment of vessel diameter was considered positive. The criterion was adopted based on the approximate loss of vessel lumen area - 75% - with reduction understood as having reached the parameters for ischemia. Therefore, lower than 50% obstructions of vessel diameter were classified as mild obstructive disease; higher than 50% - in at least one coronary bundle-branch – significant obstructive coronary disease.

The present study did not focus the characterization of drugs currently being used, since as mentioned earlier, this is a restrospective study including other diagnostic criteria for ET that had been previously carried out, and for which recommended actions regarding the discontinuation of drugs with potential for false diagnosis had already been taken in compliance with regular protocol.

The group of 246 patients as a whole was used for sample characterization. However, for the specific purpose of the present study, only the 165 patients with positive ET were analyzed following the criterion mentioned earlier. The 165 patients with positive ET were divided into 2 groups: Group A (study), made up of 50 patients (30.3%) with RPP above 30,000 mmHg.bpm and age range 36-72 years of age (mean 59.2±7.4, median 60), 54.0% of them males; Group B, made up of 115 patients (60.6%) with RPP at or lower than 30,000 mmHg.bpm and age range 28-79 years of age (mean 59.0±9.8, median 59.5), 53.0% of them males (P>0.05 for age and gender comparison between the groups).

Study protocol was approved by the Ethics Committee at São José do Rio Preto School of medicine, opinion number 037/2004.

Data analysis was carried out by Fisher exact test and Odds Ratio calculation with Confidence Interval 95%, in addition to ET Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive Likelihood Ratio. $P \leq 0.05$ was considered significant.

RESULTS

In Group A, RPP ranged from 30,200 to 43,200 mmHg.bpm, mean at 34,502±3,572 mmHg.bpm (median 34,090 mmHg.bpm). In that group, 12 patients (24%) reported significant obstructive coronary artery disease and 38 (76%) were normal or reported mild obstructive coronariopathy.

In Group B, RPP ranged from 12,480 to 29,760 mmHg.bpm, mean at 23,455±4,230 mmHg.bpm (median 24,600 mmHg.bpm). In that group, 56 patients (48.7%) reported significant obstructive coronary artery disease and 59 (51.3%) were normal or reported mild obstructive coronariopathy.

It was found that the incidence of patients with CAD was significantly lower among those with ET+ associated to a RPP > 30,000 mmHg.bpm when compared to those with ET+, but reporting RPP ≤ 30,000 mmHg.bpm (Fisher exact test; P= 0.0034; Odds Ratio 0.3327 (IC95% 0.1579 a 0.7009). Table 1

Table 1 - Incidence in patients following values for RPP and the presence of significant coronary artery disease or not at cinecoronariography

	Relevant CAD	Mild or no CAD	TOTAL
RPP > 30,000 mmHg.bpm	12	38	50
RPP ≤ 30,000 mmHg.bpm	56	59	115
	68	97	165

RPP- rate-pressure product; CAD- coronary artery disease; Fisher exact test (P=0.0034)

From all patients (n=246), Sensitivity was 0.8095 (CI 95% 0.7096 to 0.8872); Specificity was 0.4012 (CI95% 0.3248 to 0.4812); Positive Predictive Value was 0.4121 (CI95% 0.3360 to 0.4909) and Negative Predictive Value was 0.8025 (CI95% 0.6992 to 0.8827); and Positive Likelihood Ratio was 1.352. Incidence of patients following ET and significant coronary artery disease or not can be found in Table 2.

At later data recalculation, considering patients in Groups A (RPP> 30,000 mmHg.bpm) as negative tests, the following results were obtained: Sensitivity 0.6667 (CI95% 0.5559 to 0.7657); Specificity 0.6358 (CI95% 0.5574 to 0.7097); Positive Predictive Value 0.4870 (CI95% 0.3930 to 0.5820); Negative Predictive Value 0.7863 (CI95% 0.7058 to 0.8533; Positive Likelihood Ratio changed to 1.831 (table 3).

Table 2 - Incidence in patients following results for ET and the presence of significant coronary artery disease or not at cinecoronariography

	Significant CAD	Mild or no CAD	TOTAL
Positive ET	68	97	165
Negative ET	16	65	81
	84	162	246

ET- exercise test ; CAD- coronary artery disease

Table 3 - Incidence in patients following results for ET and the presence of significant coronary artery disease or not at cinecoronariography after considering Group A as negative for test results

	Significant CAD	Mild or no CAD	TOTAL
Positive ET	56	59	115
Negative ET	28	103	131
	84	162	246

ET- exercise test; CAD- coronary artery disease

DISCUSSION

Despite the wide number of tests used for diagnosis and prognosis of patients with suspicion of coronary artery disease, the ET on treadmill is still the easiest and most widely used for that purpose[25]. The present study tried to use an objective, easily obtainable indicator to validate positive ET. The proposal was to use maximum RPP above 30,000 mmHg.bpm as the cutting point to characterize the truly positive tests (RPP<30,000) as opposed to false positives (RPP>30,000).

Indeed, statistical analysis allowed evidence to show that in the positive test patient group – although RPP was above 30,000 mmHg.bpm – the risk for significant obstructive coronariopathy in at least one major bundle-branch was significantly lower when the test was positive, but RPP was low. Additionally, considering ET+ with RPP>30,000 as negative, Positive Likelihood ratio was improved, which means higher test accuracy. Such data emphasize the value of that variable in separating individuals with and without significant CAD when ET is positive.

In a meta-analysis published in 1989 by Detrano et al[2] – where RPP is mentioned – values varied from 16,300 mmHg.bpm to 28,000 mmHg.bpm (mean 22.430±3.789 mmHg.bpm) with sensitivity and specificity for the detection of any degree of coronary

obstruction > 50%, with respective ranges between 0.46 and 0.90 (P= 0.04) and 0.37 and 0.93 (P=0.93).

ET is known not to significantly change diagnosis level in low or high risk patients for CAD; it is actually most effectively indicated for intermediate risk patients. The present study population was divided into 2 groups, with similar number of patients for gender and age (Group A – median 60 years of age, 54% males; Group B – median 59.5 years of age, 53% males) – the very population ET stands for best predictive value.

While associating ET results with those of radionuclide ventriculography during exercise in 1983[20], Currie et al em, added a positive predictive value for CAD, although that was not obtained by the use of any of the tests isolatedly. In fact, among patients reporting no coronariopathy condition, RPP was 31,900±6,200 mmHg.bpm, while for all remaining 65 patients with significant CAD, RPP reached 26,300±7,200mmHg (p<0.001). When comparing with results from the present study, the authors have confirmed that the RPP found in patients who were free of significant coronary injury was higher as compared to those reporting significant injuries at angiography.

In a male population studied through the use of multiple, non-invasive tests, Hung et al[21] found patients with normal coronaries and whose RPP was 33,600±5,500 mmHg.bpm; reporting one-vessel CAD, RPP was 28,600±7,300mmHg.bpm; and multiple-vessel CAD, 23,600±7,000 mmHg.bpm. The tendency fowars higher RPP in angiographically normal individuals is to be pointed out.

Berman et al[32] were successful in managing to increase ET negative predictive value for the absence of CAD when RPP was higher than 30,000mmHg.bpm. In the present study, while considering ET+ with RPP>30,000 as negative, we have obtained a 0.8025 reduction in the negative predictive value (CI95% 0.6992 to 0.8827) for 0.7858 (CI95% 0.7058 to 0.8533). However, Positive Likelihood Ratio was increased to 1,831, thus showing improvement in test accuracy. The fact that Berman et al[32] have increased negative predictive value of negative ET for the absence of CAD is most likely due to the lower probability of detecting significant disease in tests with no ST segment changes (normal), or else, to the variety of populations under study for CAD prevalence.

While correlating ET using a multiple lead system and hemodynamic response on exertion for CAD diagnosis, Chaitman et al[33] have found RPP at the point ischemia was detected electrocardiographically as a useful predictive parameter for the disease. In that study, only 2/21 (10%) of patients with three-vessel coronary disease were able to reach RPP higher than 25,000 mmHg.bpm at the moment the test turned positive. Such findings related to RPP agree with those found by Hsu et al[34], where RPP helped differentiate CAD patients

from those with X Syndrome at the time ischemia was electrocardiographically detected, since in this group mean RPP was 21,115±5,250 mmHg.bpm whereas in the obstructive coronariopaths it was 18,444±4,375 mmHg.bpm (p<0.05).

In the study by Wasir et al[35], using both univariate and multivariate ET analysis, peak exertion RPP was highly discriminating among patients reporting multiarterial injuries and the group with one-vessel injury, or those with normal coronary arteries. In that paper, none of the patients with 2 or 3-vessel injuries succeeded in reaching a 30,000mmHg.bpm RPP. In the present study, out of the 50 patients with RPP>30,000mmHg.bpm, 12 reported coronary injury – 1,2, or 3-vessel, indistinctively. That could be due to the fact that cinecoronariography analyzes the anatomy of coronary artery tree: therefore, injuries considered anatomically significant may not determine extensive myocardial ischemia, with ventricular function kept close to normal. Likewise, coronary injuries considered "non-significant" at cinecoronariography may prove to be significant at intracoronary ultrasound, resulting in extensive ischemia and severely impairment of myocardial contractility.

In the study by Faris et al[27] onw can see – among other variables – that RPP at exercise peak and RPP variation (delta HR x SBP) were lower in patients with significant CAD as compared to those with without significant CAD. Such findings agree with our results in the sense that in most individuals with increased RPP in our population no significant coronary injury was found, thus presupposing better ventricular function during exercise.

In daily medical practice, the decision to refer a patient to cineangiocoronariography is complex, and frequently depends on clinical evaluation in association with prognosis and physician's or patient's option to confirm or rule out CAD diagnosis[25]. Therefore, as mentioned earlier, different authors have proposed methods that incorporate clinical variables, electrocardiographic variables at rest and on exertion, data collected from other exams – such as perfusion myocardial cintilography, Holter monitoring, echocardiogram on exertion and thoracic radiogram. Prognostic scores were then made available, as mentioned earlier[24-30] to provide unquestionably useful information on decision making about how to proceed when a patient reports coronary disease suspicion. What happens is that many of those scores are hard to put into use in daily clinical practice, either due to compliance reasons, to the requirement of computer or calculator analysis, or costly procedures. Which is to say, because they are not compatible with domestic Brazilian scenario, as well as for their cost-effectiveness ratio.

In the light of such scenario, we do believe our study – which invorporates easily obtainable variables at exertion test - has been made available as an invaluable method for non-invasive investigation of coronary artery disease.

Based on data collected in the present investigation, it has been demonstrated that RPP above 30,000 mmHg.bpm stands as a relevant variable to predict the absence of significant obstructive coronariopathy in individuals with positive ET and as a useful tool in making clinical decisions.

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