Importance of heart rate analysis in exercise tolerance test*

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ABSTRACT

After many years away from the limelights, at the beginning of this century, exercise tolerance testing has earned back an important position in international medical journals. The different sorts of information derived from a variety of studies based on it have shown us that this propedeutic method has a highly valuable prognostic impact. Because of its low cost and easy applicability, the exercise testing reinforces its position in the clinical practice of the cardiologist. In the early 70's, research relating the influence of the autonomic nervous system in heart rate behavior in all phases of an exercise tolerance testing began. Ever since, a number of hypotheses tried to clarify which would be the mechanisms related to the chronotropic response during effort and its performance in the recovery period. In this updating article the authors deal with an important data referring to the chronotropic deficit and the abnormal heart rate recovery, commenting on the prognostic implication of keeping the focus on the potential of its clinical impact. In other words, approaches that can be used whenever there is someone performing a monitored exercise tolerance testing.

Key words: Heart rate behavior. Prognosis. Exercise resistance test.

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INTRODUCTION

At the beginning of last century, in 1908, Eithoven described changes of ST segment during physical strain[1]. In the 30's, for the first time, physical strain-related electrocardiography was used as a diagnostic tool for patients with angina[2]. Since then, exercise tolerance testing became to be used as a diagnostic method to detect obstructive coronary disease. It was a time when the idea of ischemia, reflected by obstruction of the epicardial coronary arteries, was dominant, and some limitations of the method became evident: sensitivity of about 70%, and specificity of 80% for the anatomic diagnosis of coronary arteries obstruction[3].

In mid-80's, however, the focus of electrocardiogram assessment shifted, and new horizons came into view, not only in seeking diagnostic information, but also highly valuable prognostic information started to be explored. At that point, functional capability started to be seen as an important variable for prediction of cardiovascular and overall mortality[4-7]. By measuring test duration, the number of METs reached, and the maximum oxygen uptake, through a comprehensive cardiopulmonary test, cardiologists who use the exercise test could stractify patients as to higher or lower risk of death in the mid- and long-term. The opposite was also true, as there is a potential for reversion of this diagnosis through physical training, as evidenced by Blair *et al.*[8]. For a 1 minute increment in the duration of the exercise resistance test there is a 7.9% decrease in the risk of death. Following this line of investigation, the next step was to establish prognostic scores, such as Duke and Veterans Affair (VA), to analyse ST changes, functional capability, and presence of coronary heart failure symptoms (fig. 1).

With this information, ergometry made the prognostic value of the exercise test a reality all through the world. At the same time, and not by chance, there was a change in the concept of coronary heart failure, and the anatomic theory was put aside, in favor of the one supporting functional manifestation of ischemia.

Being easy to apply, of low cost, and providing really important information in a low complexity manner, ergometry continued to explore new horizons, seeking more

DUKE SCORE = METS – (5x ST Depression in mm) – (4x Angina Index)

Angina Index = "0" if angina is absent,
"1" if angina occurs during test,
"2" if angina causes test to be halted.

VETERANS AFFAIRS SCORE
VA = 5x (CHF/Dig) + ST Depression (mm) + Change in PAS – METS score

Change in the PAS Score: 0 for increase in subjects older than 40 years
5 for decrease below rest level.

***Fig. 1** – Duke and Veterans Affairs (VA) formulas to calculate prognostic score*

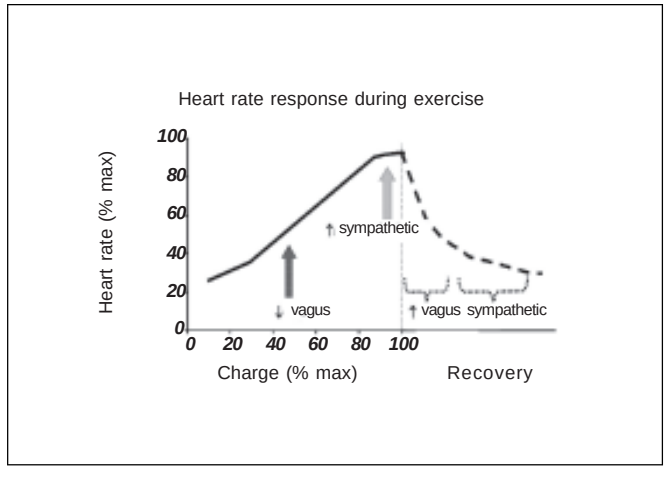

***Fig. 2** – Role of the autonomic nervous system for heart rate progression at exertion and in recovery from exercise resistance test*

prognostic information. Within this framework, came the method to assess heart rate (HR) upon exertion, and its behavior in the recovery stage (post-exertion).

1) Heart rate response at exertion and its determinants (fig. 2)

Over the last three decades, a number of investigators explored the influence of the autonomic nervous system on HR behavior throughout an exercise resistance test. In 1986, Araújo showed the vagal role at the initial recovery moments[9]. Later, Colucci *et al.*[10] noted significant difference in HR variation between normal subjects and heart failure patients. This was made evident as both groups were estimulated with isoproterenol, and those with heart failure presented beta-adrenergic desensitization as the cause of chronotropic deficit. In a paper published in 1991, Ribeiro *et al.*, evidenced that at the beginning of exertion, there is a parasympathetic withdraw and a progressive sympathetic activation[11]. Arai *et al.* demonstrated, through spectral analysis, that, as exertion progresses, there is a progressive decrease of vagal activity, and increase in the sympathetic system activity until the peak of exertion, and a higher vagal role at the beginning of recovery[12]. Imai *et al.*, assessing athletes and patients with cardiac disease, support these findings, showing sympathetic activity at the peak of exertion, and the importance of parasympathetic action between the 30th second and the second minute of recovery time[13].

2) Vagal activity and prognosis

Modulation of the vagal tone is indirectly correlated with the risk of death in post-myocardial infarction patients and in healthy adults[14-16]. Patients with diminished vagal activity, evidenced by a decrease of RR variability or of baroreflex sensibility, have an increased risk for sudden death. Increase of sympathetic activity is an arrhythmia-triggering factor and an important death risk marker for heart failure patients[17]. A number of studies point to the parasympathetic protection from cardiovascular and overall death. These facts generated the hypothesis that HR behavior under exertion could be a reliable indirect measure of autonomic activity, and can be correlated to a higher or lower risk of death.

3) Main studies on HR assessment at exercise resistance test

A number of studies have been carried out showing HR prognostic value at ERT, and the Cleveland Clinic group stands out in this line of research.

3a) Chronotropic deficit

The first impact study published by Lauer *et al.*[18] assessed, through a cohort of Framinghan's second generation, 1,575 healthy males, mean age of 43 years, non-users of beta-blockers, who were submitted to submaximal ERT under Bruce's protocol. The tests were halted when 85% of the maximum heart rate (HR max) established for their age was reached. Chronotropic deficit was assessed in three aspects: inability of reaching 85% of HR max, HR variation at rest (HR rest) and at peak exertion, and a chronotropic index, introduced in the world literature for the first time by this study. In this investigation, the index was assessed at the end of the second stage (the ability to reach the second stage was an inclusion criteria), and was defined by the formula:

$$\frac{\text{HR } 2^{nd} \text{ stage} - \text{HR rest} \times 100}{\text{HR max predicted} - \text{HR rest}}$$

The purpose of this variable is to minimize, upon assessment of the chronotropic competence, influences of age, gender, HR at rest, and functional capability. After a follow-up of 7.7 years, in average, three variables were predictive as to incidence of coronary heart disease and overall deaths ($p < 0.01$): inability of reaching the expected HR, smaller variation of HR and the chronotropic index. After a multivariate analysis, HR variation was inversely correlated to the risk of coronary heart disease ($p = 0.0003$) and death ($p = 0.04$). The authors concluded that chronotropic incompetence was an independent predictor of deaths and incidence of coronary heart disease.

Afterward, the same group[19] investigated 2,953 patients (1,877 males, mean age of 58 years), non-users of beta-blockers, who were submitted to limited-symptom ERT during miocardial perfusion scintigraphy. The purpose was to assess association of chronotropic deficit with perfusion defects and incidence of overall death for a period of two years, in average. In this study, chronotropic deficit was considered to be the inability of reaching 85% of HR max expected for that age (220 – age), and another chronotropic index was used. The index was assessed according to the HR of maximum exertion, and considered to be abnormal if smaller than 80%.

$$\frac{\text{HR max} - \text{HR rest} \times 100 > 80}{220 - \text{age} - \text{HR rest}}$$

A low chronotropic index was an independent predictor of death (RR = 2.19; 95% CI; 1.43-3.44; $p < 0.001$), as was the inability in reaching 85% of HR max (RR = 1.84; 95% CI; 1.13-3.00; $p = 0.01$). The authors also observed a independent and additive association between chronotropic deficit and risk of death. It is also to be mentioned that there was a higher incidence of perfusional defects in the tests where chronotropic deficit was noted. These findings raised the issue on calling the test invalid or non-diagnostic if chronotropic deficit was present, and the importance of collecting the two data (chronotropic response and perfusion defects), as fundamental elements of prognostic analysis.

3b) Heart rate recovery

The most important study in this field was the one published by Cole *et al.*[20], whose main focus was related to the fall of HR at peak exertion during the first minute of recovery. In this experiment, the authors also assessed, indirectly, vagal activity. For an average of 6 years, 2,428 patients were followed-up, 63% of them males, mean age of 57 years, no history of heart failure, pacemaker use or heart surgery, all of them submitted to limited-symptom ERT for the first time, during miocardial scintigraphy. Fall of HR was assessed at the first minute, according to an active recovery protocol, where treadmill velocity was kept at 2.4 km/h, with a 2.5% inclination for at least 2 minutes. After a statistical adjustment, the best HR cutoff value was reached, to identify risk of death from all causes. The cutoff point was 12 beats, i.e., fall of HR at peak exertion within the first recovery minute smaller than or equal to 12 was considered abnormal.

In this study, abnormal HR recovery was strongly associated to risk of death within 6 years, being the adjusted relative risk of 2.0 (95% CI, 1.5-2.7; $p < 0.001$), with sensitivity of 56% and specificity of 77%. It was also observed a significant association between low functional capability and abnormal HR recovery.

With the purpose of finding if abnormal HR recovery also had prognostic value in submaximal ERT, Cole[21] *et al.* used the initial assessment of Lipid Research Clinics (a study that investigated prevalence of dyslipidemia), which included submaximal ERT. The used protocol consisted of ERT, which was halted when 85 to 90% of HR max was reached and sustained for 1 minute. Passive recovery was done by having the patient sat immediately after exertion. For this experiment, it was established that HR decrease lesser than or equal to 42 beats at the second recovery minute was an abnormal response. After a 12-year follow-up, abnormal recovery was predictive of death, with relative risk of 2.6 (95% CI, 2.06 – 3.02 $p < 0.001$), which remained significant after adjustments for risk factors, practice of physical activities, for both rest and exertion heart rate. It was also observed association between abnormal HR recovery and no regular practice of physical exercises (sedentary attitude).

Abnormal HR recovery and Duke score are independent death predictors. Association between both of them was investigated by Nishime *et al.*[22] in 9,454 patients, mean age of 53 years (78% males), all submitted to limited-symptom exercise resistance test in a major hospital. Recovery was active (speed of 2.4 km/hour and inclination of 2.5%), and cutoff point was 12 beats within the first minute. Abnormal recovery and Duke score were independent death factors over the 5.2 years of follow-up. When abnormal recovery was associated to a low score, prognosis was even worse.

Active recovery has been criticized for its lower sensitivity to detect ischemia, compared to passive recovery. Watanabe *et al.*[23] followed, for 3 years, 5,438 patients with no history of heart failure or valvular diseases, who were submitted to echocardiography with pharmacologically-induced stress and limited-symptom ERT. HR fall to 18 beats or less, from peak exertion to the first recovery minute,

was considered abnormal. Abnormal recovery was assessed together with left ventricular function. From this association, the authors noted that abnormal recovery presented a relative risk of death of 3.9 (95% CI; 2.9 – 5.3; $p < 0.0001$), and that increased risk does not depend on left ventricule dysfunction (ejection fraction ≤ 40%), being and independent and additive risk factor.

In order to validate this prognostic tool in another big populational sample, another important group, known worldwide for their exercise resistance test studies, investigated HR abnormal recovery from ERT. Shetler *et al.*[24] followed 2,193 men (mean age of 59 years), for a period of 7 years, all of them submitted to ERT to assess chest pain in two Veterans Affairs (VA) centers. All patients were further referred to cardiac catheterization. The used protocol was symptom-limited exercise resistance test with a treadmill, with passive recovery in supine position. Another objective of this study was to assess the diagnostic power of abnormal recovery for coronary artery failure. This study allowed validation of the HR recovery figures previously published as abnormal for mortality prediction, and the best cutoff point for death among this sample was less than 22 beats at the second recovery minute. In other words, the risk of death for an HR abnormal recovery at the second minute post-exertion was 2.6 times higher than in subjects with physiological HR recovery. It is to be stressed, however, that abnormal recovery has not shown to be a good diagnostic tool for obstructive coronary lesions ≥ 50%. Finally, this study also showed an association between abnormal recovery and low physical fitness and independent and additive death predictors.

COMMENTS AND FINAL CONSIDERATIONS

HR response during ERT is an important tool for prognostic analysis of a functional test. The mechanisms by which chronotropic deficit is related to a worse prognosis are not fully clear. It has been shown that beta-adrenergic desensitization is present in heart-failure patients[10]. Chronotropic deficit, on its turn, is predictive of coronary heart disease[24], and incipient CHD could be a possible explanation for increased risk of death. An association often seen was between low functional capability and chronotropic deficit, which could be related to a higher risk of death.

On the other hand, post-exertion HR recovery is closely connected to vagal tone modulation. A higher risk of death with the decrease of parasympathetic activity is well established. Abnormal HR recovery is a simple and reliable tool to assess decrease of vagal activity. For this tool to be used in the medical practice, one should be careful in applying to HR recovery assessment the values that are closer to our population and the recovery protocol used, whether active or passive.

In conclusion, it is time for us to look more carefully to the scientific evidences related to chronotropic response upon exertion and within the first recovery minutes. In the ERT reports, informations from Duke score and HR assessment should be always included, as they provide accessible information of high prognostic value, which complement the diagnostic assessment so broadly used.

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