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Significance of Heart Rate Profile during Treadmill Stress Test - A Critical Appraisal

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Review Article

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Abstract

Several studies have tried to correlate heart rate profile during treadmill stress test with presence and severity of coronary artery disease and long term prognosis. These studies have concluded that higher resting heart rate, inability to increase heart rate commensurate with increase in work load (chronotropic incompetence), and inadequate decline in heart rate after stopping exercise (abnormal heart rate recovery) are all associated with increased long term mortality. Detailed evaluation, however, shows that these studies had important limitations e.g.(i) failure to exclude subclinical myocardial ischemia and/or left ventricular dysfunction (ii) failure to exclude subclinical systemic diseases by thorough clinical and laboratory evaluation (iii) not excluding symptomatic patients (iv) failure to correlate heart rate parameters with clinical and electrocardiographic parameters (v) failure to correlate their observation with echocardiographic and angiographic findings (vi) failure to perform multivariate analysis to find independent significance of heart rate parameters. Therefore, these studies do not provide any conclusive evidence of any diagnostic or prognostic significance of various heart rate parameters observed during treadmill stress test. Well-designed studies are needed.

Keywords: Cardiovascular Events; Coronary Artery Disease; Heart Rate; Mortality; Treadmill Test

Introduction

Conventionally ST segment changes are considered most relevant in interpretation of treadmill stress test. However, several other variables also need consideration [1]. One of these is heart rate. Evaluation of resting heart rate and changes in heart rate during exertion and recovery are considered important [2,3], We have reviewed the literature to find present status of significance of heart rate response to exercise.

Resting Heart Rate

Normal resting heart rate is between 60 to 90 per minute. It is maintained by balance between sympathetic and parasympathetic systems. Several large scale trials with follow up of many years have shown that higher resting heart rate during treadmill test is associated with increased incidence of all cause and cardiovascular mortality [4]. Jouven, et al. [5] followed 5713 asymptomatic men for 23 years and found significantly higher incidence of sudden death in persons with resting heart rate of more than 75 beats per minute at the time of baseline bicycle exercise test. Cooney, et al. [6] followed 21553 men and women. They observed significant increase in incidence of cardiovascular mortality among persons with resting heart rate of more than 90 beats per minute as compared to those with resting heart rate of less than 60 beats per minute at the time of entry in study.

However, these studies did not evaluate various causes of higher resting heart rate and their impact on long term morbidity and mortality. Anxiety and apprehension are important causes of tachycardia in persons undergoing treadmill stress test for the first time. Anaemia, occult thyrotoxicosis, subclinical cardiac dysfunction, chronic infection or chronic low grade inflammation could all affect resting heart rate and long term mortality. This is important because most of the studies have shown increase in 'all cause' mortality rather than mortality only from cardiac causes. Incidence and impact of various cardiovascular risk factors and presence of cardiovascular disease at entry in the study has also not been properly evaluated. Although these studies showed relation between higher resting heart rate and increased mortality, no cut off value can be deduced which can be applied to a given patient undergoing treadmill stress test? Authors of these studies have also not given any satisfactory explanation as to how higher resting heart rate at a point in time caused higher incidence of 'all cause' mortality after several years (at times after decades). Autonomic imbalance (increased sympathetic drive or decreased parasympathetic activity) has been considered as responsible and have been correlated with increased mortality from cardiac causes in persons with decreased heart rate variability. Autonomic dysfunction has not been documented in these studies. Further, it is not clear as to how autonomic imbalance increased mortality from all causes including conditions like cancer. Correlation with any particular cause of death is also not clear.

Etiopathogenetic correlation between relatively higher resting heart rate and long term mortality from a particular cause and it's clinical implications are not clear. It is also not clear that how to apply these observations to a given patient undergoing treadmill stress test.

On the contrary Hinkle, et al. [7] observed increased risk of cardiac death in middle - aged men with slow heart rates. They postulated that it was due to ischemia of sinus node. Jose and Taylor have observed that intrinsic heart rate becomes slower as myocardial contractility declines [8]. Thus; it appears that slow resting heart is also associated with increased risk of cardiovascular mortality.

Heart Rate Response to Graded Exercise

Heart rate increases linearly with work load and oxygen uptake [9]. Initial increase is caused by withdrawal of the parasympathetic system where as remainder increase is largely due to increased sympathetic drive. Heart rate response is also influenced by age, physical fitness, cardiac function and drugs being taken by the patient [9].

Abnormal Responses can Occur at Various Levels of Exercise

Inappropriate Increase at the Beginning of Exercise: It may occur in patients who are anxious about exercise test. Heart rate stabilizes after about 30 to 60 seconds [10]. It does not have any diagnostic or prognostic significance.

Inappropriate Increase at Low Work Load: It can occur in patients with atrial tachyarrhythmias (atrial flutter, atrial fibrillation, atrial tachycardia). Physically deconditioned, hypovolemic, anaemic and those having marginal left ventricular function can also have inappropriate increase in heart rate of low work load [7]. Significance to risk stratify patients with suspected or established coronary artery disease is not clear [11]. Above mentioned conditions perse are likely to adversely affect long term survival.

Heart Rate Change at Initial Exercise Work Load

- Savonen, et al. [12] performed symptom limited exercise test on 1387 men (42 to 61 years) with neither prior coronary heart disease nor use of beta blockers at baseline and followed them for 11.4 years. They observed that slope of heart rate increase during exercise test was steeper in survivors when compared with those who died due to cardiovascular disease. Authors also observed that blunted heart rate increase between 40 to 100% of maximal work load was associated with increased cardiovascular mortality. Authors felt that reduced ability to increase sympathetic activity could be the culprit. However, the study had some limitations. Firstly only males were enrolled. Secondly the influence of age, underlying diseases, regular physical activity and cardiovascular medications was not evaluated. Finally, during a conventional treadmill stress test, it is difficult to separate the slope of increase in heart rate up to 40% of work load from the slope after 40% of work load. Further, it is not clear if this observation has any significance in addition to total chronotrpic response and ST segment changes.

- On the contrary, Leeper, et al. [13] in a follow up study of 1954 patients referred for clinical exercise test observed that heart rate rise at one third of the total exercise capacity significantly predicted both all cause and cardiovascular risk after adjustment for confounders. However, they also observed that Duke Treadmill score was superior to all heart rate measurements in the prediction of cardiovascular mortality. It is thus clear that heart rate change at initial exercise workload does not provide any significant information in addition to or above Duke Treadmill score.

Heart Rate Change During Total Exercise Test

Predicted Maximal Heart Rate: Since the beginning of exercise stress test, it became clear that maximal heart rate at peak exercise decreased with aging. Apoptosis of sino-atrial node pacemaker cells [14] and decreased influx of calcium [15] probably contribute to this decline. Fox, et al. [16] Suggested that maximal heart rate for a given patient could be calculated as 220-age. Subsequently different formulae were developed for both sexes and with consideration of habitual physical activity [17-23]. However, the differences are small. Some authorities recommend the use of formula of Tanks and associates (208-0.7 x age) for both sexes and regardless of habitual physical activity [24]. Although it is argued that formula of 220-age underestimates maximal heart rate in persons above the age of 40 years, it is simple easy to apply and calculate and has been used successfully in most of the studies over several years and is still being used by most of the stress test systems for calculating 'target heart rate'.

There is a great deal of variability around the regression line between maximal heart rate and age [9]. Therefore age related maximal heart rate estimates are relatively poor index of maximal effort [9]. As prediction of maximal heart rate is inaccurate, some authorities recommend that exercise should be symptom limited and not targeted at attaining a certain heart rate [9,25]. Diagnostic information can be obtained even if certain target heart rate is not achieved [9] and achieving 85% of maximum predicted heart rate without electrocardiographic changes does not exclude single or even multiverses disease [24]. Further, stopping exercise prematurely once 85% of an estimated maximal heart rate is achieved decreases exercise testing sensitivity and minimises the opportunity to access ischemia [25]. Pinkstall, et al. [26] also observed that age predicted maximal heart rate should not be used as a sole criterion to determine as to when a test should be terminated.

Inability to Increase Heart Rate Commensurate With Increase in Work Load (Chronotropic Incompetence).

Various criteria have been used by different workers to define chronotropic incompetence. These include inability to increase heart rate to at least 85% of age predicted maximum heart rate (usually based on 220-age equation), [10,26] peak heart rate achieved with maximal exercise , heart rate reserve [27] (peak heart rate minus resting heart rate) heart rate reserve used [10,28], (Heart rate reserve/220 minus age minus heart rate at rest), and chronotropic index (ratio between heart rate reserve used/metabolic reserve <80%) [29-32]. Most of the studies have used the criteria of inability to increase heart rate to at least 85% of age predicted maximum using the formula of 220-age [33-35]. This is because it is directly visible on screen and does not need any calculation.

Initial studies felt that chronotropic incompetence was a reliable sign of poor myocardial function[1], underlying coronary artery disease [36] and angiographic severity of coronary artery disease [37,38]. Long term follow up studies have suggested that chronotropic incompetence is associated with higher incidence of coronary death [26-30,32-35,39-41]. All-cause mortality, [28-29,31-35,42-40] progressive heart failure [43] and complete occlusion of bypass grafts [44]. Chronotropic incompetence has been attributed to autonomic imbalance [45,46,47] and increased mortality has been correlated with increased mortality in persons with decreased heart rate variability.

However several issues need consideration before the clinical implications of these observations can be accepted.

- It is difficult to understand as to how chronotropic incompetence alone could increase 'all cause' mortality including cancer on long term follow up [30,33,35]. In most of the studies [48,45,40] patients were not thoroughly evaluated for chronic underlying disease that could contribute to increased all cause mortality on follow up. There is a long list of these diseases like chronic lung disease (eg. asthma, COPD, emphysema, interstitial fibrosis), systemic hypertension, diabetes mellitus, thyroid disorders, chronic renal failure chronic hepatitis, chronic inflammatory diseases, autoimmune disorders, haematological disorders and early stage of neoplasia. Therefore, it cannot be concluded that chronotropic incompetence had any relation to increase in all cause mortality on long term follow up.

- Most of the studies correlating chronotropic incompetence with subsequent occurrence of cardiac events included symptomatic patients [35,37-39] or patients referred for treadmill stress test for clinical reasons [49]. Other studies excluded coronary artery disease by absence of symptoms [31,33] or absence of history of known CAD. Some studies excluded CAD by normal resting ECG [32]. We know that resting ECG could be normal even in presence of severe CAD. Some studies excluded CAD by absence of clinical or electrocardiographic findings on achieving 85% of age predicted maximal heart rate. However such a negative finding does not exclude single or even multivessel disease [24,25,50]. It is therefore, likely that patients with angina or remote myocardial infarction may have been included [51]. These patients are likely to have higher incidence of myocardial infarction or sudden death on follow up irrespective of presence or absence of chronotropic incompetence.

- Some studies have concluded that chronotropic

incompetence correlated with increased incidence of underlying coronary artery disease [36] or angiographic severely of coronary artery disease [37,38]. However, the observations have not been correlated with clinical and other electrocardiographic parameters that suggest severe coronary artery disease. Some more questions need to be answered. Was the effect independent of other parameters? Can we diagnose presence and severely of coronary artery disease merely by presence of chronotropic incompetence in absence of other parameters? What magnitude of chronotropic incompetence suggests severe coronary artery disease? How can these observations about higher incidence of coronary artery disease be applied to a given patient undergoing treadmill stress test? What is the correlation between magnitude of chronotropic incompetence, number of vessels involved and severely of disease.

- Chronotropic incompetence could be due to non chronotropic cause e.g. angina, claudication, ischemia, ECG changes, arrhythmias, incipient left ventricular failure or left ventricular failure precipitated by exercise, sinus node dysfunction, premedication with betablockers, etc. [1,10,35,45,51,52] It is important that patient may not complain of classical angina and 'angina equivalents' may not be correctly interpreted by the operator . Further, ischemia may not produce classical ECG findings due to cancellation by changes in opposite walls. It is also important that conventional treadmill test does not record right sided chest leads and posterior chest leads. Ischemia in these areas is likely to be missed but can result in premature stopping of exercise and wrong impression of chronotropic incompetence. Thus, abnormal autonomic dysfunction is only one of the reasons for chronotropic incompetence [35] and underlying diseases are contributory to increased cardiovascular mortality during follow up.

- To correct for the effect of betablockers on exercise induced increase in heart rate, a lower threshold (<65% of age predicted maximal heart rate or chronotropic index of 0.6[9]) was suggested to define chronotropic incompetence [29,32]. However , some authorities disagree. It has been shown that betablockers do not produce chronotropic incompetence in patients with chronic heart failure receiving optimal medical medical therapy [53-55]. Savonen, et al. [12] studied only men between 41 years and 61 years. Effect of age, underlying medicines was not evaluated. Those with lower chronotropic incompetence had higher age, higher serum LDL, and higher systolic blood pressure at rest, higher BMI and increased history of cardiovascular disease. Thus, patients with chronotropic incompetence had higher incidence of cardiovascular risk factors that could have contributed to increased mortality irrespective of chronotropic incompetence.

None of the studies have evaluated any correlation between presence and magnitude of chronotropic incompetence with the cause of mortality and the time period lapsed between entry in study and death.

Gulati, et al. [22] observed that in asymptomatic women, inability to achieve 85% of age predicted maximal heart rate was not an independent predictor of mortality where as other criteria of chronotropic incompetence (chronotropic index) was a better predictor of all cause mortality. On the other hand Brener, et al. [37] observed that peak heart rate and percentage maximal heart rate achieved was independent negative predictor of both significant and severe CAD but chronotropic index predicted severe CAD only.

Pratt, et al. [38] evaluated symptomatic women with chest pain who could not attain target heart rate as having significant coronary artery disease on angiography. Patients with severe coronary artery disease are very likely to terminate exercise prematurely and are likely to be interpreted as having chronotropic incompetence. Chronotropic incompetence in these cases is, therefore, an effect of coronary artery disease.

➢ **Some More Questions Need To Be Answered**.

- These studies did not correlate the presence and magnitude of chronotropic incompetence with other clinical and electrocardiographic markers of severely of coronary artery disease. Independent significance of chronotropic incompetence in this context is, therefore, not clear.
- Can we comit severity of coronary artery disease in a given patient only on the presence of chronotropic incompetence without any consideration of other parameters?
- These studies did not correlate magnitude of chronotropic incompetence with number of vessels involved, site and severely of lesion.

Heart Rate Decline During Recovery (Heart Rate Recovery)

In a normal individual, there is a rapid fall in heart rate during first thirty seconds followed by a slower fall there after [56]. Reactivation of parasympathetic system [57] and deactivation of sympathetic system are responsible for decline in heart rate during recovery. Return of heart rate towards normal indicates circulatory efficiency and fitness [58].

Abnormal heart rate recovery has been defined according to type of recovery protocol used. For those who

undergo an upright - cool down protocol with a slow walk during the first two minutes after exercise, a heart rate recovery of < 12 beats per minute in the first minute of recovery is defined as abnormal [59]. For patients assuming a supine position immediately after the exercise stress test, a heart rate reduction of < 18 beats per minute of recovery has been defined as abnormal [60]. In supine position, venous return is increased. This results in distension of cardiac chambers and reflex decrease in heart rate. For those who assume a sitting position after an exercise stress test, a heart rate reduction of < 22 beats per minute within 2 minute of recovery is considered abnormal [61]. Most of the patients feel giddy on suddenly stopping treadmill at peak exercise. A small duration (20 to 30 seconds) of cool down walk before stopping treadmill, is better tolerated. Shifting the patient to bed takes another few seconds. Some patients, especially those with exercise induced breathlessness, may find it difficult to lie down immediately after exercise. Thus, it may not be possible to record artefact free tracing during first minute of recovery in all patients. It is more convenient to record correct heart rate at the end of two minutes in most patients.

The MRFIT study [33] demonstrated that a delayed heart rate recovery (< 50 beats after 3minutes) was an independent predictor of all cause death in asymptomatic men. Antelmi, et al. [62] in a study of 485 healthy asymptomatic individual without any clinical or laboratory evidence of heart disease found no significant correlation between heart rate recovery and heart rate variability in 1st and 2nd minute after exercise. They observed significant correlation between heart rate variability indices and heart rate recovery only in the third and fourth minute after exercise. Johnson and Goldberger [63] also observed that heart rate recovery after two minute may be independent predictor of adverse cardiovascular outcome. Therefore trend of heart rate recovery over few minutes after cessation of exercise may be easy to use and more informative [36,63].

Previous workers have given rigid values e.g. < 12 beats /minute or < 18 beats/minute. In practice the recorded value may be marginally lower. It may be difficult to categorise these responses as normal or abnormal.

Slow heart rate recovery is considered to be a predictor of severity of coronary artery disease [61,64,65], cardiovascular event [65] and all-cause mortality [59,61,65-67,69] in future. Although slower heart rate recovery can suggest impaired cardiac function and/or myocardial ischemia, a given value does not provide any objective correlation with ejection fraction and number and severity of obstructed coronary arteries. Significance of heart rate recovery in context of coronary artery disease has not been evaluated independent of level of exercise, drug intake, symptoms, signs and electrocardiographic findings during stress test. Detailed evaluation of the work of Watanabe, et al. [60] shows that the group with abnormal heart rate recovery had significantly lower peak heart rate (P=0.0001), proportion of heart rate reserve used (P=0.0001), peak MET (P=0001) and significantly higher incidence of angina (P=0.001), echocardiographic evidence of ischemia (P=0.001) and increase in left ventricular size after exercise (P=0.001). It becomes clear that only a multivariate analysis including various clinical parameters and stress test parameters can answer if slow heart rate recovery has any independent significance.

Detailed analysis of the data of Watanabe, et al. [60] reveals high incidence of various cardiovascular risk factors in the group of patients with decreased heart rate recovery. Group with abnormal heart rate recovery were significantly older (P<0.0001), had significantly higher prevalence of peripheral vascular disease (P<0.0001), prior CAD (P<0.001), prior coronary angioplasty (P<0.006), prior coronary artery bypass (P=0.001), prior myocardial infarction (P=0.001), higher resting systolic BP (P=0.0001), diabetes and LVEF < 40% (P<0.0001). Study sample of Cole, et al. [59] and Shelter, et al. [61] consisted of patients referred for treadmill test due to clinical indication including patients referred for coronary angiography. It means that in these patients clinicians had high suspicion of coronary artery disease. Study sample of Cole, et al. [68] and Watanabe, et al. [60] included subjects with heart disease.

It is also difficult to understand correlation of slow heart rate recovery with 'all cause' mortality. In the study of Watanabe, et al. [60] patients in the group with abnormal heart rate recovery were significantly older (P< 0.0001) had chronic obstructive pulmonary disease (P<0.0001) and diabetes (P<0.0001). In the study of Nishime, et al. [66], patients in the group with abnormal heart rate recovery were elder (P<0.001), hypertensive (P<0.001), smokers (P<0.001), diabetic (P<0.001) and had chronic obstructive pulmonary disease (P<0.001). It is thus clear that higher incidence of several comorbidities at entry in the study contributed to increased 'all cause' mortality in the patients who had abnormal heart rate recovery. Further, although heart rate recovery improves following exercise training [69-71], it does not the improve survival [72]. This also shows that abnormal heart rate recovery per se is not the cause of increased 'all cause' mortality. An abnormal heart rate recovery has been related to abnormal heart rate variability [73] However, in a study of 485 healthy asymptomatic individuals without any evidence of heart disease after careful clinical and laboratory examination, Antelmi, et al. [62] found no significant correlation between heart rate recovery and heart rate variability in first and second minute after exercise [74,75].

Conclusion

Most of the studies performed in the past have important short comings. Their conclusions are, therefore, not acceptable. To find any correct significance of various heart rate parameters observed during treadmill test, studies should include young asymptomatic males and females without cardiovascular risk factors and without any evidence of heart disease or any other comorbidity by thorough clinical and laboratory evaluation. Further, in the era of availability of echocardiography and coronary angiography at every corner, there is no justification in making "guess" based on studies that have significant limitations. In presence of ST segment depression, exercise induced angina and hypotension, heart rate adequacy becomes irrelevant.

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