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Heart rate variability as a predictive factor for coronary artery disease

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Abstract

Background and Objective: Heart rate variability (HRV) is the amount of heart rate fluctuations around the mean heart rate and can be used as a mirror of the cardiorespiratory control system. It is a valuable tool to investigate the sympathetic and parasympathetic functions of the autonomic nervous system. This variation during respiration is called respiratory sinus arrhythmia (RSA). RSA reflects heart rate control system, especially a cardiac parasympathetic activity which can be evaluated by some proper tests such as standing test. Researches show HRV alters among patients with coronary artery diseases (CAD).

Materials and Methods: In this study, we intended to calculate amount of HRV in patients with chest pain before diagnostic exercise stress test (EST) and to compare the obtained results with EST results. 66 (19 women and 47 men) with chest pain. Volunteers and unknown CAD referred for EST with a mean age of 50 years were participated in this study. Each volunteer underwent deep breathing (6 breaths/minute) and standing up tests prior to EST for HRV measurements.

Results: There was less variation in heart rate during both deep breathing and standing up tests in patients with positive result of EST than in patients with negative result of EST.

Conclusion: Our study suggests that HRV is depressed in individuals who have unknown coronary artery disease with an immediate positive EST result.

Keywords: Heart rate variability, Respiratory sinus arrhythmia, Coronary artery diseases

1. Introduction

Heart rate variation (HRV) means variation in consecutive R-R intervals that is a physiological phenomenon (1). HRV is non-invasive method to study general cardiac health as well as sympathetic and parasympathetic function of the autonomic nervous system that regulates cardiac activity (1, 2). This variation during respiration is called respiratory sinus arrhythmia (RSA). RSA reflects heart rate control system, especially cardiac parasympathetic activity (3) which function can be assessed by different manoeuvres such as standing test (4). Coronary artery disease (CAD) usually caused by atherosclerosis is a major health concern and underlying cause for nearly one-third of all deaths (2). It has been suggested that development of CAD is associated with impaired parasympathetic activity (5-7). In addition, it has been reported that the relation between parasympathetic cardiac control and degree of respiratory sinus arrhythmia is linear (3, 8). We conducted this study to investigate possible predictive value of HRV in patients with chest pain before diagnostic exercise stress test. In other words, we wanted to know whether HRV is different in people who have chest pain in the absence of CAD as compared to those who have chest pain due to CAD.

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2. Materials and Methods

2.1. Subjects

We investigated sixty-six patients (19 women and 47 men) aged 32-70 years, with chest pain who were referred to the Tehran Heart Center Hospital to perform an exercise stress test to detect CAD. Patients were excluded if they had history of diagnosed heart disease, diabetes, hypertension, kidney disease, thyroid disease and if they were professional athlete. All study contributors gave written informed consent before entering the study. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

2.2. Preparing for exercise stress test

We asked the participants not to eat or drink anything except water for 3 hours before the test. The patients were also prohibited from doing heavy work and smoking prior to the procedure. Cardiologists of the Tehran Heart Center experienced in EST reading were blind to the results of HRV in order to prevent adjudication of the EST.

2.3. Tests of autonomic nervous function

Each volunteer underwent deep breathing (6 breaths/minute) and standing up tests prior to EST for measurement of autonomic nervous function which were performed in the morning to avoid the effect of circadian rhythm fluctuations on HRV.

2.4. Deep breathing test

The deep breathing test was conducted after explaining the procedures to participants and asking them to lie on the supine position for at least 12 minutes while connected to the limb lead of the standard electrocardiography. After taking the ECG to reject any non-sinusoidal rhythms, only individuals who had normal sinus rhythm could participate in the study. Before beginning the test, patients were taught to breathe at a rate of 6 respiration cycles per minute: 5 seconds for each inhalation and 5 seconds for each exhalation (5). The mean of the difference between the maximum and minimum R-R interval that was determined during each breath considered as HRV in deep breathing test. Simultaneous recording of electrocardiogram (ECG) and respiratory wave form was performed using a commercial data acquisition system power lab (Model ML865 ADInstrument) and chart 5 software (AD Instrument) (figures 1 and 2). The ECG signal was recorded by using lead II standard limb leads (MLA0112/D ECG Lead Switch Box, AD Instrument) and respiratory wave form was monitored using a pneumatic belt placed around the subject's abdomen (MLT 1132 Piezo Respiratory Belt, AD Instrument).

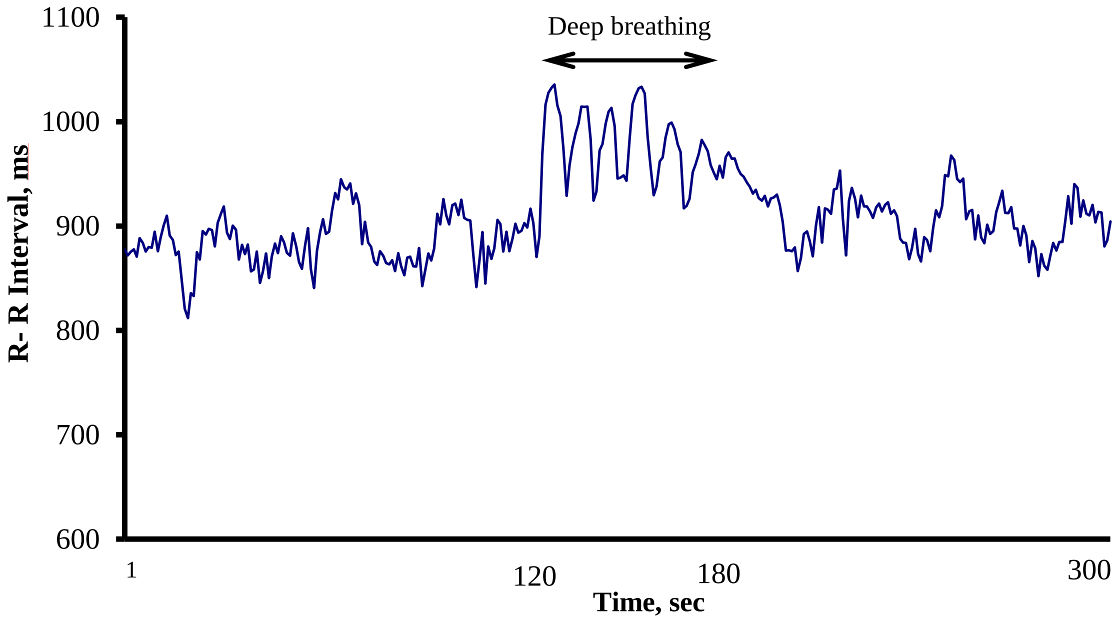


Fig 1. Heart rate response during a minute of deep breathing and 2 minutes of normal spontaneous breathing before and after that are shown in a 47-year-old woman with a negative exercise stress test

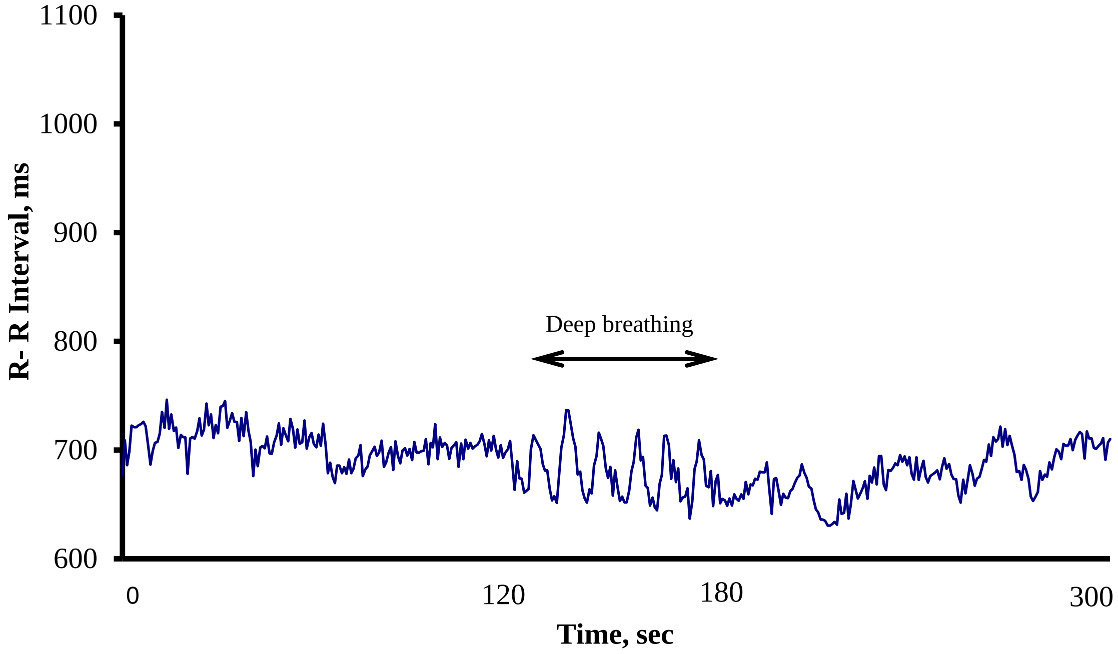
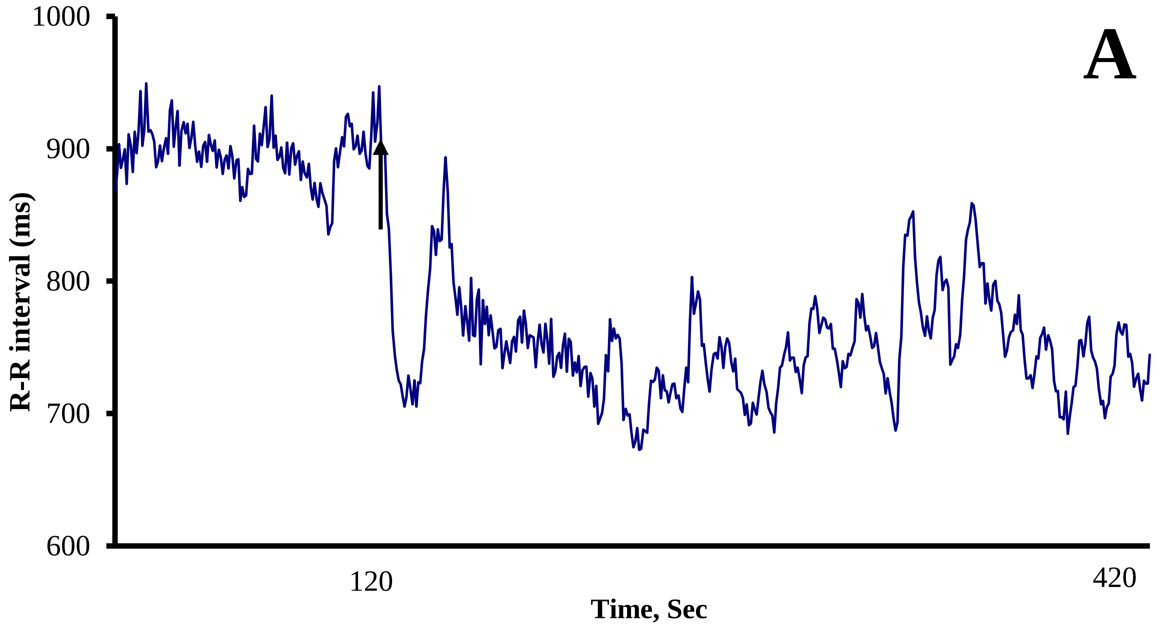


Fig 2. Heart rate response during one minute of deep breathing and 2 minutes of normal spontaneous breathing before and after that are shown in a 64-year-old man with a positive exercise stress test

2.5. Standing up test

After deep breathing test, all volunteers were asked to rest for at least 5 minutes. They were then requested to stand up quickly and ECG recording was done in pre- and post-changing posture (figures 3 and 4). The ratio between the longest R-R interval at around the 30th beat after standing to the shortest R-R interval at around the 15th beat after standing considered to show the response of the heart rate to standing (the 30:15 ratio).



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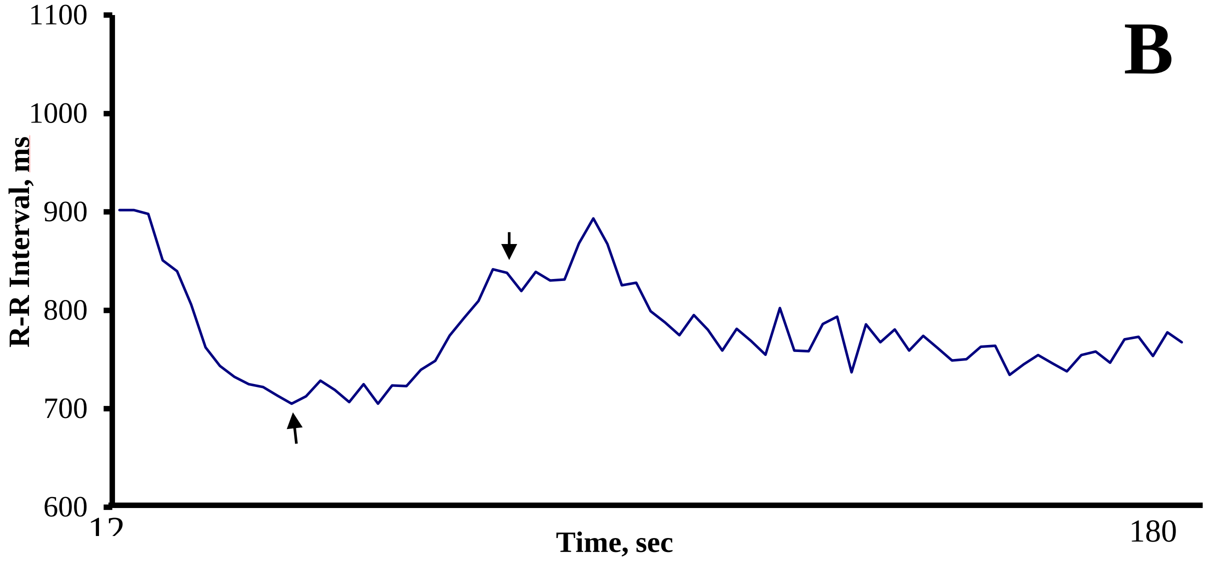

Fig 3. Heart rate response is shown during two minutes before and five minutes after active standing up test in a 47-year-old woman with a negative exercise stress test. Arrow shows the start of change posture form supine to standing (A). The first minute heart rate changes evoked by standing up were shown. Arrows indicate shortest and longest R-R interval after standing (B).

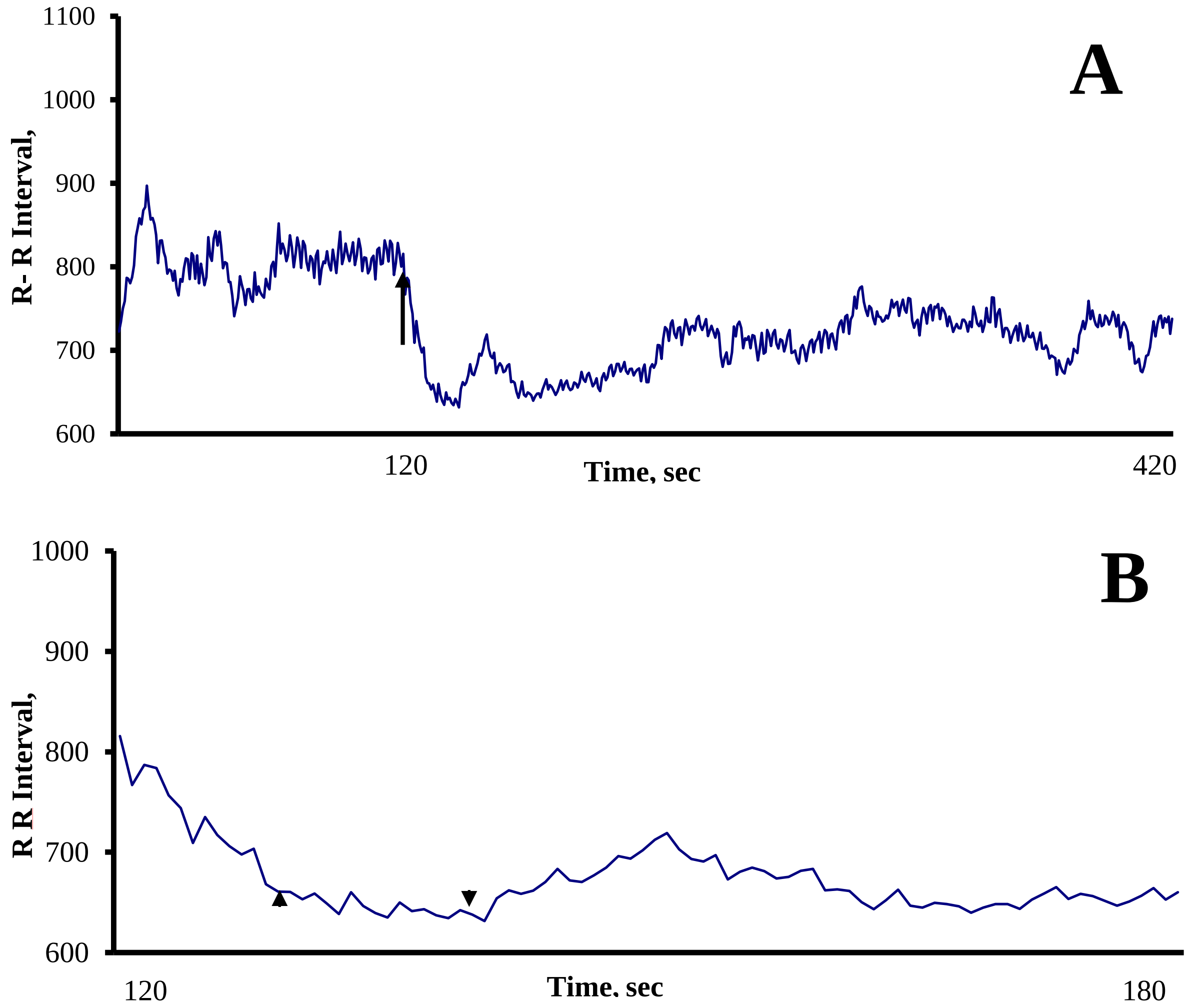

Fig 4. Heart rate response is shown during two minutes before and five minutes after active standing up test in a 40-year-old woman with a positive exercise stress test. Arrow shows the start of change posture form supine to standing (A). The first minute heart rate changes evoked by standing up were shown. Arrows indicate shortest and longest R-R interval after standing (B).

2.6. Statistical analysis

Data are presented as mean ± SEM. Data normality was assessed with Kolmogorov-Smirnov test. Independent t-test used to compare means between two groups. Differences were considered statistically significant if $p < 0.05$.

3. Results

3.1. Heart rate variability in deep breathing test

There was more variation in heart rate as shown in figure 5 during deep breathing ($p = 0.001$) in patients with negative result of exercise stress test (n=16, RSA= 213.70 ± 0.01 ms) than in patients with positive result of exercise stress test (n=50, RSA= 121.83 ± 0.01 ms).

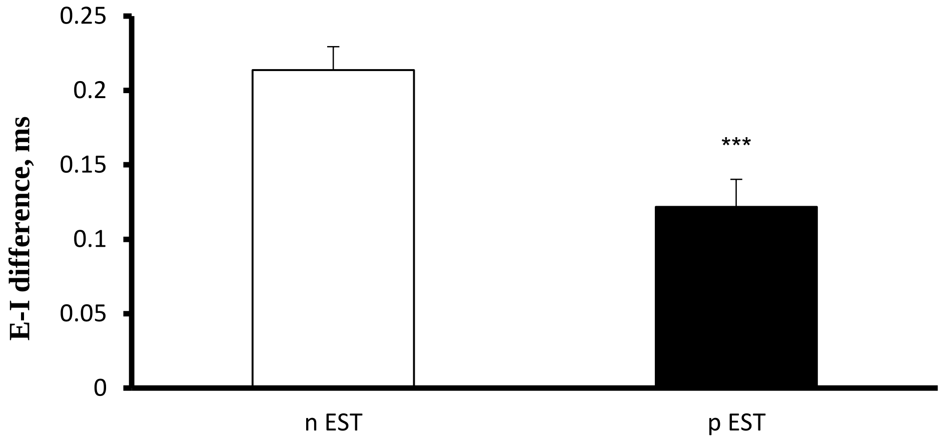

Fig 5. The mean differences for R-R interval during expiration and inspiration (E-I difference) with deep breathing (6 cycles per minute) in patients with negative exercise stress test (n EST, n = 50) and positive exercise stress test (p EST, n = 16). Statistical comparison between groups was performed using independent samples t-Test. *** $p < 0.001$ as compared to n EST group.

3.2. Heart rate variability in Standing up test

Figure 6 shows that variation in heart rate elicited from standing up, ratio 30th R-R interval to the 15th R-R interval after standing, was significantly influenced by CAD ($p < 0.001$). The 30:15 ratio was higher in patients with negative result of exercise stress test (1.27 ± 0.02, n=50) than those who had positive result of exercise stress test (1.01±0.02, n=16).

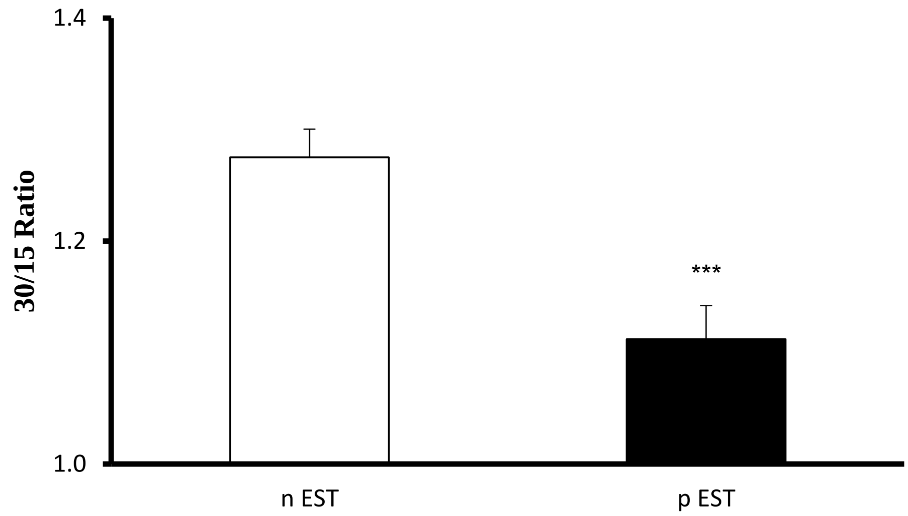

Fig.6. The changes in the maximum/minimum 30:15 ratio of R-R interval during active standing up test in patients with negative exercise stress test (n EST, n = 50) and positive exercise stress test (p EST, n = 16). Statistical comparison between groups was performed using independent samples t-Test. *** $p < 0.001$ as compared to n EST group.

4. Discussion

In the present study, parasympathetic control of cardiac activity was lower in individuals who were suspected to CAD due to chest pain with subsequent positive EST results than those with subsequent negative EST results.

It has been identified that the direct interaction between medullary control centers of respiration and cardiovascular system as well as peripheral physiological reflexes including baroreceptors, pulmonary stretch receptors, and Bainbridge contributes to normal value of HRV. Since vagotomy and atropine reduce RSA and HR oscillation during respiration and also due to the fact that cardiac vagal efferent activity is closely related to the degree of RSA, it can be suggested that parasympathetic is essentially responsible for control of heart rate oscillation. Accordingly, measurement of RSA has emerged as one of the main non-invasive methods to investigate cardiac parasympathetic function (9, 10).

It has been documented that the symptoms of CAD in patients are associated with changes in the automatic regulation of the heart (5, 6). Particularly, study of HRV in patients with stable CAD showed reduced parasympathetic activity (11). Furthermore, Hayano et al. reported that reduction of HR oscillation correlates with the angiographic severity of CAD (12). The exact underling mechanisms for the observed clinical associations are unknown. Altered cardiac autonomic regulation is considered to be the result of ischemia in CAD patients in which cardiac receptor damage is one of the possible reasons (13). However, serial quantitative coronary angiograms have shown that reduced HR variability is responsible for the enhanced progression of coronary atherosclerosis, rather than being a consequence of ischemia (14). Therefore, there is the possibility that reduced HR oscillation is as a risk factor for CAD development. The predictive value of HRV independent from other risk factor has been shown in prediction of mortality rate after myocardial infarction (15). Previously published articles have also described occurrence of neuropathy in diabetic patient which is associated with lower HRV earlier than clinical symptoms of neuropathy (16-18). The results of the current study showed significant reduction in HRV during both deep breathing and standing up tests among individuals who subsequently had positive result of EST as compared with negative result of EST. The present observations suggest the predictive value of HRV measurement for impending CAD. Consistent with our results Goldenberg et al. during prospective clinical study showed that low HRV is associated with the presence of myocardial ischemia in low- to intermediate-risk individuals without known CAD (19). The HRV measurements are non-invasive and easy to perform. Moreover, they have good reproducibility under standard conditions (1, 20). Given the significance to cardiac complications of exercise test, such as arrhythmias and sudden cardiac death, low HRV may provide useful information to identify those that are mostly at risk of such complications. Thereby, they may receive more attention and care in relation to possible complications during exercise testing. Moreover, decrease of heart rate oscillations is introduced as a risk factor for ischemic heart disease. More clinical studies are deserved to determine whether interventions such as medication types and exercise protocols or reduced sympathetic activity that target to increase vagal activity may have particular therapeutic value among patients who have had CAD with reduced HRV.

Conclusion

Two simple tests for HR oscillations measurement, deep breathing and standing up tests, have the ability to provide the clinician with supplemental information to predict CAD.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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