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# Prognostic Value of Normal Exercise Echocardiography in a One-Year Follow-up

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**Background:** Exercise echocardiography is a well-validated technique for the diagnosis of coronary artery disease. In addition to the diagnostic role, it also provides useful prognostic information.
**Objectives:** The aim of this cross sectional study was to assess the prognosis of patients with negative exercise echocardiographic results over a one-year period follow-up.
**Patients and Methods:** The outcomes of 336 patients who had normal exercise echocardiograms were examined. All clinical and exercise echocardiogram parameters were recorded. Patients were followed up for 1 year. End points were defined as cardiac death, non-fatal myocardial infarction, hospital admission for coronary artery disease, and coronary revascularization.
**Results:** Mean age was 54.55 ± 10.34 years. 63.4 % were women. The most frequent risk factor was hypertension. There was no significant statistical difference between men and women regarding the prevalence of systemic hypertension, diabetes mellitus, and history of coronary artery bypass grafting. 5.67% of men and 8.9 % of women had positive exercise tolerance test for ischemia. Hemodynamic parameters, diastolic function, severity of mitral regurgitation, pulmonary artery pressures, peak strain rate were not significantly different between men and women, but rest strain rates were significantly lower in women. Total exercise times and exercise capacity were higher in men. After a 1-year follow-up there was no cardiac events and mortality.
**Conclusions:** Patients with normal exercise echocardiogram results regardless of ischemia or chest pain during the test had excellent outcomes over a one-year follow-up.

*Keywords:*Outcome assessments; Exercise; Echocardiography; Prognosis

## 1. Background

Myocardial ischemia was defined as sequences of events that are also referred to as the ischemic cascade. The first event is localized hypoperfusion in the distal bed of stenotic coronary artery and it causes metabolic changes in myocardial tissue. Diastolic and systolic dysfunctions are subsequent changes in the territory of the involved coronary artery. In later stages, ST segment depression appears in the electrocardiogram (ECG). In the current guidelines exercise ECG is the first investigation in patients who are able to exercise maximally and their electrocardiograms are diagnostic. Exercise ECG can diagnose ischemia in the later stage of ischemic cascade in which it reduces the sensitivity of the test. The accuracy of exercise echocardiogram test is more than the exercise ECG. Exercise echocardiography is a valuable technique for the diagnosis and localization of coronary artery disease by direct observation of myocardial performance (1-3).

## 2. Objectives

The present study sought to determine the normal exercise echocardiograms after the normal exercise echocardiogram during a 1-year follow-up and indeed we want to evaluate prognostic information of normal results.

## 3. Patients and Methods

### 3.1. Study Group

From January 2010 to December 2011, 951 patients were referred for clinical-indicated exercise echocardiogram. Patients treated with digoxin, those with underlying ECG abnormalities such as a left bundle branch block (LBBB), Wolff Parkinson white (WPW) or Q wave on the surface ECG, individuals with suboptimal two dimensional images and patients with dilated, hypertrophic, or restricted cardiomyopathy were excluded.

On the basis of these criteria, 336 were interpreted as normal and they formed the study group. There were no other clinical or technical exclusions. These Patients were divided into 5 groups according to the reason for referral (1). Patients with moderate coronary artery stenosis (50-

70%) in their angiogram, to determine the hemodynamic significance of the lesions (2). Patients with a history of minimal coronary artery disease (CAD) in their previous angiogram over the past 3-5 years, whom presented with symptoms of suspected ischemia (3). Patients with a positive or weakly positive exercise test which their symptoms did not match with exercise results (4). Patients with non-diagnostic exercise testing (5). Patients with a history of open heart surgery or angioplasty who presented with symptoms suspicious for ischemia. The baseline demographic information, coronary artery risk factors, exercise, and echocardiographic data were prospectively recorded.

### 3.2. Exercise Echocardiography Protocol

The exercise stress test was performed on all patients with the Bruce protocol and the McMaster USA 2007 treadmill. The hemodynamic response such as peak heart rate, blood pressure, and electrocardiogram were recorded at the beginning and at every stage. Exercise test was interrupted with occurrence of serious arrhythmia, ST segment elevation of 1mm or more in leads without Q wave or ST segment depression of 3 mm or more, hemodynamic disturbances, including blood pressure equal or greater than 220/120 mmHg or systemic hypotension (below the baseline level), severe symptoms (fatigue, moderate to severe angina, severe dyspnea). The recording ECGs were interpreted by a cardiologist who was blinded about the aims of the study.

A complete resting 2-dimensional (2D) echocardiogram was performed in the left lateral decubitus position by an experienced fellowship of echocardiography using VIVID 7 GE Horton, Norway 2007. Images were obtained at rest in all standard views and immediately after the completion of the exercise within the first 60 to 90 seconds. The recorded images were analyzed according to the standard published protocol. A normal exercise echocardiogram was defined as normal or hyperdynamic motion of all 16 left ventricular segments. We also evaluated LV diastolic function with mitral inflow velocities (E, A, deceleration time) pattern, which usually can be defined as various stages of diastolic dysfunction. Systolic pulmonary artery pressure (SPAP) measured by echocardiographic parameters. Mitral regurgitation (MR) grades were assessed using the proximal isovelocity surface area (PISA) method, color Doppler flow mapping, jet eccentricity, and integrating jet expansion within the left atrium (jet area to atrial area). Strain and strain-rate (SR) imaging (deformation parameters) as a new non-invasive method for assessment of myocardial function were determined at rest and immediately after test completion. Peak systolic SR was determined as the maximal negative SR value during ejection time, end-systolic strain as the magnitude of strain at aortic valve closure. All parameters were 2D based. Due to non-linear relation between peak strain value and peak exercise heart rate, peak strain data did not consider for statistical analyses.

### 3.3. Follow-up

Follow-up was obtained by telephone interview or intermittent regular visits. Patients who could not be followed for at least 12 months were not included in the statistical analysis.

### 3.4. End Points

Patients were followed in terms of cardiovascular events such as death, nonfatal myocardial infarction, need for revascularization, and hospitalization for acute coronary syndromes, cardiac arrest, or any unexplained sudden death.

### 3.5. Statistical Analysis

Analyses were performed using SPSS Statistics 16 for Windows. Baseline clinical, exercise and echocardiographic characteristics of the study group were recorded. Continuous variable were described using mean value ± standard deviation and as a percentage for categorical variables. Distributions of quantitative variables were evaluated by kolmogrov-Smirnov test. For statistical analysis, t-student, one-way ANOVA, and Pearson tests were used for the quantitative variables with normal distribution. Comparisons of the quantitative variables with non-normal distribution were performed by Mann-Whitney, Kruskal-Wallis, and Spearman test.

## 4. Results

### 4.1. Baseline Clinical Characteristics

The study group consisted of 123 men (36.6%) and 213women (63.4%); mean age was 54.55 ± 10.34 years. In this study, there was no significant statistical difference between male and female age (P = 0.419). Clinical characteristics of patients are summarized in Table 1. Systemic hypertension was the most frequent coronary artery disease risk factor in both groups. There was no significant statistical difference between men and women regarding the prevalence of systemic hypertension, diabetes mellitus, and history of coronary artery bypass grafting (P = 0.250, 0.722, 0.729, respectively) but the prevalence of hyperlipidemia was higher in men (P = 0.001). Previous positive or non-diagnostic exercise tolerance tests (ETT) were more common in women (P = 0.001).

### 4.2. Exercise Echocardiographic Characteristics

The patients' exercise echocardiographic test results are summarized in Table 2. The mean work load and total exercise time were higher in men (P = 0.001, 0.001) but hemodynamic responses were similar in both groups. The number of positive ETT results and experiences of angina during ETT were higher in women, but the difference is not statistically significant. Presence of left ventricular hypertrophy, the peak strain rate, stage of diastolic function and SPAP level at rest and peak exercise did not differ statistically between men and women but rest strain rate was significantly lower in women.

**Table 1.** Clinical Characteristics of Patients [a, b]

| Characteristics | Male | Female | Total |
|---|---|---|---|
| **Hypertension** | 43 (35.0) | 88 (41.3) | 131 (39) |
| **Diabetes mellitus** | 33 (26.8) | 61 (28.6) | 94 (28.0) |
| **Hypercholesterolemia** | 26 (21.1) | 5 (2.3) | 31 (9.2) |
| **Smoking** | 7 (5.7) | 5 (2.3) | 12 (3.6) |
| **Previous angioplasty** | 26 (21.1) | 11 (5.2) | 37 (11.0) |
| **Previous angiography** | | | |
| Single vessel disease | 33 (26.4) | 29 (14.4) | 62 (19) |
| Two vessel disease | 9 (7.2) | 8 (4) | 17 (5.2) |
| Minimal CAD | 0 (0.0) | 7 (3.5) | 7 (2.1) |
| Muscle bridge | 0 (0.0) | 3 (1.5) | 3 (0.9) |
| **Previous exercise test** | | | |
| Positive | 3 (2.4) | 27 (12) | 30 (8) |
| Weakly positive | 3 (2.4) | 10 (6.4) | 13 (4) |
| Non diagnostic | 44 (35.5) | 99 (46.5) | 143 (44.0) |

[a] Abbreviation: CAD, coronary artery disease.
[b] Data are presented as No. (%).

**Table 2.** Exercise Echocardiographic Characteristics of Patients [a, b]

| Characteristics | Male | Female | Total | P Value |
|---|---|---|---|---|
| **Max SBP,mmHg** | 150.83 ± 21.31 | 150.09 ± 24.29 | 150.36 ± 23.21 | 0.608 |
| **Max DBP,mmHg** | 85.16 ± 9.90 | 83.31 ± 7.05 | 83.99 ± 8.24 | 0.188 |
| **Max HR,beat/min** | 158.52 ± 16.89 | 156.21 ± 12.17 | 157.05 ± 14.10 | 0.029 |
| **Positive exercise result** | 7 (5.67) | 19 (8.9) | 26 (7.7) | 0.338 |
| **Angina during TMET** | 0 (0) | 4 (1.9) | 4 (1.2) | 0.126 |
| **MET** | 10.21 ± 2.29 | 8.74 ± 2.09 | 9.28 ± 2.27 | 0.001 |
| **Total exercise time, min** | 7.46 ± 2.61 | 5.96 ± 2.04 | 6.51 ± 2.37 | 0.001 |
| **Rest EF, %** | 60.16 ± 5.50 | 62.25 ± 2.89 | 61.48 ± 4.16 | 0.001 |
| **Peak EF, %** | 62.16 ± 5,80 | 64.00 ± 2.93 | 63.48 ± 4.2 | 0.001 |
| **Diastolic function at peak of exercise** | | | | 0.407 |
| Normal | 8 (6.5) | 15 (7.0) | 23 (6.8) | |
| Grade I | 115 (93.5) | 195 (91.5) | 310 (92.3) | |
| Grade II | 0 (0) | 3 (1.4) | 3 (9.0) | |
| Grade III or IV | 0 (0) | 0 (0) | 0 (0) | |
| **Diastolic function at** | | | | |
| **peak of exercise** | | | | 0.331 |
| Normal | 8 (6.5) | 18 (8.5) | 26 (7.7) | |
| Grade I | 115 (93.5) | 192 (90.1) | 307 (91.4) | |
| Grade II | 0 (0) | 3 (1.4) | 3 (9.0) | |
| Grade III or IV | 0 (0) | 0 (0) | 0 (0) | |
| **Rest strain rate** | -1.15 ± 0.40 | -1.10 ± 0.36 | -1.21 ± 0.38 | 0.011 |
| **Peak strain rate** | -1.92 ± 0.89 | -2.02 ± 0.80 | -1.98 ± 0.89 | 0.187 |

[a] Abbreviations: Max, maximal; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TMET, treadmill exercise test; METs, metabolic equivalents; EF, ejection fraction.
[b] Data are presented as No. (%) or Mean ± SD.

### 4.3. Follow-up

All patients were followed for 12 months. There was no cardiovascular mortality, myocardial infarction, sudden death, or revascularization. Five patients were admitted to the emergency department, but there was no evidence of myocardial infarction or ischemia in their evaluations.

## 5. Discussion

Exercise echocardiography is a useful technique for the early detection, evaluation, and localization of coronary artery disease with direct observations. The sensitivity and specificity of exercise echocardiography (85% and 81%, respectively) were comparable to the exercise single-photon emission computed tomography (SPECT) (88% and 72%, respectively) but it is relatively low in cost and it has fewer side effects in comparison with SPECT technique. The exercise echocardiography shows the ischemia in earlier stages than exercise electrocardiography and it also demonstrates wall motion changes before the occurrence of chest pain. We can also evaluate any simultaneous valvular, myocardial, and pericardial disorders (2).

The present cross-sectional study was conducted on 336 patients and it included patients with known coronary artery disease (previous coronary artery bypass grafting (CABG) 2.1%, percutaneous coronary intervention (PCI) 11.0%, single vessel disease 19.0%, two vessels disease 5.2%, and minimal CAD 2.1%) or patients with positive exercise electrocardiography test (12.7%) and patients who did not have any history of CAD. All of them had normal exercise echocardiogram results. There were 312 (63.4%) women in our study. The mean age of patients was 54.55 ± 10.34 years, which it was similar to other investigations such as the McCully et al. and Marwick et al. study (3-7). The most common risk factor in Bouzas-Mosquera et al. (8) study was systemic hypertension which was similar to our study.

In the present study, the percentage of patients who were referred because of positive and weakly positive exercise ECG test results did not compatible with their symptoms or patients with non-diagnostic exercise test findings were higher in women than men (64.7% vs. 40.3%, P = 0.001). These findings were consistent with other studies (9). The diagnosis of coronary artery disease in women is complicated by the frequent abnormal exercise ECGs findings which are most probably secondary to the estrogen effects or hyperventilation in the absence of significant coronary artery disease; hence exercise tolerance test is associated with more false positives results in women. Tomas Marwick et al. (10) in a series of 161 women confirmed that the accuracy of exercise echocardiography for detecting coronary artery disease is higher than exercise electrocardiography.

Arruda-Olson et al. (9) also demonstrated that exercise echocardiography provided incremental value for the predicting cardiac event and mortality in comparison with exercise electrocardiography, rest echocardiogram, and clinical findings. We also found that 7.7% of patients had a positive exercise electrocardiography during exercise echocardiography, and had neither positive exercise echocardiograms nor cardiovascular event during 12 months follow-up but Al-Mallah et al. (5) reported 11% positive exercise electrocardiography results in their evaluation and after 95 months of follow-up, 8.6% of patients had cardiovascular events and they emphasized that the most important predictors of mortality during the test, are the activity level which patients achieved (characterized by metabolic equivalents or MET) and occurrence of chest pain. We think the most probable reason for the low mortality rate in our study is the short term follow-up.

Although ST segment depression is the standard diagnostic index of a positive ETT, this variable in isolation is not strong predictors of prognosis. Low work load and development of angina during the exercise test are two independent predictors of cardiac events (8). Low work load are defined as achievement to activity level of < 7MET for men and < 5MET for women because the expected maximum exercise level is higher in men than in women. Thus, numerous studies have demonstrated that patients who can exercise into stage 4 of the Bruce protocol (> 10 METS) have a desirable outcome, even if they have 3 vessel coronary artery diseases or significant ST segment depression during exercise test (11). In the present study, on average, women's METs were 8.74 ± 2.09 and men's METs were 10.21 ± 2.29 and men achieved higher METs than women (P = 0.001) and similar to the other studies, patients who achieved higher METs had excellent prognosis.

In our study, the degree of diastolic dysfunction, pulmonary artery pressure, and mitral regurgitation severity did not differ significantly at rest and at the peak of exercise in both groups. This finding was also confirmed the absence of significant ischemia in these patients. The necessity of a more quantitative method for stress echocardiography interpretation is dependent on the usage of new imaging modalities. 2D strain imaging is reliable for the evaluation of myocardial regional function (12-14); it has high sensitivity for early detection of myocardial dysfunction and ischemia in patients who are asymptomatic (15). It is not influenced by the angle of the incidence of the ultrasound beam and can be potentially used in any myocardial section without paying too much attention to the heart orientation (16).

In the presence of inducible ischemia, longitudinal abnormalities precede the decrease in radial deformation. In our evaluation, the rest strain rate was significantly lower in women (P = 0.011) but there were no significant statistical difference regarding the peak strain rate (P = 0.187). Respect to our result, the peak strain rate of more than -1.98 ± 0.89 at basal segment may predict normal exercise echocardiogram result and good prognosis. So according to our study and other investigations, 2D strain rate provide incremental accuracy to visual interpretation of stress echocardiogram

This study demonstrated that patients' outcome after normal exercise echocardiogram results were excellent during 1-year follow-up even though the proportion of patients had abnormal exercise electrocardiography or significant coronary artery stenosis. Total time of exercise, level of METs that obtained, and strain rate value provided additional information.

### 5.1. Study Limitations

The numbers of patients who were included in our study were low because we wanted to prevent inter-observer variability in the interpretation of stress echocardiography and all data were gathered by one expert fellowship of echocardiography. Another limiting factor was short term follow-up and the prognostic value of a normal exercise echocardiogram may reduce over time with progression of coronary artery disease.

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## Authors' Contributions

Data collection and acquisition: Dr Afsoon Fazlinezhad and Dr Mona Adibian, Study concept and design: Dr Afsoon Fazlinezhad, Dr Ali Azari, and Dr Leila Bigdelu. Analysis and interpretation of data: Dr Mona Adibian, Dr Ali Azari and Dr Leila Bigdelu. Drafting of the manuscript: Dr Leila Bigdelu. Critical revision of the manuscript for important intellectual content: Dr Afsoon Fazlinezhad and Dr Leila Bigdelu. Statistical analysis: Dr Mona Adibian.

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