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Original Article

# Non-invasive Evaluation of Electromechanical Transmission in Patients with Hypertensive Response to Exercise Stress Test

## *Egzersiz Stres Testine Hipertansif Yanıt Veren Hastalarda Elektromekanik İletimin Non-invaziv Değerlendirmesi*

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## ABSTRACT

**Objective:** Excessive hypertensive response to exercise testing is associated with adverse cardiovascular events such as left ventricular hypertrophy and atrial fibrillation (AF). In this study, we examined the relationship between electromechanical delay and excessive hypertensive response to exercise testing.

**Methods:** Twenty-five people who had a hypertensive response to the exercise stress test and 28 people who were similar in age and gender with a normal blood pressure response in the exercise stress test as the control group were included in the study.

**Results:** There was no statistical difference between the study groups in blood pressure holter values, conventional echocardiography findings, and exercise stress test findings. Lateral PA-TDI time (the time from the beginning of the P wave measured by tissue Doppler imaging to the beginning of the A′ wave), left atrial electromechanical delay, and interatrial electromechanical delay were observed to be significantly longer in the hypertensive response group to exercise stress test compared with the control group (74.0±6.3 vs. 68.8±5.7, p=0.003; 24.7±7.0 vs. 19.6±7.1, p=0.013; 36.8±8.5 vs. 30.6±6.6, p=0.003, respectively).

**Conclusions:** Early detection of electromechanical delay non-invasively may be useful in this patient group in predicting the development of new AF risk.

**Keywords:** Exercise stress test, hypertensive response, electromechanical transmission

## ÖZ

**Amaç:** Egzersiz testine aşırı hipertansif yanıtın sol ventrikül hipertrofisi ve atriyal fibrilasyon (AF) gibi istenmeyen kardiyovasküler olaylarla ilişkili olduğu bilinmektedir. Bu çalışmada, elektromekanik gecikmenin egzersiz testine aşırı hipertansif yanıtla ilişkisini inceledik.

**Yöntemler:** Egzersiz stres testine hipertansif yanıt veren 25 kişi ile egzersiz stres testinde tansiyon yanıtı normal olan yaş ve cinsiyet bakımından benzer 28 kişi kontrol grubu olarak çalışmaya alındı.

**Bulgular:** Çalışma grupları arasında kan basıncı holter değerleri, konvansiyonel ekokardiyografi bulguları ve egzersiz stres testi bulguları arasında istatistiksel fark yoktu. Lateral PA-TDI süresi (doku Doppler ile ölçülen P dalgasının başlangıcından A′ dalgasının başlangıcına kadar geçen süre), sol atriyal elektromekanik gecikme ve inter-atriyal elektromekanik gecikme, egzersiz stres testine hipertansif yanıt veren grupta kontrol grubuna kıyasla anlamlı olarak daha uzun gözlendi (74,0±6,3 vs. 68,8±5,7, p=0,003; 24,7±7,0 vs. 19,6±7,1, p=0,013; 36,8±8,5 vs. 30,6±6,6, p=0,003, sırasıyla).

**Sonuçlar:** Elektromekanik gecikmenin non-invaziv olarak erken tespiti, bu hasta grubunda yeni AF riskinin gelişimini öngörmede faydalı olabilir.

**Anahtar kelimeler:** Egzersiz stres testi, hipertansif yanıt, elektromekanik iletim

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## INTRODUCTION

Exercise testing is routinely used to determine cardiovascular risk[1]. During exercise testing, blood pressure is measured in the initial phase and in all phases of the test, including the phase when the test has maximum exercise intensity[2]. Increased blood pressure during exercise increases cardiac output, which meets the increased oxygen demand in the blood.

Although there is no consensus about the extreme hypertensive response to exercise (EHRE), a blood pressure value exceeding the 90$^{th}$ percentile; it is defined as above 210 mmHg in men and above 190 mmHg in women[3-5]. Physicians checking stress tests routinely report extreme blood pressure response to exercise, but little attention is paid to such reports because of the limited information available about its causes, prognosis, and treatment.

When compared with the normal population, the frequency of atrial fibrillation (AF) increases in patients with hypertension, which is thought to be caused by increased left atrial pressure and fibrosis[6-8]. Fibrosis and enlarged left atrial tissue may prolong the action potential in the left atrial tissue, leading to AF with many microenteric foci. Two non-invasive methods can be used to predict the development of AF:

1) To measure the duration from the onset of the P wave in electrocardiography (ECG) to the beginning of the A' wave in tissue Doppler imaging (PA-TDI time). 2) To evaluate P wave dispersion in ECG. PA-TDI time, derived from echocardiography to assess total atrial conduction time, reflects the left atrial structural and electrical remodelling[9]. Previous studies have shown that echocardiography-derived parameters showing atrial conduction time, such as PA-TDI duration, can be used to identify patients at risk of AF[10]. In clinical practice, the measurement of PA-TDI time is a simple, inexpensive, and easily applicable method. However, there are limited data on the non-invasive evaluation of electromechanical conduction (PA-TDI duration) that can be used to predict future AF in patients with an EHRE test. Therefore, in this study, we aimed to evaluate the interatrial conduction characteristics between participants with an EHRE test and those with a normal exercise stress test.

## MATERIALS and METHODS

The research is an observational study, with participants whose effort test was performed for suspected coronary artery disease and whose effort test was found to be normal in the research. It was accepted by the Dicle University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee with decision number 90 on 15.02.2018. Verbal and written confirmation documents were acquired from the patients for participation in the research.

Participants who could not participate in the study for various reasons or who disapproved of participating in the research were excluded from the evaluation. As a consequence of 24-hour ambulatory blood pressure measurement, 14 participants were diagnosed with hypertension and excluded from the study. Twenty five participants of similar age and gender with an excessive hypertensive response to the exercise stress test and 28 participants without an excessive hypertensive response to the exercise stress test as the control group were included in the study. The previous laboratory parameters of the participant were recorded by scanning the hospital information operating system. No invasive procedures were applied to the participant, and no blood samples were taken.

Participants aged 20-60 years who applied to the cardiology outpatient clinic and decided to perform an exercise test and had no known history of hypertension were included in the research. Those with any cardiovascular disease, myocardial infarction, heart failure, hypertension, diabetes, renal or hepatic disease, cerebrovascular accident, and pregnant women were excluded from the study. The exclusion criteria of the participants were determined as noted below: hypertension diagnosed and/or treated in the past, presence of previously diagnosed and/or treated cardiovascular disease (ischemic heart disease/ischemic stroke), positive exercise stress test, inadequate exercise test, acute or chronic renal or liver deficiency, obstructive sleep apnea syndrome, advanced valve problem (stenosis and/or regurgitation), left ventricular ejection fraction <50%, bundle block, pace rhythm, preexcitation syndromes, AF, ischemia is suspected on ECG taken during recovery, other important systemic or orthopedic problems.

In our study, we compared 25 participants who responded excessively to the stress test and did not have a history of hypertension disease with 28 participants whose effort test was considered normal. To rule out white coat hypertension, 24-hour blood pressure holter was worn on the participants. Atrial electromechanical delay (EMD) was determined non-invasively by the tissue Doppler method. Atrial electromechanical conduction time was discovered to be significantly prolonged in the group with excessive hypertensive response to the stress test. With this finding, we attempted to determine the importance of excessive hypertensive response in exercise testing.

### Statistical Analysis

During the statistical analysis, continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. Normally distributed variables are expressed as the mean and standard deviation. Whether the numerical variables were normally distributed or not was evaluated with subjective methods such as histogram curve and probability curves (Q-Q plots and P-P plots), as well as Lilliefors and Shapiro-Wilk tests, which are objective methods. Normally distributed numerical variables were evaluated using the parametric Student's t-test. The chi-square test was used to determine how categorical variables changed between groups. Specificity and sensitivity values were calculated using the receiver-operator characteristic (ROC) curve to predict interatrial conduction characteristics. A p-value of <0.05 was considered important.

## RESULTS

Demographic characteristics and clinical findings of the groups are compared in Table 1. In our study, there were 53 individuals, 30 males (56%) and 23 females (44%). Fourteen (56%) of the EHRE group were male and 16 (57%) of the control group were male. There was no statistically significant difference in demographic and laboratory findings between the EHRE group participating in the study and the control group.

In Table 2, the parameters of interatrial conduction pathways measured by tissue Doppler echocardiography and left atrial sizes are compared. Left atrial size did not differ between the EHRE and control groups (20.9±4.4 vs. 19.8±3.4, p=0.383). The septal PA-TDI time in each study group was 49.6±4.5 ms vs. 49.0±4.0 ms (p=0.589), the tricuspid PA-TDI time was 37.1±4.4 ms vs. 36.9±4.1 ms (p=0.896), and the right atrial EMD was 12.7±4.9 ms vs. 12.2±5.2 ms (p=0.759). Accordingly, no statistically significant difference was discovered between the EHRE and control groups with regard to septal PA-TDI time, tricuspid PA-TDI time, and right atrial EMD. However, the lateral PA-TDI time was 74.0±6.3 ms vs. 68.8±5.7 ms (p=0.003), the left atrial EMD was 24.7±7.0 ms vs. 19.6±7.1 ms (p=0.013), and the inter-atrial EMD was 36.8±8.5 ms vs. 30.6±6.6 ms (p=0.003). Accordingly, a statistically significant difference was discovered between the EHRE and control groups with regard to lateral PA-TDI time, left atrial EMD, and interatrial EMD. Lateral PA-TDI time left atrial EMD, and interatrial EMD are shown in Figure 1 as a histogram curves. The left-atrial PA-TDI time, interatrial EMD, and left-atrial EMD between the EHRE test group and the control group are shown in Figure 2 with the boxer's bag graphic.

ROC analysis results are given in Table 3 and Figure 3 to distinguish between the EHRE and control groups in terms of lateral PA-TDI time, left atrial EMD and interatrial EMD.

ROC analysis showed statistically significant prolongation in participants with excessive hypertensive response to the lateral PA-TDI time, left atrial EMD, and interatrial EMD exercise test in proportion to the control group (p=0.005, p=0.022, p=0.004).

**Table 1. Comparison of demographic, clinical, and laboratory characteristics of patients according to blood pressure response to exercise stress test.**

| Parameters | EBPR (n=25) | Control (n=28) | p-value |
|---|---|---|---|
| Age (year) | 43±9 | 40±7 | 0.157 |
| Gender (female/male) (n) | 11/14 | 12/16 | 0.935 |
| Height (cm) | 169±8 | 171±9 | 0.315 |
| Weight (kg) | 80±10 | 81±10 | 0.720 |
| BMI (kg/m²) | 28±3 | 27±3 | 0.575 |
| BSA (m²) | 1.86±0.13 | 1.93±0.15 | 0.416 |
| Glucose (mg/dL) | 99±11 | 99±17 | 0.938 |
| Total cholesterol (mg/dL) | 206±53 | 189±37 | 0.178 |
| Triglycerides (mg/dL) | 188±75 | 246 ±206 | 0.192 |
| HDL (mg/dL) | 45±11 | 46±11 | 0.778 |
| LDL (mg/dL) | 111±28 | 106±34 | 0.505 |
| GFR (mL/min/1.73) | 100±13 (n=18) | 109±17 (n=12) | 0.116 |
| Creatinine (mg/dL) | 0.8±0.1 (n=18) | 0.8±0.1 (n=12) | 0.897 |

EBPR: Exaggerated blood pressure response, BMI: Body mass index, BSA: Body surface area, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, GFR: Glomerular filtration rate

ROC analysis of the data was performed to evaluate the severity of the EMD. When the cut-off value for lateral PA-TDI time was 67.5 ms, sensitivity was 76% and specificity was 54% [area under the curve (AUC): 0.72, 95% confidence interval (CI): 0.58-0.85, p=0.005]. When the cut-off value for left atrial EMD was taken as 20.5 ms, the sensitivity was 72% and specificity was 54% (AUC: 0.68, 95% CI: 0.54-0.82, p=0.022), when the cut-off value for interatrial EMD was taken as 31.5 ms, the sensitivity was 72% and specificity was 54% (AUC: 0.73, 95% CI: 0.59-0.87, p=0.004).

## DISCUSSION

According to the results of our study, the following three important conclusions can be reached. 1) Presence of EHRE has worse scores than the control group with tissue Doppler imaging methods, which previously predicted the development of AF. 2) EHRE was thought to be more clinically important than it should be due to poor tissue Doppler times results. 3) Evaluation of electromechanical conduction with non-invasive imaging methods is one of the methods that can be used in the identification and follow-up of conditions that will cause subclinical damage.

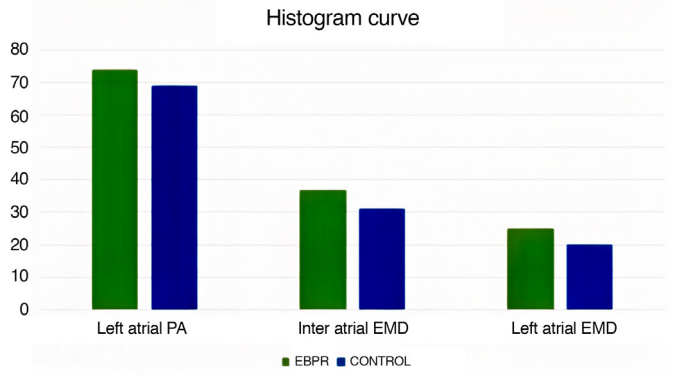


**Figure 1.** Histogram curve.

EBPR: Exaggerated blood pressure response, EMD: Electromechanical delay

At this time, there are conflicting data on the prognostic value of EHRE. In some studies, prognostic value has little or has not been in proportion to office blood pressure measurement[11,12], and in some studies, it has been found to be relevant with the risk of cardiovascular events in apparently healthy patients[13], as well as the development of essential hypertension in the future[14,15] and adverse events. It is an independent predictor of cardiac remodeling[16,17]. This uncertainty needs to be ruled out to understand whether EHRE has clinical significance. In addition, this method is cost-effective in patients admitted to the hospital with chest pain[18].

Current guidelines on existing hypertension do not provide data on the management, diagnosis, and potential clinical significance of patients with an overly hypertensive response to exercise testing[19,20]. One of the main issues in the interpretation of the findings in research conducted on patients with excessive hypertensive response to exercise is the different nature of the studies used. There are many studies on this subject published in the literature; Their designs, results, exercise modalities, exercise intensities, and participant characteristics (groups with or without coronary artery disease) are different from each other. Therefore, it does not seems possible to easily determine the clinical importance of excessive hypertensive response to exercise testing. In all of these studies, excessively increased systolic blood pressure response in moderate exercise; It can predict cardiovascular events regardless of age, office blood pressure, or other cardiovascular risk factors. Some studies showed that

**Table 2. Comparison of left atrial size and parameters showing electromechanical conduction with respect to blood pressure response to the exercise stress test.**

| | EBPR (n=25) | Control (n=28) | p-value |
|---|---|---|---|
| Left atrial size (cm) | 20.9±4.4 | 19.8±3.4, | 0.383 |
| Lateral PA-TDI time (ms) | 74±6.3 | 68.8±5.7 | **0.003** |
| Septal PA-TDI time (ms) | 49.6±4.5 | 49.0±4.0 | 0.589 |
| Triküspit PA-TDI time (ms) | 37.1±4.4 | 36.9±4.1 | 0.896 |
| Left atrial EMD (ms) | 24.7±7.0 | 19.6±7.1 | **0.013** |
| Right atrial EMD (ms) | 12.7±4.9 | 12.2±5.2 | 0.759 |
| Inter-atrial EMD (ms) | 36.8±8.5 | 30.6±6.6 | **0.003** |

EBPR: Exaggerated blood pressure response, EMD: Electromechanical delay, PA time: The time from the beginning of the p wave measured by tissue Doppler to the beginning of the A' wave

the relationship between obesity and hypertension in children and adolescents was also demonstrated by the ambulatory blood pressure measurement method, confirming the knowledge that the obese patient group is a risky patient group in terms of hypertension and hyperlipidemia[21]. Therefore, the excessive increases in systolic blood pressure can be interpreted as an increased cardiovascular risk of clinicians. However, more research is needed to explain the effect of an excessively increased hypertensive response to exercise on increased mortality, development of AF, and its physiological mechanism.

AF, the most common cardiac arrhythmia, is associated with poor prognosis, ischemic stroke, disability, heart failure, and mortality[22]. Non-invasive evaluation of electromechanical conduction can be used to predict future AF in patients with EHRE. Our study demonstrated that the durations of lateral PA-TDI, left atrial EMD, and interatrial EMD were significantly prolonged in patients with EHRE. Similar to our study, the lateral PA-TDI duration has been associated with AF in the literature[10]. The advantage of PA-TDI duration over other parameters is that it combines electrical and morphological manifestations of atrial remodelling[10]. Based on these findings, we can say that lateral PA-TDI time and left atrial and interatrial EMD are prolonged in patients with EHRE, and the risk of developing AF is higher in these patients. In addition, these parameters could be useful to risk stratify patients with EHRE who are at risk of having AF.

In the future, evaluation of PA-TDI duration as a routine echolaboratory parameter in patients with EHRE can significantly improve risk stratification and AF management.

The simple, rapid, and inexpensive measurement of PA-TDI duration shows that it is suitable for daily clinical practice. Because the PA-TDI duration reflects the different aspects and dynamics of atrial cardiomyopathy, this parameter may be useful in detecting the adverse effects of the hypertensive response on the heart. Larger randomized studies are needed to show the relationship between these findings and clinical events such as AF, stroke, and heart failure in long-term follow-up.

Our study has some limitations. In addition to being a cross-sectional study, the primary limitation of our research is that it is not known whether the participants experienced a cardiovascular event in the next period. The small number of participants was another limitation of the study. Our study is an observational study and is

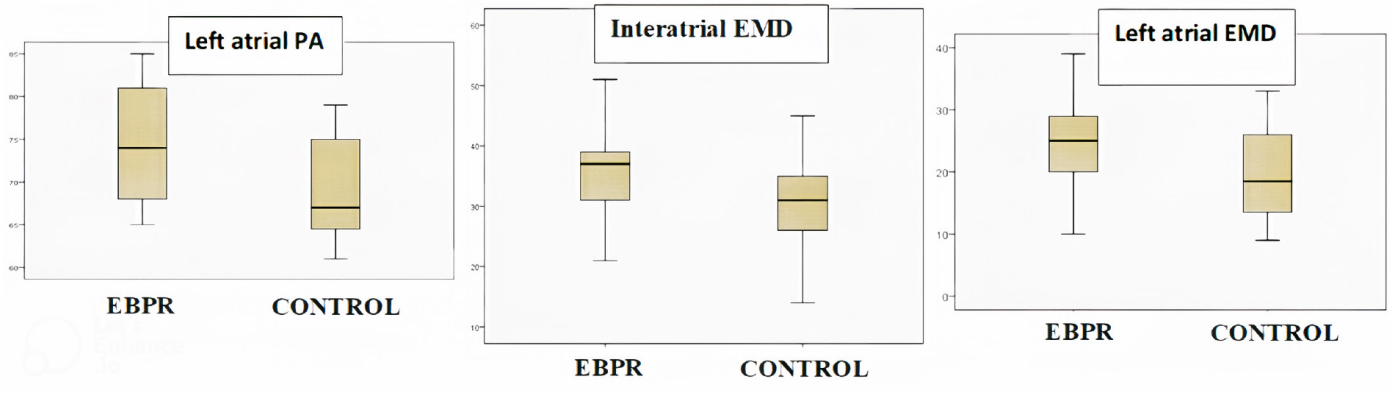


**Figure 2.** Left-atrial PA/interatrial electromechanical delay/left-atrial electromechanical delay) between the excessive hypertensive response to exercise test (EBPR) group and the control group with the boxer's bag graphic.

EBPR: Exaggerated blood pressure response, EMD: Electromechanical delay

**Table 3. ROC analysis table.**

| | Cut-off (ms) | Sensitivity | Specificity | Area under the curve | p-value | %95-CI |
|---|---|---|---|---|---|---|
| Lateral PA-TDI time | 67.5 | 76% | 54% | 0.72 | 0.005 | 0.58-0.85 |
| Left atrial EMD | 20.5 | 72% | 54% | 0.68 | 0.022 | 0.54-0.82 |
| Interatrial EMD | 31.5 | 72% | 54% | 0.73 | 0.004 | 0.59-0.87 |

EMD: Electromechanical delay, CI: Confidence interval, ROC: Receiver-operator characteristic

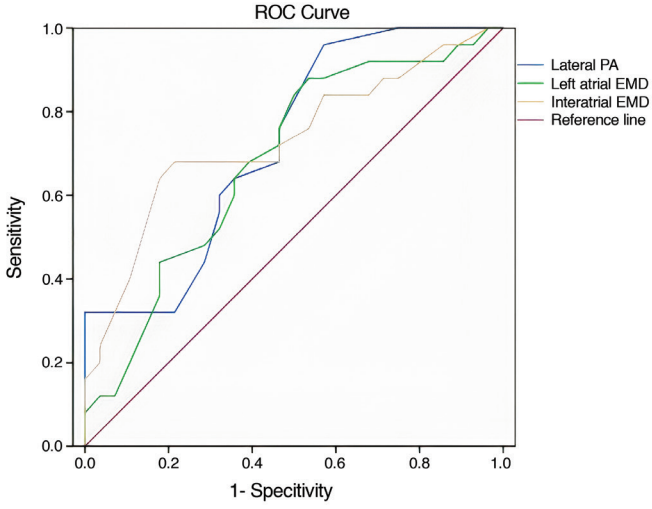


**Figure 3.** ROC curve graphic.

EMD: Electromechanical delay, ROC: Receiver-operator characteristic

single-centered; therefore, larger and more randomized controlled studies are needed to verify these findings.

## CONCLUSION

The duration of lateral PA time, left atrial EMD, and interatrial EMD was significantly longer in the group with excessive hypertensive response to the exercise test than in the control group. Because target organ damage, such as carotid artery atherosclerosis and left ventricular hypertrophy, is associated with AF, it is associated with poor cardiovascular endpoints in previous studies performed in patients with excessive hypertensive responses in exercise testing. Left ventricular diastolic dysfunction, which is frequently caused by arterial hypertension, constitutes most patients presenting with heart failure in the cardiology clinic. In addition, there is a higher risk of AF in hypertensive patients. Atrial EMD in patients with normal sinus rhythm has recently gained interest as a non-invasive predictor of AF. Early detection of EMD non-invasively may be useful in this patient group in predicting the development of new AF risk.

### Ethics

**Ethics Committee Approval:** The study was approved by the Dicle University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee with the decision number 90 in 15.02.2018.

**Informed Consent:** An informed consent for publication was obtained from all patients.

**Peer-review:** Externally and internally peer-reviewed.

### Author Contributions

Surgical and Medical Practices: R.K., M.O., Concept: A.F.K., M.H.O., C.Y., Design: A.F.K., M.H.O., C.Y., Data Collection and/or Processing: A.F.K., R.K., M.O., Analysis and/or Interpretation: A.F.K., M.O., H.K., Literature Search: A.F.K., C.Y., Critical Revision: R.K., H.K., Supervision: M.O., H.K., C.Y., Writing: A.F.K., C.Y., H.K.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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