

## Endothelial Dysfunction in Young Adults: The Limited Prognostic Value of Electrocardiographic Parameters and the Need for Advanced Diagnostic Methods

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### Abstract

**Objective:** Endothelial dysfunction (ED) is an early indicator of cardiovascular disease and plays a key role in the initiation of atherosclerosis. ED is characterized by decreased bioavailability of nitric oxide (NO), increased oxidative stress, and inflammatory responses, which trigger atherosclerotic plaque formation. Early detection of ED is important for preventing cardiovascular risk in young adults. This study aims to investigate the relationship between ED and electrocardiographic (ECG) parameters.

**Methods:** Between January 2024 and June 2025, 60 patients aged 18–45 years without chronic disease who applied to the cardiology outpatient clinic were included in the study. Patients were divided into ED-positive (n=30) and ED-negative (n=30) groups according to NO, ICAM-1, malondialdehyde (MDA), and flow-mediated dilation (FMD) measurements. ED was defined as NO <10 µmol/L, ICAM-1 >10 ng/mL, MDA >1,500 ng/mL, and FMD <7%. Electrocardiogram (ECG) parameters were analyzed using a 12-lead ECG.

**Results:** In the ED-positive group, NO levels were lower (4.8 vs. 5.0 µmol/L, p=0.438), ICAM-1 (10.2 vs. 6.5 ng/mL, p<0.001) and MDA (1796 vs. 305 ng/mL, p<0.001) were higher, and FMD was lower (6% vs. 10%, p<0.001). Among ECG parameters, only S-wave amplitude was higher in the ED-positive group (0.43 vs. 0.27 mV, p=0.004). Regression analysis showed that S-wave amplitude was an independent predictor of ED (odds ratio 2.662, 95% confidence interval 1.664–4.253, p<0.001).

**Conclusion:** Biomarkers and FMD are superior to routine ECG in detecting ED. Only the S-wave amplitude was associated with ED, indicating the limited prognostic value of ECG. Biomarkers and FMD are recommended for early cardiovascular risk detection.

**Keywords:** Cardiovascular diseases; electrocardiography; intercellular adhesion molecule-1; nitric oxide.

## Genç Yetişkinlerde Endotel Disfonksiyonu: Elektrokardiyografik Parametrelerin Sınırlı Prognostik Değeri ve İleri Tanı Yöntemlerine İhtiyaç

### Özet

**Amaç:** Endotel disfonksiyonu (ED), kardiyovasküler hastalığın erken bir göstergesi olup aterosklerozun başlangıcında kilit rol oynar. ED, nitrik oksit (NO) biyoyararlanımında azalma, oksidatif stres artışı ve inflamatuvar yanıtlarla karakterizedir, bu da aterosklerotik plak oluşumunu tetikler. ED'nin erken tespiti, genç yetişkinlerde kardiyovasküler riskin önlenmesi için önemlidir. Bu çalışma, ED ile elektrokardiyografik (EKG) parametreler arasındaki ilişkiyi incelemeyi amaçlar.

**Yöntem:** Ocak 2024–Haziran 2025 arasında kardiyoloji polikliniğine başvuran, 18–45 yaş arası, kronik hastalığı olmayan 60 hasta çalışmaya dahil edildi. Hastalar, NO, ICAM-1, malondialdehit (MDA) ve akıma bağlı dilatasyon

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(FMD) ölçümleriyle ED pozitif (n=30) ve ED negatif (n=30) gruplarına ayrıldı. ED; NO <10 µmol/L, ICAM-1 >10 ng/mL, MDA >1,500 ng/mL, FMD <7% kriterleriyle tanımlandı. EKG parametreleri 12 derivasyonlu EKG ile analiz edildi.

**Bulgular:** ED pozitif grupta NO (4,8 vs. 5,0 µmol/L, p=0,438) düşük, ICAM-1 (10,2 vs. 6,5 ng/mL, p<0,001), MDA (1796 vs. 305 ng/mL, p<0,001) yüksek, FMD (6% vs. 10%, p<0,001) düşük bulundu. EKG'de yalnızca S dalga amplitüdü ED pozitif grupta yüksekti (0,43 vs. 0,27 mV, p=0,004). Regresyon analizi, S-dalga amplitüdünün ED için bağımsız öngörücü olduğunu gösterdi (OR 2,662, 95% GA 1,664–4,253, p<0,001).

**Sonuç:** ED tespitinde biyobelirteçler ve FMD, rutin EKG'ye üstündür. Yalnızca S-dalga amplitüdü ED ile ilişkili olup EKG'nin sınırlı prognostik değerini gösterir. Erken kardiyovasküler risk için biyobelirteçler ve FMD önerilir.

**Anahtar sözcükler:** Kardiyovasküler hastalıklar; elektrokardiyografi; hücreler arası adezyon molekülü-1; nitrik oksit.

## Introduction

Endothelial dysfunction (ED) is considered an early stage in the pathogenesis of cardiovascular disease (CVD) and plays a critical role in the initiation of atherosclerosis.<sup>[1]</sup> The endothelium is a fundamental structure that regulates vascular tone, controls thrombotic and inflammatory processes, and maintains vascular integrity.<sup>[2]</sup> ED is characterized by decreased bioavailability of nitric oxide (NO), increased oxidative stress, and activation of inflammatory responses. These processes trigger the formation of atherosclerotic plaques, laying the groundwork for serious cardiovascular events such as coronary artery disease, hypertension, and stroke.<sup>[3]</sup> Early detection of ED offers a critical opportunity for the prevention of cardiovascular risk, especially in young adults without comorbidities, as early interventions in this population can halt or delay disease progression.<sup>[4]</sup>

In the evaluation of ED, biomarkers and non-invasive methods such as NO, intercellular adhesion molecule-1 (ICAM-1), malondialdehyde (MDA), and flow-mediated dilation (FMD) are widely used.<sup>[5]</sup> NO is the main mediator of endothelium-dependent vasodilation and a fundamental indicator of ED.<sup>[6]</sup> ICAM-1 reflects the inflammatory activation of endothelial cells, while MDA clearly demonstrates the damage caused by lipid peroxidation in the vascular wall and increases endothelial injury by triggering LOX-1 receptor and nicotinamide adenine dinucleotide phosphate oxidase activation.<sup>[7]</sup> FMD, on the other hand, is a non-invasive method that measures endothelium-dependent vasodilation capacity in the brachial artery and is strongly associated with cardiovascular risk prediction.<sup>[8]</sup> While these biomarkers and FMD provide high sensitivity and specificity in the early diagnosis of ED, the use of routine electrocardiography (ECG) for this purpose, particularly in young and asymptomatic populations, remains controversial.<sup>[9]</sup>

Early diagnosis of ED in young adults is vital for identifying cardiovascular risk and implementing preventive strategies. In this context, our study aims to investigate the relationship between ED – evaluated using blood biomarkers (NO, ICAM-1, MDA), and FMD – and ECG parameters in young adults aged 18–45 years who presented to the cardiology outpatient clinic. Our hypothesis is that ECG parameters have limited prognostic value in detecting ED, and that advanced diagnostic methods such as biomarker profiling and FMD are needed for early risk classification.

## Materials and Methods

### Study Population

A total of 60 patients aged 18–45 years who presented to the cardiology outpatient clinic between January 2024 and June

2025 were included in the study. Ethical approval was obtained from the İstinye University Faculty of Medicine Ethics Committee on January 23, 2024, with decision number 24–257. In addition, written informed consent was obtained from each study participant. The study was conducted in accordance with the Declaration of Helsinki. Participants were individuals without known CVD, diabetes, hypertension, asthma, hyperlipidemia, or other chronic conditions; with a body mass index between 18 and 30 kg/m<sup>2</sup>; consuming fewer than two alcoholic beverages per day; not using illicit drugs; not taking regular medications (except oral contraceptives); and without a history of professional athletic activity. Patients were divided into ED-positive (n=30) and ED-negative (n=30) groups based on a composite scoring system derived from NO, ICAM-1, MDA, and FMD measurements.

### Biomarker and FMD Measurements

Blood samples were analyzed for NO (µmol/L), ICAM-1 (ng/mL), and MDA (ng/mL) using standard laboratory techniques. Analyses were performed on the ARCHITECT c16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA) using Thermo Scientific DRI Assay, and blood samples were stored at –40°C.

FMD was measured in the brachial artery using high-resolution ultrasound.<sup>[2]</sup> The measurement was performed as follows: After an 8-hour fast, patients were rested for 10 min in a quiet environment, and the right brachial artery was visualized in a longitudinal plane using a Philips Affiniti 70°C ultrasound system (Philips Healthcare, Andover, MA, USA) equipped with a 7–12 MHz linear probe. After recording the baseline artery diameter, a cuff was placed on the upper arm and inflated to 200 mmHg for 5 min to induce transient ischemia. Sixty to ninety seconds after the cuff was released, the change in arterial diameter was measured, and the FMD percentage was calculated as (post-ischemic diameter – baseline diameter)/baseline diameter × 100. ED was defined as NO <10 µmol/L, ICAM-1 >10 ng/mL, MDA >1,500 ng/mL, and FMD <7%. A composite ranking score was created to identify the study cohort's patients with the most severe ED and those with the best-preserved endothelial function. Each parameter was standardized to its corresponding cutoff value for each participant (cutoff divided by patient value for MDA and ICAM-1, given their inverse directionality; patient value divided by cutoff for NO and FMD). A composite score was created by adding the four normalized values. All four parameters were given equal weight in the composite score.

**Table 1. Biomarker and FMD measurements in ED-positive and ED-negative groups**

Parameter	ED-positive (n=30)	ED-negative (n=30)	p
Nitric Oxide ( $\mu\text{mol/L}$ )	4.8 (4.3–5.5)	5.0 (4.5–5.4)	0.438
ICAM-1 (ng/mL)	10.2 (8.0–19.2)	6.5 (5.0–8.2)	<0.001
MDA (ng/mL)	1796 (1.231–2.000)	305 (250–446)	<0.001
FMD (%)	6 (5–6.5)	10 (8–11)	<0.001

Mann-Whitney U test. Data are presented as median (interquartile range). ED: Endothelial dysfunction; ICAM-1: Intercellular adhesion Molecule-1; MDA: Malondialdehyde; FMD: Flow-mediated dilation.

**Table 2. ECG parameters in ED-positive and ED-negative groups**

Parameter	ED-positive (n=30)	ED-negative (n=30)	p
RR interval (ms)	737.4 (672.2–833.1)	709.8 (636.1–756.4)	0.315
P-wave amplitude (mV)	0.048 (0.034–0.059)	0.041 (0.032–0.048)	0.101
P-wave duration (ms)	54 (50–62)	60 (50–67)	0.243
PQ interval (ms)	107.5 (99.7–122.7)	107.5 (90.2–125.2)	0.424
Q-wave amplitude (mV)	0.032 (0.017–0.078)	0.051 (0.021–0.081)	0.456
R-wave amplitude (mV)	0.97 (0.65–1.24)	0.92 (0.72–1.24)	0.734
S-wave amplitude (mV)	0.43 (0.25–0.59)	0.27 (0.17–0.35)	0.004
QRS interval (ms)	91 (81–98)	96 (86–102)	0.147
QT interval (ms)	319 (304–332)	315 (302–336)	0.723
QTc interval (ms)	367 (359–387)	384 (359–390)	0.337
T-wave amplitude (mV)	0.21 (0.11–0.30)	0.20 (0.10–0.28)	0.134

Mann-Whitney U test. Data are presented as median (interquartile range). ED: Endothelial dysfunction; ECG: Electrocardiogram; QTc: Corrected QT interval.

This composite score was only utilized to rank patients and indicate the extremes of endothelial function in the cohort. Participants were divided into two equal-sized groups based on their composite score, with the higher half being defined as having ED and the lower half as having normal endothelium function (control group).

Importantly, the composite score was not meant to be a diagnostic index of ED, but rather a practical tool for enriching group comparison using several endothelium markers.

### ECG Recording and Analysis

ECG recordings were obtained from patients in the supine resting position using a Nihon Kohden® (Tokyo, Japan) device with a paper speed of 50 mm/s and a voltage of 10 mm/mV in 12 leads. Sinus rhythm was visually confirmed by an expert cardiologist. P-wave amplitude and duration, PR interval, QRS duration, Q-, R-, and S-wave amplitudes, QT interval, and T-wave measurements were analyzed in leads II and V5 using digitized data in Excel (Microsoft Office®, Washington, USA). QTc was calculated using Bazett's formula [QTc (ms) = QT/√RR (s)], with QTc >440 ms defined as prolonged.<sup>[10]</sup> Measurements were standardized by applying a noise filter and were conducted by two independent observers.<sup>[11]</sup>

### Statistical Analysis

All statistical analyses were performed using IBM the Statistical Package for the Social Sciences Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov

test was used to assess the normality of data distribution. Between-group comparisons were made using the Mann–Whitney U test. Data were presented as median with interquartile range. To evaluate the relationship between ECG parameters and ED, univariate regression analysis was applied. A  $p < 0.05$  was considered statistically significant.

## Results

### Biomarker and FMD findings

Table 1 summarizes the biomarker and FMD results. Compared to the ED-negative group, the ED-positive group showed lower NO (4.8 vs. 5.0  $\mu\text{mol/L}$ ,  $p = 0.438$ ), significantly higher ICAM-1 (10.2 vs. 6.5 ng/mL,  $p < 0.001$ ), significantly higher MDA (1796 vs. 305 ng/mL,  $p < 0.001$ ), and significantly lower FMD (6% vs. 10%,  $p < 0.001$ ).

### ECG findings

Table 2 presents the ECG parameters. Only the S-wave amplitude (0.43 vs. 0.27 mV,  $p = 0.004$ ) showed a significant difference between the ED-positive and ED-negative groups. RR interval, P-wave amplitude and duration, PQ interval, Q- and R-wave amplitudes, QRS duration, QT and QTc intervals, and T-wave amplitude did not show significant differences ( $p > 0.05$ ).

### Regression Analysis

Univariate regression analysis showed that S-wave amplitude was a significant predictor for ED (odds ratio 2.662, 95% confidence interval 1.664–4.253,  $p < 0.001$ ).

## Discussion

ED is of significant clinical importance as an early indicator of CVD. The endothelium is a key structure that regulates vascular tone, controls thrombosis and inflammation, and maintains the integrity of the vessel wall.<sup>[1]</sup> ED is characterized by reduced NO production, increased oxidative stress, and activation of inflammatory processes; this can trigger the early stages of atherosclerotic plaque formation.<sup>[2]</sup> In our study, elevated ICAM-I (10.2 ng/mL) and MDA (1796 ng/mL) levels, along with low FMD (6%) in the ED-positive group, indicate that these mechanisms are active even in young adults. In particular, the increase in MDA levels supports the critical role of oxidative stress in ED. Nielsen et al.<sup>[7]</sup> reported a strong correlation between MDA, as a marker of oxidative stress, and ED, noting that lipid peroxidation in the vascular endothelium is a triggering factor for ED. This finding supports that the high MDA levels (1796 ng/mL) in the ED-positive group in our study indicate vascular damage.

The clinical significance of ED is not limited to being an early marker of atherosclerosis; it also plays a critical role in predicting cardiovascular event risk and guiding early intervention strategies. ED has been associated with serious cardiovascular outcomes such as hypertension, coronary artery disease, and stroke.<sup>[3]</sup> Early detection of ED in young adults provides an opportunity to prevent disease progression through lifestyle modifications (e.g., diet, exercise) and pharmacological interventions (e.g., antioxidant therapy or statins).<sup>[4]</sup> In our study, low NO levels (4.8  $\mu\text{mol/L}$ ) and low FMD values (6%) in the ED-positive group indicate impaired endothelium-dependent vasodilation and suggest that early cardiovascular risk may be present in this population. These findings emphasize that detecting ED in young adults should be considered as a routine assessment in clinical practice.

FMD is increasingly recognized as a non-invasive method for assessing ED in clinical practice. FMD provides an early indicator of cardiovascular risk by measuring endothelium-dependent vasodilatory capacity.<sup>[2]</sup> In a study by Kitta et al.,<sup>[12]</sup> low FMD values were shown to be independent predictors of cardiovascular events and have strong prognostic value, particularly in predicting coronary artery disease risk. In our study, FMD was significantly lower in the ED-positive group (6% vs. 10%,  $p < 0.001$ ), supporting the sensitivity of this method in detecting ED in young adults. The clinical advantages of FMD include its non-invasive nature, reproducibility, and relatively low cost; these features make it a valuable tool for cardiovascular risk stratification, especially in young and asymptomatic populations. However, the standardization of FMD measurements, operator dependency, and potential influence of environmental factors are limitations that must be considered in clinical application.<sup>[8]</sup> In our study, performing FMD measurements with standardized protocols (e.g., 8-h fasting, calm environment, 7–12 MHz probe) increased the reliability of the results.

Among ECG parameters, only S-wave amplitude showed a significant association with ED ( $p = 0.004$ ). The observed variation

in S-wave amplitude between individuals with and without ED may be the result of underlying changes in cardiac electrical properties linked to compromised endothelial function. While overt epicardial ischemia can impact QRS amplitudes in the presence of a myocardial infarction,<sup>[13,14]</sup> the current findings are more likely to be explained by microvascular ischemia. ED corresponds to reduced FMD,<sup>[8]</sup> increased inflammatory activation, and increased oxidative stress,<sup>[3]</sup> as established by significantly lower FMD values and significantly higher ICAM-I and MDA levels in the ED group. These abnormalities can impair coronary microcirculatory perfusion and elicit subtle alterations to ventricular depolarization.<sup>[13]</sup>

Regardless of the absence of severe obstructive coronary artery disease, prior research has shown that microvascular ischemia, oxidative stress, and inflammatory endothelium activation can affect ECG voltage characteristics.<sup>[13,15,16]</sup> Therefore, rather than overt epicardial ischemia, the decrease in S-wave amplitude seen in this study may be an electrophysiological correlate of coronary microvascular dysfunction.

However, the lack of significant differences in other ECG parameters (RR interval, P-wave amplitude and duration, PQ interval, Q- and R-wave amplitudes, QRS duration, QT and QTc intervals) indicates that routine ECG provides limited utility in detecting ED. The limited prognostic value of ECG underscores the need for more sensitive methods for early ED detection, such as biomarker profiling (ICAM-I, MDA) and FMD.

## Study Limitations

This study has several limitations. First, the study population was relatively small ( $n = 60$ ), and validation with larger cohorts is needed to generalize the results to broader populations. Second, FMD measurements are operator-dependent and potentially influenced by environmental factors, which may affect reproducibility; however, the use of standardized protocols minimized this effect. In addition, only univariate regression analysis was performed, and the effects of other potential parameters were not evaluated with multivariate analyses. Since this study has a cross-sectional design, it could not assess the relationship between ED and long-term cardiovascular outcomes. Finally, the limited prognostic value of ECG parameters may necessitate investigation of more sensitive electrophysiological methods (e.g., high-resolution ECG) for early detection of ED in young and asymptomatic populations.

## Conclusion

In young adults without comorbidities, blood biomarkers (ICAM-I, MDA) and FMD are superior to routine ECG in detecting ED. The limited prognostic value of ECG was demonstrated by the fact that only S-wave amplitude showed a significant association. Clinicians should prefer comprehensive diagnostic approaches that include biomarker and FMD assessments to identify individuals at risk for early CVD.

The authors declare no conflicts of interest, and no financial support was received for this study.

## Disclosures

**Ethics Committee Approval:** The study was approved by the İstinye University Faculty of Medicine Ethics Committee (no: 24–257, date: 23/01/2024).

**Informed Consent:** Written informed consent was obtained.

**Conflict of Interest Statement:** None declared.

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