Incremental diagnostic value of color M-mode propagation velocity of the descending thoracic aorta to exercise electrocardiography

İnen torasik aortun renkli M-mod yayılım hızının egzersiz elektrokardiyografi testinin tanısal değerine katkısı

Yılmaz Güneş, M.D., Hasan Ali Gümrükçüoğlu, M.D., Yüksel Kaya, M.D.,[#] Mustafa Tuncer, M.D.

Cardiology Departments of, Medicine Faculty of Yüzüncü Yıl University and
[#]Van Yüksek İhtisas Education and Research Hospital, both in Van

Objectives: Exercise electrocardiography test (EET) has limited sensitivity and specificity. Recently, color M-mode-derived propagation velocity of the descending thoracic aorta (APV) has been shown to be associated with coronary artery disease (CAD). We evaluated the incremental value of APV for better prediction of CAD in EET-positive patients.

Study design: Color M-mode APV was measured in 342 patients undergoing EET for chest pain and an intermediate likelihood of CAD. Coronary angiography was performed in 199 patients having a positive EET.

Results: The mean APV was 44.5±20.8 cm/sec in patients with a positive EET compared to 63.5±19.6 cm/sec in those with a normal test. Significant CAD was detected in 134 patients (67.3%), involving one vessel (n=41), two vessels (n=52), and three vessels (n=41). Patients with CAD had significantly lower APV values compared to patients with normal coronary arteries (33.8±13.2 *vs.* 66.6±15.6 cm/sec, p<0.001). An APV value of ≤41 cm/sec predicted CAD with 85.1% sensitivity and 93.8% specificity. An APV of >61 cm/sec had 94% specificity for the estimation of normal coronary arteries. A threshold of >41 cm/sec and a threshold of >61 cm/sec would have avoided unnecessary coronary angiography in 30.7% (61/199) and 21.6% (43/199) of patients with a positive EET but high APV values, with negative predictive values of 75.3% and 84.3%, respectively. In correlation analysis, APV was significantly correlated with Duke treadmill score (r=0.587, p<0.001) and the number of coronary vessels involved (r=-0.767, p<0.001), but not with any of the echocardiographic parameters.

Conclusion: Measurement of APV may improve diagnostic value of EET and may be specifically valuable to exclude false positive EET results, leading the physician to other noninvasive tests for further evaluation of CAD probability.

Key words: Aorta, thoracic/ultrasonography; coronary artery disease/ultrasonography/diagnosis; echocardiography, Doppler, color/methods; electrocardiography; exercise test.

Amaç: Egzersiz elektrokardiyografi testinin (EET) duyarlığı ve özgüllüğü sınırlıdır. Son zamanlarda inen torasik aortun renkli M-mod yayılım hızının (AYH) koroner arter hastalığı (KAH) ile ilişkili olduğu gösterilmiştir. Bu çalışmada EET pozitif saptanmış olan hastalarda KAH'yi öngörmede AYH'nin ek katkısı olup olmadığı araştırıldı.

Çalışma planı: Çalışmada, göğüs ağrısı olan ve orta derecede KAH olasılığı nedeniyle EET yapılan 342 hastada AYH ölçüldü. Egzersiz testi pozitif bulunan 199 hastaya koroner anjiyografi yapıldı.

Bulgular: Ortalama AYH değeri EET pozitif olan hastalarda 44.5±20.8 cm/sn, normal olan hastalarda 63.5±19.6 cm/sn idi. Yüz otuz dört hastada (%67.3) ciddi KAH saptandı; bunların 41'inde tek damar, 52'sinde iki damar, 41'inde üç damar hastalığı vardı. Normal koronerleri olan hastalara göre KAH saptananlarda AYH anlamlı olarak daha düşüktü (33.8±13.2 ve 66.6±15.6 cm/sn, p<0.001). Koroner arter hastalığını öngörmede AYH ≤41 cm/sn değerinin duyarlığı %85.1, özgüllüğü %93.8 bulunurken, AYH >61 cm/sn değeri ise %94 özgüllük ile normal koroner arterleri öngörmekteydi. Egzersiz elektrokardiyografi testi pozitif, fakat AYH değeri yüksek olan hastalarda, AYH eşiği >41 cm/sn ve >61 cm/sn olarak alınmış olsaydı, hastaların sırasıyla %30.7'sinde (61/199) ve %21.6'sında (43/199) gereksiz anjiyografi yapılmamış olacaktı (negatif öngörü değerleri sırasıyla %75.3 ve %84.3). Korelasyon analizinde AYH, Duke skoru (r=0.587, p<0.001) ve tutulan koroner arter sayısı (r=-0.767, p<0.001) ile anlamlı ilişki gösterdi. Diğer ekokardiyografik parametreler ile AYH arasında anlamlı ilişki saptanmadı.

Sonuç: Renkli M-mod AYH ölçümü özellikle yanlış pozitif EET'lerin dışlanmasını sağlayarak EET'nin tanısal değerini artırabilir, klinisyenleri KAH'nin değerlendirilmesinde diğer invaziv olmayan yöntemleri kullanmaya yönlendirebilir.

Anahtar sözcükler: Aort, torasik/ultrasonografi; koroner arter hastalığı/ultrasonografi/tanı; ekokardiyografi, Doppler, renkli/yöntem; elektrokardiyografi; egzersiz testi.

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Correspondence: Dr. Hasan Ali Gümrükçüoğlu. Yüzüncü Yıl Üniversitesi Araştırma Hastanesi, Kardiyoloji Kliniği, 65100 Van, Turkey.
Tel: +90 432 - 216 47 56 e-mail: hasanaliq80@yahoo.com

Due to widespread availability, safety, relatively low cost, and availability to assess functional capacity, exercise electrocardiography (ECG) is the most frequently used screening test in the evaluation of coronary artery disease (CAD).[1-3] However, it has limited sensitivity and specificity for this purpose. Thus, there is a growing tendency toward the utilization of imaging modalities in combination with exercise ECG.[4,5]

Ultrasound methods enable valid, repeatable evaluation of structures and their function via flow- and pressure-related waveforms.[6] Atherosclerosis not only involves medium-sized vessels, but also develops in the great vessels such as the thoracic aorta. Thickening and stiffening of the arterial wall leads to increased arterial resistance, which may be reflected by a decrease in flow propagation velocity within the arterial lumen. Recently, we have shown that color M-mode-derived propagation velocity of the descending thoracic aorta (aortic propagation velocity-APV) is associated with coronary and carotid atherosclerosis and brachial endothelial function[6] and it may be useful for the prediction of CAD.[7] In this study, we aimed to evaluate the additive diagnostic value of APV to exercise ECG testing in the evaluation of CAD.

PATIENTS AND METHODS

Color M-mode propagation velocity of the descending thoracic aorta was measured in 342 patients undergoing exercise treadmill ECG test for chest pain and with an intermediate pretest probability of CAD. Coronary angiography was performed in patients having a positive exercise test. Exclusion criteria were the presence of the following: a previous history of CAD including documented acute coronary syndrome, coronary revascularization and/or angiographic evidence for CAD; left bundle branch block, paced rhythm, atrial fibrillation, frequent premature beats, Q waves, left ventricular hypertrophy or strain on the electrocardiogram at rest; beta-blocker, calcium channel blocker, digitalis or antiarrhythmic therapy; significant valvular heart disease, nonischemic dilated cardiomyopathy, congenital heart disease, chronic renal disease, severe obstructive pulmonary disease, aortic aneurysm; inadequate echocardiographic image quality, and refusal of coronary angiography. Left ventricular systolic function was normal or near normal in the whole study population (ejection fraction >45%). The study was approved by the hospital ethics committee. All participants were informed about the study and their consents were obtained.

Exercise electrocardiography. Symptom-limited treadmill exercise ECG was performed with the modified Bruce protocol. Test result was defined as positive in case of horizontal or down-sloping ST-segment depression ≥1 mm measured 80 msec after the J point in two or more contiguous leads, being V5 to V6 in case of right branch bundle block and typical angina increasing in severity with exercise. Duke treadmill score (DTS) was calculated with the following equation: DTS=Duration of exercise (min) - (5 x maximal ST deviation) - (4 x angina score) where angina scores were 0 (no angina), 1 (non-test limiting angina), and 2 (exercise-limiting angina).[8] Indications to terminate the test were as follows: achievement of 85% of the maximal predicted heart rate, severe ischemia (ST-segment depression >2 mm or elevation >1 mm), severe symptoms, ventricular or supraventricular

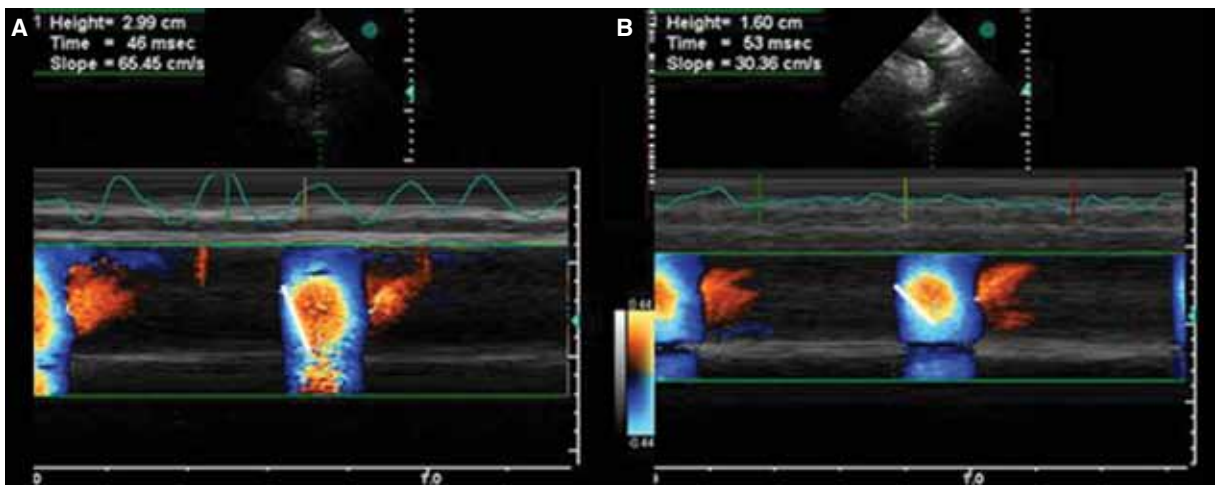

Figure 1. Measurement of propagation velocity of the descending aorta in a patient with **(A)** normal coronary arteries and **(B)** coronary artery disease.

tachyarrhythmias, exaggerated blood pressure elevation (systolic ≥250 mmHg, diastolic ≥120 mmHg), and ≥10 mmHg decrease in systolic blood pressure.

Transthoracic echocardiographic examination. Echocardiographic examination was performed at rest, with the patient in the left lateral decubitus position, using a Vivid 3 device (General Electric, Chicago, IL, USA) with a 3.0 MHz transducer according to established standards[9] by two experienced echocardiographers who were blinded to the clinical data and ongoing therapy. From the suprasternal window and in the supine position, color M-mode Doppler recordings were obtained with the cursor parallel to the main flow of direction in the descending aorta. The Nyquist limit was adapted to 30-50 cm/sec and switching to M-mode with the recorder sweep rate of 200 mm/sec, and flame-shape M-mode spatio-temporal velocity map was displayed (Fig. 1). If the slope of the flame was unclear, the baseline shifting was used to change the aliasing velocity until a clear delineation of isovelocity slope was obtained. Aortic flow propagation velocity was then calculated as the division of the distance between the points corresponding to the beginning and end of the propagation slope, by the duration between the corresponding time points. Thus, APV corresponds to the velocity at which the flow is propagating down the artery. The mean of at least three measurements was recorded as the APV value. The intra- and inter-observer variations were less than 10% and nonsignificant for the measurement of APV.

Coronary angiography. Diagnosis of single-, two-, or three-vessel coronary artery disease was based on the detection of stenosis of at least 50% of the diameter of one, two, or three major epicardial arteries, respectively. Patients with 50% or more stenosis of the left main coronary artery were considered to have two-vessel disease.

Table 1. Clinical and echocardiographic findings of the patients undergoing coronary angiography due to a positive exercise test result

	Coronary artery disease (n=134)			Normal coronary arteries (n=65)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			56.6±8.2			53.7±7.8	0.089
Sex							0.112
Male sex	93	69.4		37	56.9		
Female	41	30.6		28	43.1		
Hypertension	54	40.3		26	40.0		1.0
Diabetes	26	19.4		11	16.9		0.846
Smoking	24	17.9		13	20.0		0.703
Family history of coronary artery disease	40	29.9		13	20.0		0.172
Body mass index (kg/m^2)			27.7±3.1			28.2±3.3	0.387
Total cholesterol (mg/dl)			189.1±38.8			197.1±40.9	0.181
LDL-cholesterol (mg/dl)			116.9±32.5			122.9±33.2	0.225
HDL-cholesterol (mg/dl)			40.3±10.6			41.7±10.5	0.365
Triglyceride (mg/dl)			183.1±94.7			187.4±79.7	0.749
Systolic blood pressure (mmHg)			130.6±15.3			132.5±18.6	0.373
Diastolic blood pressure (mmHg)			81.2±10.8			82.8±10.4	0.444
Left ventricular ejection fraction (%)			58.6±5.9			60.6±4.8	0.082
Mitral inflow deceleration time (msec)			234.6±47.5			222.5±42.2	0.080
Isovolumetric relaxation time (msec)			108.4±16.4			104.5±14.3	0.132
E/A			0.90±0.26			0.95±0.24	0.209
Em/Am			1.10±0.56			1.20±0.59	0.304
Sm (cm/sec)			8.1±1.4			8.6±1.6	0.096
Aortic velocity (m/sec)			1.12±0.17			1.19±0.19	0.084
Color M-mode propagation velocity of the descending thoracic aorta (cm/sec)			33.8±13.2			66.6±15.6	**<0.001**
Single-vessel disease (n=41)			44.1±16.5				
Two-vessel disease (n=52)			30.9± 9.1				
Three-vessel disease (n=41)			27.3±6.7				
Metabolic equivalents			7.8±1.8			8.7±1.2	**0.002**
Duke treadmill score			-7.1±4.6			-0.8±2.2	**<0.001**

Table 2. Comparison of various cut-off values of aortic flow propagation velocity (APV) to predict coronary artery disease

	Coronary artery disease (n=134)		Normal coronary arteries (n=65)		
APV cut-off (cm/sec)	n	%	n	%	*p*
≤32	66	49.3	0		**<0.001**
>32	68	50.8	65	100.0	**<0.001**
≤41	114	85.1	4	6.2	**<0.001**
≤61	126	94.0	22	33.9	**<0.001**
>61	8	6.0	43	66.2	**<0.001**

Statistical analysis. Parametric data were expressed as mean±standard deviation and qualitative data as numbers and percentages. Differences between groups were assessed by the Student's t-test for normally distributed quantitative variables and by the Mann-Whitney U-test for variables without normal distribution, and chi-square test for qualitative variables. Among patients undergoing coronary angiography, Spearman correlation analysis was used to assess the correlations between variables. Cut-off values of APV to detect significant CAD was evaluated with the receiver operating characteristic (ROC) curve analysis. All data were computed using the SPSS package (for Windows, version 10.0). The results were considered statistically significant at the level of $p<0.05$.

RESULTS

Of 342 study subjects, 143 patients had a normal exercise test while 199 patients (58.2%) exhibited a positive result and underwent diagnostic coronary angiography. The mean APV was 44.5±20.8 cm/sec (range 14 to 84 cm/sec) in patients with a positive exercise test compared to 63.5±19.6 cm/sec (range 33 to 96 cm/sec) in those with a normal test. Significant coronary artery disease was detected in 134 patients (67.3%) with a positive exercise ECG, involving one vessel (n=41), two vessels (n=52), and three vessels (n=41). Baseline clinical characteristics were similar in patients with CAD and patients with normal or near normal coronary arteries on coronary angiography (Table 1). Patients with CAD had significantly lower APV, metabolic equivalents, and DTS than patients with normal coronary arteries (Table 1). Aortic flow propagation velocities were in the range of 33-96 (median 66) cm/sec in patients with normal coronary arteries and in the range of 14-84 (median 32) cm/sec in those with CAD. Distribution of APV values according to the number of involved vessels is shown in Figure 2.

Various cut-off values of APV were derived from the ROC analysis to predict CAD and were compared between patients with normal coronary arteries and CAD (Table 2). Sensitivity and specificity of each cut-off value were calculated (Table 3). An APV of >61 cm/sec had 94% specificity for the estimation of normal coronary arteries and an APV of ≤32 cm/sec was 100% specific for the prediction of CAD. In correlation analysis, APV was positively correlated with DTS ($r=0.587$, $p<0.001$), metabolic equivalents ($r=0.231$, $p=0.001$), and negatively correlated with age ($r=-0.145$, $p=0.041$) and the number of coronary vessels involved ($r=-0.767$, $p<0.001$). There was no correlation between APV and any of the echocardiographic parameters.

DISCUSSION

The results of this study show that color M-mode-derived APV contributes to the value of exercise ECG in the evaluation of CAD. Noninvasive evaluation of

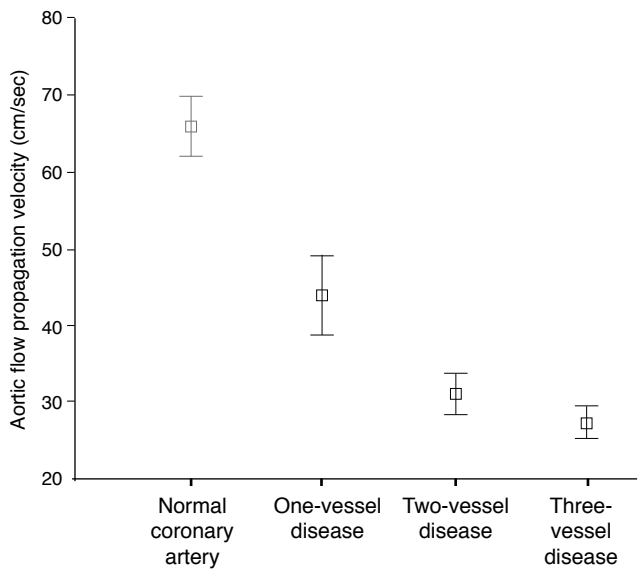

Figure 2. Distribution of aortic flow propagation velocities (mean±2 SD) according to the number of involved vessels.

Table 3. Predictive values of various cut-off values for aortic flow propagation velocity (APV) to detect coronary artery disease

APV cut-off (cm/sec)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≤32	49.3	100.0	100.0	48.9
≤41	85.1	93.8	96.6	75.3
>61	94.0	66.2	85.1	84.3

APV in patients with a positive exercise ECG test may prevent unnecessary invasive diagnostic approach in patients with intermediate likelihood of coronary ischemia.

As cardiovascular diseases is the leading cause of death, prevention of atherosclerosis and its complications is a major goal of healthcare. Individuals at highest risk are often identified using surrogate markers of atherosclerosis such as prior cardiovascular events and the number of risk factors. However, for the large population at moderate risk, better strategies are clearly needed to assess disease severity. Patients presenting with symptoms suggestive of angina pectoris are usually referred for cardiac evaluation. Despite the advent of other imaging modalities, coronary angiography remains the clinical gold standard for the determination of significant CAD. However, due to its invasive nature with serious risks, usually noninvasive tests are used to evaluate the probability of CAD. The most widely used test to obtain objective evidence for myocardial ischemia is treadmill exercise testing. However, the value of exercise ECG in evaluating suspected CAD is limited. Its diagnostic value varies depending on the population being tested. Bayes' theorem states that the probability of a positive test result is affected by the pretest probability of the disease. Hence, the higher the probability of CAD is in an individual before a test is ordered, the higher is the probability that a positive test result would be a true-positive test result. Therefore, exercise ECG is best used in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history. Several criteria may increase the probability of ischemia, such as the number of leads with ST depression, lower workloads at which ST depression occurs, the angle of slope, magnitude of depression, and length of recovery time before normalization of the ST segment. Changes in the inferior leads alone and rapid normalization of slight depressions are likely to lead to false positive results.[1-3] For the general population, the sensitivity is 68% and specificity is 70%.[1] In a recent study, we found that an APV value of ≤41 cm/sec predicted CAD with 82.4% sensitivity, 97.2% specificity, 98.7% positive predictive value, and 68.2% negative predictive value (NPV).[7] In the present study, exercise ECG alone had a positive predictive value of 67.3% and a false positive result of 32.7% for CAD. The sensitivity and specificity of APV ≤41 cm/sec for CAD were 85.1% and 93.8%, respectively, among patients with a positive treadmill test. Therefore, unnecessary coronary angiography might be avoided in patients with both a positive exercise ECG test and higher APV values, representing 30.7% of patients (61/199) for a threshold of 41 cm/sec (NPV for CAD 75.3%). A higher threshold of 61 cm/sec strongly favored normal coronary arteries with a 94% specificity (NPV for CAD 84.3%) and might have prevented invasive approach in 21.6% (43/199) of the patients. Therefore, assessment of APV may be of great importance before referral of patients to diagnostic coronary angiography after a positive exercise test.

It might be expected that the severity of atherosclerosis in the aorta reflected as decreased propagation velocity does not necessarily show coronary atherosclerosis due to uneven distribution of atherosclerosis in different vascular territories. However, there is growing evidence suggesting that aortic atheroma may be a marker of generalized atherosclerosis.[10] Ultrasound measurements such as carotid intima-media thickness (CIMT), aortic pulse wave propagation velocity (PWPV) and flow-mediated dilatation (FMD) have been associated with atherosclerosis and CAD.[11-13] Recently, we found significant correlations between APV and carotid atherosclerosis measured by CIMT and brachial endothelial function assessed by brachial FMD[6] and APV was a more powerful predictor of CAD than PWPV.[7] Several studies showed a strong association between the presence and severity of thoracic aortic plaque imaged by transesophageal echocardiography (TEE) and the presence and extent of CAD.[14,15] In a patient group having a high prevalence of CAD (67%), Fazio et al.[16] reported that the presence of atherosclerotic plaque in the thoracic aorta was a marker for significant CAD at angiography with a sensitivity

of 90% and specificity of 90% (positive predictive value 95%, NPV 82%). In another study, the presence of aortic plaque detected by TEE had a sensitivity of 93%, specificity of 82%, and positive and negative predictive values of 88% and 90%, respectively, for significant CAD.[15] However, the use of TEE for risk assessment in CAD is not feasible in daily practice. Measurement of decreased APV may be an indirect sign of atherosclerotic involvement of the thoracic aorta.

Limitations. Limited image quality may restrict the measurement of APV and reproducibility of the acquisition and reading methods may constitute a limitation. Aortic anatomy and loading conditions may influence the measurements. To confirm applicability of the method as a screening tool, large population studies are needed. The value of this method cannot be appreciated in patients with false negative exercise ECG results since patients with a normal exercise test and low APV values would not be evaluated with coronary angiography. However, low APV values may at least lead the physician to a more careful evaluation for possible CAD.

In conclusion, transthoracic echocardiographic determination of color M-mode propagation velocity of the descending aorta is an easy and practical method. It may be used in patients who are candidates for invasive cardiovascular tests, to improve cardiovascular risk estimation and to avoid unnecessary tests with inherent risks, and for initiation of preventive measures. It improves the diagnostic value of exercise treadmill ECG and may be specifically valuable to exclude false positive exercise ECG results, leading the physician to other noninvasive tests for further evaluation of CAD probability.

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