VERSITA

Cent. Eur. J. Med. • 5(3) • 2010 • 298-302
DOI: 10.2478/s11536-009-0124-4

Central European Journal of **Medicine**

SAECG in Exercise Test for Prediction of Diabetic Coronary Artery Disease

Research Article

Mohammad Ali Babaee Bigi, Amir Aslani*, Arsalan Aslani

Cardiology Department, Shiraz University of Medical Sciences, 71935-1334 Shiraz, Iran

Received 23 July 2009; Accepted 5 October 2009

Abstract: Signal averaged electrocardiogram (SAECG) is considered an important noninvasive indicator identifying patients at risk for ventricular arrhythmias. The aim of this study was to improve noninvasive prediction of CAD by integrating SAECG with the result of exercise tests in diabetic patients. Diabetic patients with stable angina pectoris underwent exercise testing and SAECG. Then a diagnostic score was derived that combined results of exercise testing and SAECG. A diagnostic score (0 to 2 points) was calculated by assigning 1 point for a positive exercise test result and 1 point for a positive SAECG. One hundred and seventy patients were included in the study. In patients with a score of 0, the likelihood of CAD is 18% whereas the likelihood of CAD is 95% in patients with a score of 2. Triple vessel CAD is present in 54%, 7% and only 1.5% of patients with score 2, 1 and 0 respectively. Therefore, patients with score 2 have a poor prognosis compared with score 1 or 0. A diagnostic score combining exercise testing and SAECG can distinguish patients with CAD from those without CAD with high accuracy in diabetic patients.

Keywords: *Coronary artery disease • Diabetes • Exercise testing • Signal average electrocardiogram*

1. Introduction

Coronary artery disease (CAD) in diabetic patients has a worse prognosis than in non-diabetics, with a higher incidence of complications and mortality [1]. Currently, biochemical markers, such as C-reactive protein and natriuretic peptides, have been used as prognostic markers in CAD [2,3]. Signal averaged electrocardiogram (SAECG) is considered an important non-invasive indicator identifying patients at risk for ventricular arrhythmias and sudden death [4-6]. It is well known that structural defects such as previous myocardial infarction or a transient defect related to ischemia may cause a lethal arrhythmia. It is reasonable to expect that by inducing ischemia one may potentially reveal or augment the arrhythmogenic substrate that late potentials represent. The aim of this study was to improve non-invasive prediction of CAD by integrating SAECG with the result of exercise test in diabetic patients.

2. Material and Methods

2.1. Study Population

Consecutive diabetics with stable angina pectoris who were referred for elective coronary angiography were included in this prospective cohort study. Diagnosis of diabetes mellitus was made according to the criteria of the American Diabetes Association [7]. All participants provided written informed consent. Coronary angiography was performed in all patients. Exercise testing was performed the day before coronary angiography. All patients underwent symptom-limited exercise testing using Bruce protocol. An abnormal response was defined as horizontal or downsloping ST-segment depression of ≥ 0.1 mV. Selective coronary angiography and left ventriculography were performed according to standard techniques. Operators performing and interpreting coronary angiographies were unaware of the results of SAECG and stress test. Coronary artery stenosis was visually estimated and expressed as percent lumen diameter stenosis. Narrowing ≥ 50% of ≥1 coronary artery or a major branch was defined as CAD.

* E-mail: draslani@yahoo.com

Table 1. Baseline Characteristics of the Study Population.

	Coronary Artery Disease		Total (n=170)	P value
	Absent (n = 80)	Present (n =90)		
Age (yrs)	50 (31–62)	61 (52–73)	59 (43–69)	0.01
Male	41 (51%)	76 (85%)	117 (68%)	0.03
Left ventricular ejection fraction (%)	70 (64–74)	59 (51–70)	61 (55–71)	0.01
Dyslipidemia	39 (49%)	82 (91%)	121 (71%)	0.01
Hypertension	14 (17%)	19 (21%)	33 (20%)	0.04
Smoker	12 (15%)	13 (14%)	25 (14%)	NS
Family history of CAD	11 (13%)	10 (11%)	21 (13%)	NS

Data are presented as medians [Inter-quartile ranges].
NS=non significant; CAD=coronary artery disease

2.2. Signal Averaged Electrocardiogram

The SAECG was obtained immediately after exercise tests performed by the same experienced technologist. Orthogonal X, Y and Z leads were recorded and approximately 200 beats were averaged to obtain a satisfactory noise reduction. Beats were digitized with a sampling frequency of 2,000 Hz and bi-directionally high-pass filtered at 25 Hz. Noisy or ectopic beats were automatically rejected. Filtered leads were combined into a vector magnitude ($X^2 + Y^2 + Z^2$). Three time-domain variables were calculated by an automated algorithm and visually inspected: (1) filtered QRS duration (msec), which indicates the degree to which the QRS was prolonged by late potentials; (2) Root-Mean-Square (RMS) voltage (μV) of the terminal 40 ms of the filtered QRS, which represents the amount of late potential energy; and (3) the duration (msec) of low amplitude signals [LAS < 40 μV] in the terminal filtered QRS. Positive SAECG was defined as presence of 2 of the following: 1) QRS duration > 114 msec; 2) RMS voltage of the terminal 40 msec of the filtered QRS < 20 μV and 3) LAS < 40 μV for > 38 msec [These definitions represent the recommendations of the American Heart Association, the American College of Cardiology, the European Society of Cardiology, and independently published sources [8-11]].

2.3. Diagnostic Score

A diagnostic score [0 to 2 points] was calculated by assigning 1 point for a positive exercise test result and 1 point for a positive SAECG result.

2.4. Exclusion Criteria

Subjects were excluded from the study if: 1) Patients with previous CAD that was documented with coronary angiography (n=6), 2) Their baseline electrocardiogram showed a bundle branch block [QRS duration > 120 msec] (n=4), 3) Electrolyte imbalance (n=2), 4) Antiarrhythmic medication (n=2), 5) Unsatisfactory noise levels of SAECG either baseline or after exercise (n=10), 6) The patient failed to achieve 90% of the target heart rate during a negative exercise test (n=7).

2.5. Statistical Analysis

Baseline results are presented as counts and percentages for dichotomous variables and as medians with interquartile ranges for continuous variables. Groups were compared with Fisher's exact test for categorical data and the Mann Whitney U test for continuous variables. A P value < 0.05 was considered statistically significant. To assess the discriminatory power of the diagnostic score, contingency table analysis was performed for each variable used and for different cut points of the score. Test statistics, including sensitivity, specificity and predictive values were calculated. Statistical analysis was performed using SPSS11 (SPSS11, Inc., Chicago, Illinois).

3. Results

A total of 170 patients were included in the study. Of these, coronary angiography showed CAD in 90 (53%) patients. Baseline characteristics, results of exercise testing and SAECG, according to the presence or absence of CAD are presented in Tables 1 and 2. Patients with CAD were older and had more cardiovascular risk factors. They also had a higher rate of positive exercise test results and were more likely to have positive SAECG compared with patients without significant coronary stenosis. Exercise tests were positive in 54 patients with CAD (60%) and 17 patients without CAD (21%). SAECG was positive in 38 patients with CAD (42%) and 10 patients without CAD (12%). Changes in the SAECG parameters with exercise are listed in Table 3. Sensitivity, specificity, positive and negative predictive values of exercise test and SAECG for diagnosis of coronary artery disease are listed in Table 4. SAECG has

Table 2. Results of Exercise Tests and Signal Average Electrocardiogram.

	Coronary Artery Disease		P Value
	Absent (n = 80)	Present (n=90)	
Exercise Capacity (METs)	9.5 ±1.3	5.5 ±1.7	<0.001
Maximum Heart Rate (beats/min)	140 ± 18	100 ±14	<0.01
Rate- Pressure Product(mm Hg × min−1 × 1,000)	32 ± 9.1	20 ± 8.7	0.02
Positive Exercise Test Result *	17 (21%)	54 (60%)	0.001
Positive Signal Averaged Electrocardiogram *	10 (12%)	38 (42%)	0.01

Data are presented as Mean ± SD.
** Positive exercise test was defined as horizontal or downsloping ST-segment depression of ≥ 0.1 mV.*
*** Positive signal average electrocardiogram was defined as presence of 2 of the followings after exercise test: 1) QRS duration > 114 msec; 2) RMS voltage of the terminal 40 msec of the filtered QRS < 20 µV and 3) LAS < 40 µV for > 38 msec.*

Table 3. Changes in the Signal Averaged Electrocardiogram Parameters with Exercise.

	Absent CAD (n=80)	Present CAD (n=90)	p value
LAS (ms)			
After exercise	31 ± 8	39 ± 8	< 0.05
Before exercise	31 ± 9	31 ± 7	NS
P value	NS	< 0.05	-
RMS40 (mV)			
After exercise	38 ± 20	49 ± 22	< 0.05
Before exercise	37 ± 21	38 ± 20	NS
P value	NS	< 0.05	-
QRS Duration (ms)			
After exercise	95 ± 7	110 ± 10	< 0.05
Before exercise	94 ± 8	94 ± 7	NS
P value	NS	< 0.05	-

Data are expressed as mean ± SD.
LAS= low amplitude signals; RMS40= root-mean-square voltage of terminal 40 ms of QRS complex; NS= not significant

Table 4. Characteristics of Exercise Test and Signal Averaged Electrocardiogram for Diagnosis of Coronary Artery Disease.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Exercise Test*	60%	79%	76%	64%
Signal Averaged Electrocardiogram**	42%	88%	79%	57%

** Positive exercise test was defined as horizontal or downsloping ST-segment depression of ≥ 0.1 mV.*
*** Positive signal average electrocardiogram was defined as presence of 2 of the followings after exercise test: 1) QRS duration > 114 msec; 2) RMS voltage of the terminal 40 msec of the filtered QRS < 20 µV and 3) LAS < 40 µV for > 38 msec.*

a greater specificity and lower sensitivity for diagnosis of CAD compared to exercise test (Specificity: 88% vs 79%; Sensitivity: 42% vs 60%, respectively). According to classification by the diagnostic score (0 to 2 points), score 0, 1 and 2 was found in 64, 58 and 48 patients respectively. Figure 1 shows the strength of various diagnostic scores for prediction of CAD. In patients with score 0, likelihood of CAD is 18% whereas likelihood of CAD is 95% in patients with score 2. Figure 2 shows the severity of CAD in three patient groups according to classification by the diagnostic score (0 to 2 points). Figure 2 shows that patients classification by the diagnostic score, has a prognostic value as triple vessel CAD is present in 54%, 7% and only 1.5% of patients with score 2, 1 and 0 respectively. Therefore, patients with score 2 have a poor prognosis compared with score 1 or 0.

4. Discussion

SAECG is promising as a noninvasive indicator of patients at risk for lethal arrhythmias [4,5,12]. The source of late potentials is not well understood, but these low amplitude, high frequency potentials at the end of the QRS complex represent delayed myocardial activation [13]. The current consensus hypothesis for the development of lethal arrhythmia requires

Figure 1. Strength of various diagnostic scores for prediction of CAD.

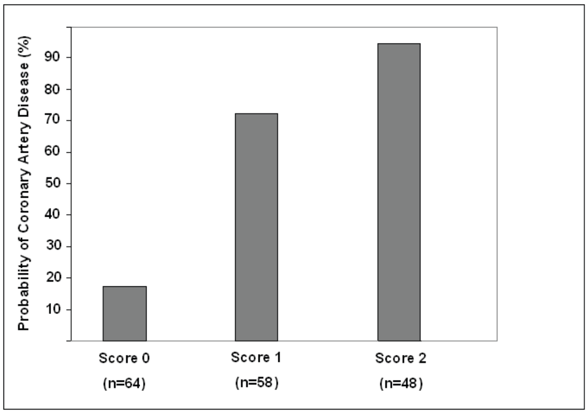
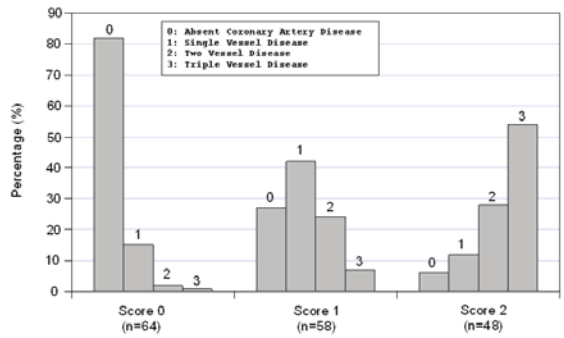


Figure 2. Severity of coronary artery disease in three patient groups according to classification by the diagnostic score (0 to 2 points).



the presence of a structural defect such as previous myocardial infarction, a transient defect related to ischemia or other causes [13,14]. It is reasonable to expect that by inducing ischemia one may potentially reveal or augment the arrhythmogenic substrate that late potentials represent. The time-domain SAECG is sensitive to the noise level. Optimal noise reduction may be difficult to achieve when recording the SAECG in the period immediately after exercise in some patients. In the present study SAECG were included in the analysis only if the noise level was ≤ 0.8 μV at 25 Hz and ≤ 0.2μV at 40 Hz. In the present study, we demonstrated that a diagnostic score using post-exercise SAECG and exercise testing can improve noninvasive prediction or exclusion of CAD in diabetic patients. The addition of post-exercise SAECG can significantly improve the discriminatory ability of noninvasive evaluation of diabetic patients with suspected CAD. In our study, study patients were referred for coronary angiography due to clinical symptoms or patient's history. This work up bias undoubtedly led to a high percentage of patient presenting with CAD on angiography. However, even in these highly selected patients, a 0 point score could rule out 2 vessel and triple vessel CAD with a negative predictive value of 96%.

4.1. Study Limitation

A significant limitation of the present study is the fact that the SAECG was recorded immediately after the completion of exercise test rather than during it and that recording during peak ischemic changes may not have been evaluated. Several studies have demonstrated that exercise associated changes persist for several minute after cessation of exercise. These include exercise-induced echocardiographic changes [15] as well as changes in body surface potential maps [16]. These investigators concluded that sampling in the early recovery period should be expected to be clinically relevant [16]. The majority of our patients with positive exercise tests maintained significant ischemic ST changes during the recording of the SAECG after exercise. In conclusion, it is concluded that a diagnostic score combining exercise testing and post-exercise SAECG can distinguish patients with CAD from those without CAD with high accuracy in diabetic patients.

References

[1] G. Ravapati, W.S. Aronow, C. Ahn, K. Sujata, L.N. Saulle and M.B. Weiss, Association of hemoglobin A1c level with the severity of coronary artery disease in patients with diabetes mellitus. Am J Cardiol 2006; 97: 968–969

[2] G. Ndrepepa, S. Braun, J. Mehilli, N. von Beckerath, W. Vogt, A. Schomig and A. Kastrati, Plasma levels of N-terminal pro-brain natriuretic peptide in patients with coronary artery disease and relation to clinical presentation, angiographic severity, and left ventricular ejection fraction. Am J Cardiol 2005; 95: 553–557

[3] M. Weber, T. Dill, R. Arnold, M. Rau, O. Ekinci, K.D. Muller, A. Berkovitsch, V.Mitrovic and C. Hamm, N-terminal B-type natriuretic peptide predicts extent ofcoronary artery disease and ischemia in patients with stable angina pectoris. Am Heart J 2004; 148: 612–620

[4] Buxton AE, Simson MB, Falcone RA, Marchlinski FE, Doherty JU, Josephson ME. Results of signal-averaged electrocardiography and electrophysiologic study in patients with nonsustained ventricular tachycardia after healing of acute myocardial infarction. Am J Cardiol 1987; 60 :80-85

[5] Vassallo JA, Cassidy D, Simson MB, Buxton AE, Marchlinski FE, Josephson ME. Relation of late potentials to site of origin of ventricular tachycardia associated with coronary heart disease. Am J Cardiol 1985; 55: 985-989

[6] Freedman RA, Gillis AM, Keren A, Soderholm-Difatte V, Mason JW. Signal-averaged electrocardiographic late potentials in patients with ventricular fibrillation or ventricular tachycardia: correlation with clinical arrhythmia and electrophysiologic study. Am J Cardiol 1985; 55:1350-1353

[7] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183–1197

[8] E.L. Conover, Signal-averaged ECG and fast Fourier transform analysis. In: M.B. Conover, Editor, Understanding Electrocardiography (8th ed.), Mosby, St. Louis, Missouri (2003), 447–454

[9] G. Breithardt, M.E. Cain, N. El-Sherif, N.C. Flowers, V. Hombach, M. Janse, M.B. Simson and G. Steinbeck, Standards of analysis of late potentials using high-resolution or signal-averaged electrocardiography: a statement by a task force committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. J Am Coll Cardiol 1991; 17: 999–1006

[10] K.A. Gatzoulis, L.A. Carlson, B.I. Rizos, P. Gialafos, P. Toutouzas and A.L. Waldo, Time domain analysis of the signal averaged electrocardiogram in patients with a conduction defect of a bundle branch block. Eur Heart J 1995; 16: 1912–1919

[11] A.S. Manolis, J.A. Chiladakis, J.S. Malakos, V. Vassilikos, T. Maonis and C.V. Cokkinos, Abnormal signal averaged electrocardiograms in patients with incomplete right bundle branch block. Clin Cardiol 1997; 20: 17–22

[12] Denes P, Uretz E, Santarelli P. Determinants of arrhythmogenic ventricular activity detected on the body surface QRS in patients with coronary artery disease. Am J Cardiol 1984; 53: 1519-1523

[13] Myerburg RJ, Epstein K, Gaide MS, Wong SS, Castellanos A, Gelband H, Bassett AL. Electrophysiologic consequences of experimental acute ischemia superimposed on healed myocardial infarction in cats. Am J Cardiol 1982; 49: 323-330

[14] Myerburg RJ, Kessler KM, Castellanos A. Pathophysiology of sudden cardiac death. Pacing Clin Electrophysiol 1991; 14: 935-943

[15] Robertson WS, Feigenbaum H, Armstrong WF, Dillon JC, O'Donnell J, McHenry PW. Exercise echocardiography: a clinically practical addition in the evaluation of coronary artery disease. J Am Coll Cardiol 1983; 2: 1085-1091

[16] McPherson DD, Horacek BM, Sutherland DJ, Armstrong CS, Spencer CA, Montague TJ. Exercise electrocardiographic mapping in normal subjects. J Electrocardiol 1985; 18: 351-360