

Acoustic cardiography to improve detection of coronary artery disease with stress testing

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Received: March 3, 2010 Revised: April 13, 2010

Accepted: April 20, 2010

Published online: May 26, 2010

Abstract

AIM: To assess if performance of 12-lead exercise tolerance testing (ETT) can be improved by simultaneous acoustic cardiography and to compare the diagnostic performances of electrocardiography (ECG) during ETT and acoustic cardiography for detection or exclusion of angiographically proven coronary artery disease (CAD).

METHODS: We conducted an explorative study with retrospective data analysis using a convenience sample of consecutive patients ($n = 59$, mean age: 62 years) from an outpatient clinic in Switzerland, who were referred for ETT by their general practitioner on suspicion of CAD, and in whom, coronary angiography was carried out. Measurements included sensitivity, specificity, likelihood ratios and receiver operating characteristic curves. A standard, symptom-limited, 12-lead ECG exercise tolerance test was performed by independent persons with simultaneous acoustic cardiography and subsequent cardiac angiography for determination of significant CAD.

RESULTS: Thirty-four of the 59 adult subjects (58%) had a final diagnosis of CAD by angiography, and in 25 subjects, CAD was excluded by angiography. Sensitivity/specificity of ST segment depression in the group

was 29%/92%, whereas the most powerful acoustic cardiographic parameter was the strength of the fourth heart sound (S₄), with corresponding sensitivity/specificity of 53%/92%. The disjunctive combination of the S₄ and ST depression had sensitivity/specificity of 68%/84%.

CONCLUSION: In this preliminary pilot study, the use of acoustic cardiography alone during ETT or disjunctively with ST depression has been shown to be a simple and convenient method for the detection of CAD, which was superior to ST depression on the standardized ECG.

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Key words: Heart sounds; Electrocardiography; Stress testing; Coronary artery disease; Acoustic cardiography

Peer reviewer: Paul Farand, MD, MSc, Assistant Professor, Cardiology Division, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, J1H 5N4, Canada

Zuber M, Erne P. Acoustic cardiography to improve detection of coronary artery disease with stress testing. *World J Cardiol* 2010; 2(5): 118-124 Available from: URL: <http://www.wjg-net.com/1949-8462/full/v2/i5/118.htm> DOI: <http://dx.doi.org/10.4330/wjc.v2.i5.118>

INTRODUCTION

The standard 12-lead electrocardiography (ECG) exercise tolerance or stress test is a commonly used procedure for detecting the presence of coronary artery disease (CAD). The diagnostic accuracy of the 12-lead ECG exercise test has important limitations, including the confounding presence of left ventricular hypertrophy and reduced performance in women^[1,2]. To improve the diagnostic accuracy of the exercise tolerance test, it is useful to use diagnostic parameters in addition to ST segment

displacement. Therefore, the exercise tolerance test is often performed in conjunction with echocardiographic or radionuclide studies. These additional tests provide independent diagnostic data that are used to augment the interpretation of the exercise tolerance test^[3-5]. However, due to the specialized equipment and personnel involved, echocardiographic and radionuclide studies are expensive and often not readily available. This is especially important since the exercise tolerance test is employed as a screening test in large patient populations.

Acoustic cardiography is a technique that records simultaneous digital ECG and heart sound data and provides computerized interpretation of the findings. It does this by using dual-purpose ECG and sound sensors that are applied to the patient's thorax in the V3 and V4 position. The rationale for using this diagnostic technique during exercise testing is that ischemia not only alters the electrical properties of myocardial cells, but also affects the mechanical properties of the ventricle. For example, acute left ventricular ischemia reduces the compliance of the left ventricular chamber and often leads to the production of a fourth heart sound (S4)^[6-9]. Therefore, we evaluated the usefulness of acoustic cardiography during stress testing as a single and additive measurement for the detection of angiographically proven CAD.

MATERIALS AND METHODS

Design overview

Consecutive patients with clinically suspected CAD who were referred for standard ECG exercise tolerance testing (ETT) were enrolled after providing informed consent. The study protocol was approved by the local medical ethics committee. If deemed appropriate by the physician performing the exercise tolerance test, the patient was then sent for a diagnostic cardiac catheterization procedure to determine the presence and extent of CAD. The physicians performing the exercise tolerance test and the catheterization were blinded to the results of the other diagnostic procedure.

Setting and participants

The exercise tolerance test and cardiac catheterization were performed in an outpatient facility in an urban setting in Switzerland. We enrolled 59 subjects with clinically suspected CAD in the study for ETT. All patients (40 men and 19 women, mean age 62 years, all Caucasian) underwent both coronary angiography and ETT with adequate ECG and acoustic cardiography. Acoustic cardiographic equipment was provided by Inovise Medical, Inc. (Portland, OR, USA) through an equipment loan program.

Randomization and interventions

ETT protocol: All subjects underwent symptom-limited stress testing using an upright bicycle ergometer. The workload of each exercise tolerance test began at 50 W and was increased at a rate of 20 W/min in men and

15 W/min in women. The test was terminated when either symptoms or a silent but diagnostic ST depression occurred. Medical therapy was not stopped or modified prior to ETT. ST depression was measured in all 12 ECG leads and a test was considered ECG-positive if there was exercise-induced horizontal or down-sloping ST depression $> 100 \mu\text{V}$ in any of the limb leads, or $> 200 \mu\text{V}$ in any of the chest leads. In each case, we measured the maximum ST segment displacement at a point 60 ms beyond the J point. ST segment displacement was measured digitally using a computerized ECG algorithm (Schiller AG, Baar, Switzerland).

Cardiac catheterization: Coronary angiography and left ventriculography were performed under light sedation in the post-absorptive state using standard techniques. Left ventricular end-diastolic pressure was recorded, left ventriculography was performed in the right anterior oblique projection, and coronary angiograms were obtained in multiple projections. CAD was considered to be present if there was a $> 70\%$ reduction in the transluminal diameter of at least one major coronary artery. In each case, ETT and cardiac catheterization were performed within 2 mo of each other.

Acoustic cardiography: In addition to the 12-lead ECG data, simultaneous acoustic cardiographic data were recorded (A200; Inovise Medical Inc.). For the purpose of the present study, we chose evidence of an exercise-related S4 as an indicator of underlying CAD. Acoustic cardiography obtained evidence of S4 by searching for discrete sounds in a frequency range of 60-180 Hz that occurred in the interval between the onset of the ECG P wave and the first heart sound. The intensity of such sounds was expressed as a continuous parameter on a scale of 0 to 10. The strength of evidence for an S4 was proportional to the value of this intensity and its persistence during the recording. The heart sound data collection, analysis and calculation of parameter values were fully automated and independent of the user. Follow-up was not performed on these subjects.

Statistical analysis

Data are presented as mean values and SD for continuous variables with normal Gaussian distribution. We analyzed the ST segment depression and the S4 strength data that were obtained at maximum heart rate for each subject. For the entire group, for the male and female subgroups, and for the symptomatic and silent ischemic patients, we determined the sensitivities and specificities of the above ST segment criteria for CAD. We then used receiver operating characteristic curves to determine the sensitivities of the S4 measurements at specificities similar to those exhibited by the ST segment criteria. Confidence intervals were calculated at the 95% level. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated using standard formulas. The analyses were performed using SPSS version 13.0

Table 1 Baseline clinical characteristics

	All (<i>n</i> = 59)	No CAD by angiography (<i>n</i> = 25)	CAD by angiography (<i>n</i> = 34)
Baseline characteristics			
Age (yr)	62 ± 11	61 ± 13	62 ± 10
History of angina	37 (63)	13 (52)	24 (71)
Echo ejection fraction (%)	59 ± 11	59 ± 7	59 ± 12
Invasive LV end-diastolic pressure (mmHg)	15 ± 7	14 ± 6	15 ± 8
Baseline heart rate (beats/min)	67 ± 12	66 ± 11	69 ± 13
Maximum heart rate during ETT (beats/min)	129 ± 19	137 ± 19	122 ± 17
Baseline ST depression	12 (20)	2 (8)	10 (29)
Maximum workload during ETT (W)	132 ± 41	149 ± 43	119 ± 34
Heart rate × SBP at rest (mmHg/min)	9357 ± 2397	8991 ± 2314	9634 ± 2457
Heart rate × SBP at peak exercise (mmHg/min)	25790 ± 5740	27870 ± 5070	24210 ± 5780
Rise in double pressure product (factor)	2.9 ± 0.9	3.3 ± 1.0	2.6 ± 0.7
Baseline SBP (mmHg)	138 ± 24	137 ± 22	140 ± 27
Maximum SBP during ETT (mmHg)	200 ± 28	203 ± 25	197 ± 29
Symptomatic ST depression (mm)	1.98 ± 0.55	NA	1.98 ± 0.55
Silent ST depression (mm)	2.05 ± 1.23	NA	2.05 ± 1.23
LBBB	1 (2)	0 (0)	1 (3)
RBBB	3 (5)	2 (8)	1 (3)
Acoustic cardiographic S3 detected	1 (2)	0 (0)	1 (3)
Acoustic cardiographic S4 detected	6 (10)	1 (4)	5 (14)
CAD risk factors			
High cholesterol (> 5.2 mmol/L)	41 (69)	18 (72)	23 (68)
Stage 1 blood pressure (SBP 140-159, DBP 90-99 mmHg)	18 (30)	7 (28)	11 (32)
Stage 2 blood pressure (SBP > 160, DBP > 100 mmHg)	14 (24)	5 (20)	9 (26)
Diabetes (fasting glucose > 6.1)	5 (8)	2 (8)	3 (9)
Body mass index (kg/m ²)			
Overweight (25-29.9)	29 (49)	11 (44)	18 (53)
Obese (> 30)	14 (24)	5 (20)	9 (26)
Age (men > 45 yr, women > 55 yr)	41 (69)	17 (68)	24 (71)
Prior myocardial infarction	13 (22)	5 (20)	8 (23)

Values are given either as mean ± SD for continuous parameters or as *n* (percentage) for dichotomous variables. Prior myocardial infarction based on medical history, echocardiography or angiography. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NA: Not applicable; CAD: Coronary artery disease; ETT: Exercise tolerance testing; LBBB: Left bundle branch block; RBBB: Right bundle branch block; LV: Left ventricular.

Table 2 Medical therapy in patients with and without CAD by angiography

Condition	All (<i>n</i> = 59)	No CAD by angiography (<i>n</i> = 25)	CAD by angiography (<i>n</i> = 34)
Hyperlipidemia	23 (70)	7 (86)	16 (62.5)
Hypertension	30 (87)	12 (92)	18 (83)
Diabetes	5 (20)	2 (0)	3 (33)

Values are given as *n* (percentage) of the group being treated with drug therapy.

(SPSS, Inc., Chicago, IL, USA) and Excel 2000 (Microsoft, Seattle, WA, USA).

RESULTS

Of the 59 subjects, 34 (58%) had CAD by angiography. Additional clinical findings of the subjects are summarized in Table 1, including accepted risk factors for CAD. All patients were in sinus rhythm, one subject had left bundle branch block, and three had right bundle branch block. The medical therapy being received by these sub-

Table 3 Extent of angiographic CAD

	All (<i>n</i> = 34)	S4 at Max HR (<i>n</i> = 18)	ST depression (<i>n</i> = 10)	S4 or ST depression (<i>n</i> = 23)
Left main artery	2 (6)	1 (6)	1 (10)	2 (9)
Left anterior descending	24 (71)	15 (83)	8 (80)	20 (87)
Right circumflex artery	17 (50)	10 (56)	7 (70)	13 (57)
Right coronary artery	24 (71)	10 (56)	6 (60)	13 (57)
One-vessel disease	13 (38)	7 (39)	3 (30)	8 (35)
Two-vessel disease	10 (29)	5 (28)	2 (20)	6 (26)
Three-vessel disease	11 (32)	6 (33)	5 (50)	9 (39)
Invasive ejection fraction (%)	65 ± 11	67 ± 11	70 ± 12	67 ± 11
Invasive LVEDP (mmHg)	15 ± 8	18 ± 9	11 ± 8	15 ± 9

Values are given either as mean ± SD for continuous parameters or as *n* (percentage) for dichotomous variables.

jects is presented in Table 2, and Table 3 describes the angiographic findings in those patients with CAD. Note that, in the whole group, there were equal proportions of subjects with one-, two- and three-vessel disease, and

Table 4 Diagnostic performances of ECG versus heart sounds in 59 patients (40 men, 19 women)

Parameter	Group	Sensitivity (%)	Specificity (%)	PLR	NLR
ST depression	All	29 (CI 17-46)	92 (CI 75-98)	3.68 (CI 0.88-15.3)	0.77 (CI 0.60-0.98)
ST depression	Men	28 (CI 14-48)	93 (CI 70-99)	4.2 (CI 0.57-30.9)	0.77 (CI 0.58-1.02)
ST depression	Women	33 (CI 12-65)	90 (CI 60-98)	3.33 (CI 0.42-26.58)	0.74 (CI 0.45-1.23)
S4 present	All	53 (CI 37-69)	92 (CI 75-98)	6.62 (CI 1.7-25.9)	0.51 (CI 0.35-0.74)
S4 present	Men	52 (CI 34-70)	93 (CI 70-99)	7.8 (CI 1.13-53.8)	0.51 (CI 0.34-0.79)
S4 present	Women	56 (CI 27-81)	90 (CI 60-98)	5.56 (CI 0.79-39.01)	0.49 (CI 0.23-1.06)
S4 or ST-depression	All	68 (CI 51-81)	84 (CI 65-94)	4.23 (CI 1.7-10.7)	0.39 (CI 0.23-0.65)

PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

that the right coronary artery and the left anterior descending artery had a similar prevalence of disease.

Table 4 shows a comparison of the diagnostic performances of the ECG and of the acoustic cardiographic findings. The data revealed that, in these subjects, the specificities of the ST segment and the S4 criteria exceeded 90% in the entire group and in the male and female subgroups, but with poor sensitivities (28%-33%). The table also shows that, at these specificities, the sensitivities of the acoustic cardiographic S4 at maximum heart rate as a single parameter exceeded the corresponding sensitivities of the ST segment criteria by 24%, 24% and 23%, respectively. In the entire group and in both subgroups, the value of S4 strength that was associated with these diagnostic performances was 3.6. The disjunctive combination of the ST segment and the S4 had sensitivity/specificity of 68%/84%. Although the disjunctive combination had improved sensitivity, both the PLR and NLR were higher for the S4 at maximum heart rate alone.

Figure 1 shows the heart rate and S4 strength trends during ETT for a patient with CAD by angiography and one without CAD by angiography.

DISCUSSION

This study confirms the limited sensitivity (Table 4, 28%-33%) of using standard ST depression criteria during a 12-lead ECG ETT, even with an intermediate pretest probability for CAD, since a majority of our patients had ≥ 2 multiple risk factors. At similar specificity, the acoustic cardiographic S4 provided improved sensitivity (52%-56%) for detection of angiographically proven CAD. The disjunctive combination of ECG or the S4 resulted in modest improvement sensitivity (68%) at the expense of reduced specificity (84%) over just the presence of S4 alone.

Although the ECG-based exercise tolerance test remains a widely used technique for detecting underlying CAD, it has been shown that its diagnostic accuracy is suboptimal^[3-5,10-12]. The reasons for this include variations in the prevalence of heart disease in the patients tested and inadequate levels of exercise performance^[10,11]. In addition, the presence of pre-existing ECG abnormalities, e.g. left ventricular enlargement or left bundle branch block is particularly problematic for diagnosing ischemia using the ST segments. This has remained the case even

when parameters such as the ST segment/heart rate slope or ST segment/heart rate index are substituted for the simple measurement of ST segment displacement^[10-12]. Typical angina during stress has a high prognostic value for the detection of CAD. In our population, the percentages of patients with symptomatic *vs* asymptomatic ischemia were similar in patients with ST depression (60% symptomatic *vs* 40% asymptomatic) or without ST depression (58% symptomatic *vs* 42% asymptomatic). However, even the detection of silent ischemia is important, because we have shown that it also has an impact on long-term follow-up^[13,14].

Therefore, echocardiographic and radionuclide studies such as single proton emission computed tomography are frequently used in conjunction with ETT^[3-5]. These tests provide orthogonal diagnostic information that is intended to augment the interpretation of associated ECG abnormalities. Their sensitivities/specificities range from 80% to 100%, depending on the extent of CAD^[15]. However, both exercise echocardiography and radionuclide stress tests are expensive and not always available in offices and clinics in which screening for CAD is desirable. In contrast, acoustic cardiography is easy to perform and requires the addition of two dual-purpose sensors. Furthermore, it requires no expertise in the interpretation of cardiac acoustic data, because the analysis of the ECG and heart sound data is computerized. Therefore, this test could be interesting for general practitioners and outpatient medicine outside the hospital.

Previous studies have shown the clinical value of various acoustic cardiographic parameters^[16-22]. In the present study, we chose to evaluate the S4 heart sound at maximum heart rate, because of the well-recognized association between acute myocardial ischemia and diastolic dysfunction as an early sign in the ischemic cascade^[23-28]. This association is due to the abrupt decrease in left ventricular compliance that occurs with the onset of ischemia^[6-9]. Figure 1A illustrates heart rate and S4 strength for a subject without CAD by angiography. The decrease in S4 strength may be explained by a vagal response and decrease in left ventricular volume and filling pressures. Figure 1B presents the heart rate and S4 strength trends during ETT in a patient with CAD by angiography. The S4 strength increased as ventricular stiffness increased with ischemia and a rise in left ventricular filling pressure.

Although auscultation has traditionally been used to

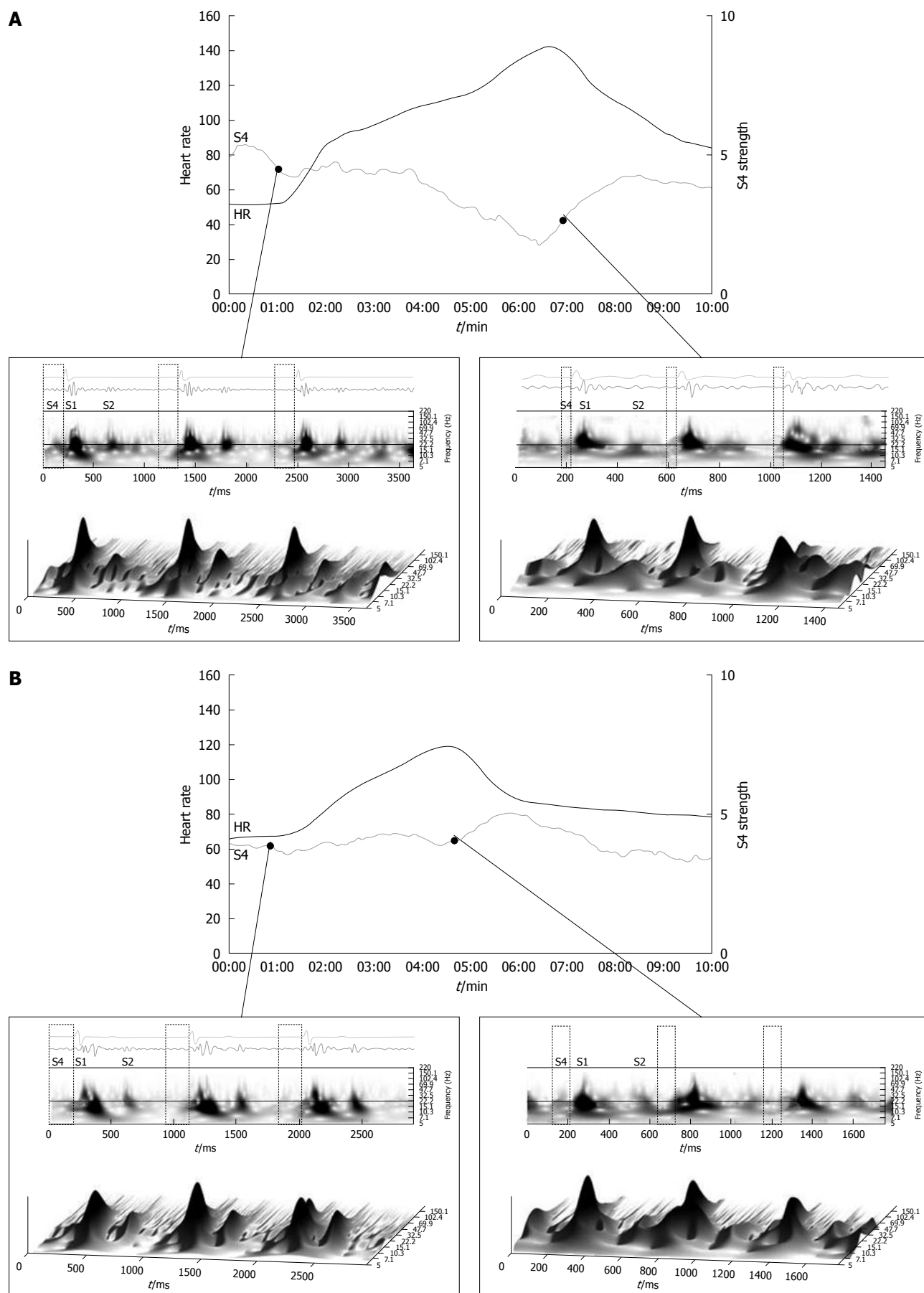


Figure 1 Heart rate and S4 strength trends during exercise tolerance testing (ETT). A: A patient without coronary artery disease (CAD) by angiography; B: A patient with CAD by angiography.

detect S4, the low frequency and intensity of this sound often make it difficult to hear. The ability of the acoustic cardiography system to amplify the recorded sounds and determine their frequencies makes S4 detection more reliable than it is with auscultation. Also, acoustic cardiography provides an automated interpretation of the diagnostic findings so that a high level of skill in either heart sound detection or ECG interpretation is not required^[29].

The findings of the present pilot study showed that, at similar diagnostic specificities, the sensitivities of the exercise-related S4 exceeded those of exercise-related ST segment depression for detecting CAD. These differences are especially important, because exercise testing is typically used as a screening test for CAD in large numbers of patients. For example, ST depression detected 10 of the 34 patients with CAD, whereas the S4 at maximum heart rate diagnosed 18 patients. Extrapolating the data shown in Table 4 to a hypothetical population of 100 women with CAD, the use of S4 detected using acoustic cardiography alone would produce 23 additional true positive test results, compared with ECG alone. Although the disjunctive combination of S4 at maximum heart rate and ST depression had better sensitivity than S4 alone, both the PLR and NLR were better with S4 alone (PLR 6.62 and NLR 0.51 for S4 alone *vs* PLR 4.23 and NLR 0.39 for the disjunctive combination). Therefore, we would like to recommend the measurement of S4 at maximum heart rate for the detection of CAD during exercise testing. Also, as indicated by Erne^[30], the use of acoustic cardiography during 24-h Holter monitoring may provide a way to detect silent ischemia during routine activities. In the present study, S4 at maximum heart rate detected 67% of the patients with CAD and silent ischemia.

For a pilot study, the number of subjects was small. In particular, the number of subjects without CAD by angiography was limited and had an impact on our results. Although we included no other tests at the termination of exercise, we verified CAD with coronary angiography in all of the patients included in this analysis. Potential bias towards higher sensitivity and lower specificity for the ECG stress test results existed, since those test results were the primary input for the decision as to which patients to refer for angiographic evaluation. Since the number of patients was small, the results shown in the subgroup analysis are not likely to be statistically relevant.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Patti Arand, PhD and Peter Bauer, PhD for the statistical analysis of the data.

COMMENTS

Background

The performance of standard 12-lead electrocardiography (ECG) exercise tolerance or stress test is well characterized, and it is understood that this has deficiencies with respect to sensitivity and specificity for the detection of coronary artery disease (CAD).

Research frontiers

Not much is known about the utility of quantified heart sounds to improve the performance of ECG stress tests for diagnosis of CAD.

Innovations and breakthroughs

For the first time, this article evaluates the utility and performance of computerized and quantitative heart sound analysis to improve the performance of ECG stress tests for the detection of CAD.

Peer review

This is an original editorial about stress testing and acoustic cardiography. But it must be made major revision.

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S- Editor Cheng JX L- Editor Kerr C E- Editor Zheng XM