Cardiac Autonomic Functions Derived From Short-Term Heart Rate Variability Recordings Associated With Nondiagnostic Results of Treadmill Exercise Testing

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Summary

Analysis of short-term (5-minute) heart rate variability (HRV) may provide useful information about autonomic nervous control of the cardiovascular system. The aim of the present study was to evaluate the association between the results of treadmill exercise testing (TET) and short-term (5-minute) HRV. Patients undertaking TET were anteriorly evaluated with short-term (5-minute) HRV over time (SDNN, RMSSD, NN50 count, pNN50) and frequency (LF, HF, total power) domains. Among 414 patients, 32 individuals (7.7%; 14 men) had nondiagnostic results. The nondiagnostic group had older age, higher body mass index, more hypertension, lower SDNN, lower LF, and higher HF than the negative group. After adjustment for potential confounders, SDNN (OR 0.94, 95% CI 0.91-0.97; P = 0.01), RMSSD (OR 0.96, 95% CI 0.93-0.99; P = 0.02), NN50 count (OR 0.98, 95% CI 0.97-1.00; P = 0.04) and LF (OR 0.96, 95% CI 0.96-0.99; P = 0.03) were negatively related to nondiagnostic results, and HF showed a positive effect (OR 1.04, 95% CI 1.01-1.05; P = 0.02). No HRV indices were significantly associated with positive results. Our study suggested that cardiac autonomic indices derived from short-term HRV recordings might predict nondiagnostic results of TET. (Int Heart J 2010; 51: 105-110)

Key words: Heart rate variability, Treadmill exercise test, Nondiagnostic

Heart rate variability (HRV) represents one of the most promising quantitative markers of autonomic activity.[1)] HRV in the time and frequency domains is a noninvasive, convenient tool for evaluation of autonomic nervous physiology.[2)] Time domain analysis estimates the variation of differences between successive RR intervals through indices developed by statistical methods. Frequency domain analysis estimates respiratory-dependent high frequency and low frequency power through spectral analysis. High frequency power is considered to be mediated mainly by vagal activity, while low frequency power has been suggested as predominantly sympathetic modulation.[3,4)] The most commonly used frequency domains include LF, low frequency power; HF, high frequency power; and total power. Short-term (5-minute) recording is a reliable tool to obtain these HRV measures.[2)]

Exercise electrocardiography is one of the most frequent noninvasive modalities used to assess patients with suspected or proven cardiovascular disease.[5)] Meta-analysis of 147 consecutively published studies involving 24,074 patients who underwent both standard exercise testing and coronary angiography revealed a wide variability and modest acceptability in sensitivity and specificity (mean sensitivity was 68%, with a standard deviation of 16%; mean specificity was 77%, with a standard deviation of 17%).[6,7)] Although the modest sensitivity of exercise electrocardiography is generally less than the sensitivity of imaging procedures, such as single-photon emission computed tomography imaging of myocardial perfusion and positron-emission tomography,[8)] exercise testing is still widely available and relatively low-cost. The interpretation of exercise test results for diagnostic and prognostic purposes requires consideration of maximal work capacity.[5,9)] When a patient is unable to complete moderate levels of exercise or reach at least 85 percent of age-predicted maximal heart rate, the level of exercise performed may be inadequate to test cardiac reserve.[5,9)] Therefore, ischemic electrocardiographic abnormalities may not be evoked and the test may be nondiagnostic. Chronotropic incompetence manifested in many of the nondiagnostic treadmill tests may reflect the autonomic drive during the exercise, either inadequate sympathetic tone or over enhancement of parasympathetic drive.

We hypothesized that the chronotropic incompetence during treadmill testing could be reflected by baseline autonomic nerve tone detected with short-term (5-minute) HRV. The aim of this study was to evaluate the association between HRV indices obtained from short-term (5-minute) electrocardiographic recordings and treadmill exercise test results.

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Methods

Study population: The study cohort consisted of 414 consecutive patients (233 men; mean age, 54 ± 12 years) who underwent symptom-limited exercise testing combined with a short-term (5-minute) HRV examination for evaluation of suspected coronary artery disease in our out-patient department between February 2007 and June 2008. Patients were recruited if they were without any peripheral vascular occlusion diseases, left ventricular hypertrophy with a strain pattern on 12-lead electrocardiography, left bundle-branch block, the pre-excitation syndrome, critical valvular heart diseases, critical pulmonary diseases, an implanted pacemaker, frequent premature atrial or ventricular contractions, or atrial fibrillation. We also excluded patients with contraindication to or inability to perform treadmill exercise testing. A review of each patient's chart and a structured interview were conducted to gather data on symptoms, medications, coronary risk factors, and other diagnoses. Traditional risk factors for coronary artery disease, including diabetes mellitus, hypertension, hypercholesterolemia, and current smoking, were all carefully evaluated in each patient. Diabetes mellitus was diagnosed if the fasting plasma glucose concentration was > 125 mg/dL on two separate occasions or if the subject was being treated with insulin or oral hypoglycemic agents. Hypertension was diagnosed if blood pressure was > 140/90 mmHg on three occasions or if the subject was taking any antihypertensive medication. Hypercholesterolemia was defined as a total serum cholesterol concentration ≥ 200 mg/dL or the use of lipid-lowering therapy. Smokers were defined as those who habitually smoked cigarettes (≥ 20 cigarettes/day) at the start of this study. A family history of premature coronary artery disease (CAD) was defined as patients whose parents, siblings, or grandparents had CAD before the age of 55 years in men and 65 years in women. Antihypertension drugs were also carefully reviewed in hypertensive patients. All patients were asked to refrain from taking their medications for one day before each test. All patients gave written informed consent for this study, and the study protocol was approved by the Human Research Committee of our hospital.

Short-term (5-minute) heart rate variability recordings: Before any testing, all measurements (including blood pressure and heart rate) were made with the patient supine for 20 minutes in a quiet, temperature-controlled laboratory at 26 ± 1°C. Version 3.0 of the "CheckMyHeart (CMH)" HRV analysis software (CheckMyHeart, Taiwan) was used for all transformations and analyses. The total recording time was 5 minutes. CMH is a single-lead electrocardiography recorder (lead I or lead II is available). Beat-by-beat RR interval values (resolution 4 ms) were obtained from the ECG signals using CMH software. The CMH software will reject irregular RR intervals (non-NN interval) automatically. However, the CMH software also provides the manual filtering of non-NN intervals. Detrended time series were cubically interpolated and resampled at 1 Hz. After detrending via least-square second-order polynomial fitting, the power spectral density of RR interval time series was estimated by discrete Fourier transformation (DFT). The powers in the low-frequency (LF ms^2, 0.04-0.15 Hz), high-frequency (HF ms^2, 0.15-0.40 Hz), and total power (TP ms^2, approximately ≤ 0.4 Hz) bands were obtained by numerical integration. Spectral analysis was also performed using the autoregressive method (Burg algorithm) with spectral decomposition and Johnson Andersen algorithm. Autoregressive model order was set at 16. Spectral powers of the LF and HF bands (LF-AR and HF-AR) were computed summing the respective spectral components. Components showing < 10% of the overall power in the band were ignored as they probably represented pure noise contributions.

We also computed time-domain HRV parameters suitable for short-term analysis: SDNN, RMSSD, NN50 count, and pNN50. The RMSSD method is preferred to pNN50 and NN50 count because it has better statistical properties. All 4 time-domain parameters were also calculated for the detrended R-R interval series for all examination periods.

Exercise protocol: All patients were tested using the standard symptom-limited Bruce's treadmill protocol with a commercially available system (CASE 6.5; GE Medical Systems, Milwaukee, WI, USA). All patients were instructed not to eat, drink caffeinated beverages, continue cardioactive medication, or smoke any kind of tobacco for 12 hours before testing, and to wear comfortable shoes and loose-fitting clothes for the test. After the standard 12-lead ECG was recorded, a torso ECG was obtained in the supine position as well as in the sitting or standing position. The 12-lead ECG, heart rate response, and blood pressure were recorded at baseline, during each stage of exercise, at peak workload and at 1-minute intervals for 8 minutes after exercise. If a patient showed ominous symptoms or signs (moderate to severe angina, a drop in systolic blood pressure of > 10 mmHg from baseline, cyanosis or pallor, sustained ventricular tachycardia, ST elevation ≥ 1.0 mm in noninfarct leads without diagnostic Q-waves, or difficult breathing), the treadmill test and recording were stopped. The results of the treadmill exercise were interpreted by three cardiologists blinded to the patients' backgrounds.

For the purpose of interpretation, the PQ junction was chosen as the isoelectric point. The development of 0.10 mv (1 mm) or greater of J point depression measured from the PQ junction, with a horizontal type or down-sloped type of ST segment, depressed ≥ 0.10 mv for 80 msec after the J point in three consecutive beats with a stable baseline, was considered an abnormal response. When the 80 msec after the J point measurement was difficult to determine at rapid heart rates, the 60 msec after the J point measurement was used.

The New York Heart Association (NYHA) functional class was also recorded for each patient according to the achieved metabolic equivalents (METs). One MET is equivalent to 3.5 mL of $O_2/kg^{-1}/min^{-1}$ of body weight. NYHA functional class I was defined as METs ≥ 7; II as METs between 5 and 6; and III as METs between 2 and 4. NYHA functional classes II and III were considered impaired exercise capacity. We excluded patients with impaired exercise capacity.

Classic criteria for myocardial ischemia include horizontal ST segment depression observed when both the J point and ST 80 depression are 0.1 mV or more and ST segment slope is within the range of 1.0 mV/sec. Downsloping ST segment depression occurs when the J point and ST 80 depression are 0.1 mV and the ST segment slope is -1.0

mV/sec. When a patient is unable to reach at least 85% of age-predicted maximal heart rate and has none of the classic criteria for myocardial ischemia, the result of treadmill exercise test is nondiagnostic.[5)]

Statistical analysis: Continuous variables are presented as the mean ± standard deviation (SD). Differences between groups were compared using Student's *t*-test or chi-square test, as appropriate. For descriptive purposes, the patients were divided into three groups on the basis of the results of treadmill exercise testing. Multiple logistic regression analyses were used to assess the independent factor for the treadmill exercise test results. Statistical significance was set at $P < 0.05$ based on a two-sided calculation. All analyses were performed using SPSS software, version 11.5 for Windows (SPSS Inc., Chicago, IL).

Results

Among 414 patients, 32 individuals (7.7%; 14 men) had a nondiagnostic result for the treadmill exercise test, 53 individuals (12.8%; 32 men) had a positive result, and 329 individuals (79.5%; 187 men) had a negative result.

Comparison between nondiagnostic group and negative group: The nondiagnostic group had older age (59 ± 11 years versus 51 ± 12 years; $P < 0.01$) and higher body mass index (26.3 ± 3.5 kg/m^2 versus 25.0 ± 3.3 kg/m^2; $P < 0.05$). There was more hypertension (62.5% versus 37.1%; $P < 0.01$) in the nondiagnostic group. There were no differences in waist circumference, other risk factors, or drug history between these two groups (Table I). The nondiagnostic group had a lower baseline heart rate before testing (65 ± 9 beat/min versus 74 ± 11 beat/min; $P < 0.001$), and shorter exercise duration (427 ± 111 s versus 539 ± 122 s; $P < 0.001$) (Table II). In time domain analysis, there was only lower SDNN (26 ± 13 ms versus 37 ± 21 ms; $P < 0.01$) in the nondiagnostic group. In frequency domain analysis, there were lower LF (52 ± 23 n.u. versus 63 ± 17 n.u.; $P < 0.01$) and higher HF (47 ± 22 n.u. versus 37 ± 17 n.u.; $P < 0.01$) in the nondiagnostic group (Table II). No other parameters of heart rate variability were significantly different between these two groups.

Comparison between positive group and negative group: The positive group had older age (57 ± 9 years versus 51 ± 12 years; $P < 0.01$), higher systolic blood pressure (141.1 ± 23.8 mmHg versus 133.1 ± 21.8 mmHg; $P < 0.05$), and higher pulse blood pressure (54.2 ± 26.2 mmHg versus 47.8 ± 17.1 mmHg; $P < 0.05$). Hypertension (45.3% versus 37.1%; $P < 0.01$) and β-blocker use (45.3% versus 21.9%; $P < 0.001$) were greater in the positive group. There were no differences in waist circumference, body height, body weight, body mass index, other risk factors, or drug history between these two groups (Table I). The positive group had shorter exercise duration (492 ± 83 s versus 539 ± 122 s; $P < 0.01$) (Table II). In time domain analysis, SDNN (31 ± 10 ms versus 37 ± 21 ms; $P < 0.05$) and NN50 count (9 ± 12 versus 20 ± 36 ms; $P < 0.05$) were lower in the positive group (Table II). No other parameters of heart rate variability were significantly different between these two groups.

Association between heart rate variability and nondiagnostic and positive results of treadmill exercise testing: We used a multivariate logistic regression model to determine the association between nondiagnostic and positive results of treadmill exercise testing. After adjustment for potential confounders, SDNN (odds ratio 0.94, 95% confidence interval 0.91-0.97; $P = 0.01$), RMSSD (odds ratio 0.96, 95% confidence interval 0.93-0.99; $P = 0.02$), NN50 count (odds ratio 0.98, 95% confidence interval 0.97-1.00; $P = 0.04$), and LF (odds ratio 0.96, 95% confidence interval 0.96-0.99; $P = 0.03$) were negatively related to nondiagnostic results,

Table I. Baseline Characteristics of All Subjects

Treadmill test result factors	Nondiagnostic $n = 32$	Positive $n = 53$	Negative $n = 329$
Age (years)	59 ± 11**	57 ± 9**	51 ± 12
Male	14 (43.8%)	32 (60.4%)	187 (56.8%)
Waist circumference (cm)	86.9 ± 10.0	86.4 ± 8.2	84.6 ± 9.8
Body height (cm)	158.8 ± 8.5*	162.3 ± 7.3	162.9 ± 8.5
Body weight (kg)	66.4 ± 11.1	65.7 ± 10.3	66.6 ± 10.9
Body mass index (kg/m^2)	26.3 ± 3.5*	25.8 ± 7.8	25.0 ± 3.3
Systolic blood pressure (mmHg)	135.3 ± 16.3	141.1 ± 23.8*	133.1 ± 21.8
Diastolic blood pressure (mmHg)	82.6 ± 13.9	87.0 ± 12.6	85.2 ± 11.7
Pulse pressure (mmHg)	52.7 ± 15.8	54.2 ± 26.2*	47.8 ± 17.1
Background			
Diabetes mellitus	7 (21.9%)	10 (18.9%)	38 (11.6%)
Hypertension	20 (62.5%)**	24 (45.3%)**	122 (37.1%)
Hyperlipidemia	13 (41.9%)	17 (32.1%)	120 (36.5%)
Transient ischemic accident	0 (0.0%)	0 (0.0%)	1 (0.3%)
Stroke	0 (0.0%)	0 (0.0%)	1 (0.3%)
Smoker	7 (21.9%)	13 (24.5%)	69 (21.0%)
β-Blocker use	9 (28.1%)	24 (45.3%)***	72 (21.9%)
Angiotensin-converting enzyme inhibitor use	2 (6.3%)	2 (3.8%)	14 (4.3%)
Angiotensin II receptor blocker use	3 (9.4%)	3 (5.7%)	22 (6.7%)
Statins	4 (12.5%)	5 (9.4%)	26 (7.9%)

Results are shown as mean ± SD and number (%).
***: < 0.001, **: < 0.01, *: < 0.05, compared to negative result group.

Table II. Values for Variables Recorded From Treadmill Exercise Testing and Short-Term 5-Minute Heart Rate Variability Recordings

Treadmill test result factors	Nondiagnostic n = 32	Positive n = 53	Negative n = 329
Basal heart rate (beat/minute)	65 ± 9***	74 ± 9	74 ± 11
Exercise capacity (METs)	10.5 ± 10.4	9.8 ± 1.5	11.3 ± 7.4
Exercise duration (seconds)	427 ± 111***	492 ± 83**	539 ± 122
% of maximal predicted heart rate	75.4 ± 4.8***	90.7 ± 7.6***	94.8 ± 6.6
< 85% of maximal predicted heart rate	32 (100%)***	10 (18.9%)***	(0%)
Heart rate variability			
Time domains			
SDNN (ms)	26 ± 13**	31 ± 10*	37 ± 21
RMSSD (ms)	21 ± 13	18 ± 8	26 ± 31
NN50 count	12 ± 24	9 ± 12*	20 ± 36
Frequency domains			
LF (n.u.)	52 ± 23**	62 ± 16	63 ± 17
HF (n.u.)	47 ± 22**	38 ± 16	37 ± 17
LF/HF ratio (%)	1.8 ± 1.9	2.2 ± 1.7	2.5 ± 2.0

Values are mean ± SD. MET indicates metabolic equivalents; SDNN, standard deviation of all NN intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals; NN50 count, number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; pNN50, NN50 divided by the total number of all NN intervals; LF (n.u.), power in low frequency range and in normalized unit; and HF (n.u.), power in high frequency range and in normalized unit.
***: < 0.001, **: < 0.01, *: < 0.05, compared to negative result group.

Table III. Association Between Short-Term 5-Minute Heart Rate Variability Recordings and Nondiagnostic and Positive Results of Treadmill Exercise Testing

Treadmill test result factors	Nondiagnostic		Positive	
	Odds ratio (CI)	P	Odds ratio (CI)	P
Time domains				
SDNN (ms)	0.94 (0.91-0.97)	0.01	0.99 (0.97-1.01)	0.15
RMSSD (ms)	0.96 (0.93-0.99)	0.02	0.98 (0.96-1.01)	0.08
NN50 count	0.98 (0.97-1.00)	0.04	0.99 (0.98-1.01)	0.10
Frequency domains				
LF (n.u.)	0.96 (0.96-0.99)	0.03	1.00 (0.98-1.01)	0.76
HF (n.u.)	1.04 (1.01-1.05)	0.02	1.01 (0.99-1.02)	0.68
LF/HF ratio (%)	0.95 (0.78-1.18)	0.40	0.95 (0.91-1.11)	0.51

Models were adjusted for age, sex, baseline heart rate, body mass index, systolic blood pressure, diastolic blood pressure, diabetes mellitus, and hypertension.
CI indicates confidence interval; SDNN, standard deviation of all NN intervals; LF (n.u.), power in low frequency range and in normalized unit; and HF (n.u.), power in high frequency range and in normalized unit.

and HF showed a positive effect (odds ratio 1.04, 95% confidence interval 1.01-1.05; P = 0.02). However, no heart rate variability markers were found to be associated with positive results of treadmill exercise testing (Table III).

Discussion

In the present study, we showed that cardiac autonomic indices derived from short-term (5-minute) HRV recordings were important predictors for nondiagnostic results of treadmill exercise testing.

Nondiagnostic results and heart rate variability: Although treadmill exercise testing is often used as the diagnostic method for evaluation of suspected coronary artery disease in out-patient departments, one limitation of this testing modality is the high rate of nondiagnostic results that result from the patients' failure to reach age-predicted heart rate.[10] Nondiagnostic results are more common in patients with peripheral vascular disease, orthopedic limitation, or neurological impairment and in patients with poor motivation.[9,11] In addition, it has also been suggested that patients with diabetes mellitus and obese patients may also have an increased probability of having a nondiagnostic treadmill exercise test.[12] For patients in whom the physician is concerned that the treadmill exercise test may be nondiagnostic, an alternative strategy is employed, requiring the patient to undergo more expensive tests, such as cardiac stress imaging modalities, which frequently entail prolonged evaluation.[13-16] Subjects with a nondiagnostic treadmill exercise test often undergo additional testing which is time-consuming and costly. Identification of subjects either at low or high risk for such a nondiagnostic result would therefore help guide the evaluation of these patients. After adjustment for potential confounders, in the present study, we found lower SDNN, lower LF, and higher HF were independent predictors for nondiagnostic results of treadmill exercise testing.

Nondiagnostic results and chronotropic incompetence: The issue of chronotropic incompetence in patients with nondiagnostic result of treadmill exercise test is somewhat more complex. A precise definition for chronotropic incompetence is still lacking. Chronotropic incompetence is usually defined as the inability of the heart to increase its rate in proportion to exercise and the metabolic requirement or as a failure to achieve 85% of the age-predicted maximal heart rate.[17,18] Chronotropic incompetence is also defined as failure to achieve ≥ 80% of the heart rate reserve given by (HR_{peak}-HR_{rest}) × 100%/(predictive maximal HR-HR_{rest}), where HR refers to heart rate.[19] Our current study showed that all patients in the nondiagnostic group had chronotropic incompetence using either one of the above definitions. The possible mechanisms of chronotropic incompetence largely involve abnormalities in autonomic balance, including an altered parasympathetic response to cardiac mechanoreceptors, β-receptor insensitivity, and postsynaptic desensitization of the sinoatrial node to sympathetic stimulation.[20-22] It has been suggested that chronotropic incompetence is a manifestation of abnormal cardiovascular autonomic control and provides information that is analogous to that of low HRV.[23] HRV is a complex measure of modulation of heart rate that incorporates sympathetic effects, parasympathetic effects, and their interaction. In the time-domain analysis, SDNN represents a general measurement of autonomic nervous system balance.[24] SDNN is related to the total power. Heart rate is dominated by cardio-inhibitory parasympathetic activity. Both the normalized LF and HF reflect the sympathetic and parasympathetic nervous systems, respectively, and the effects of total power on the values of HF and LF.[24] SDNN is significantly decreased in patients with congestive heart failure who have chronotropic incompetence.[25,26] Our present study also demonstrated that the nondiagnostic group had lower SDNN than the negative group. In the frequency-domain analysis, the LF represents mainly the sympathetic and the HF reflects mainly the parasympathetic nervous system. We have shown that both inadequate sympathetic tone (lower LF) and over enhancement of parasympathetic drive (higher HF) might be associated with the nondiagnostic results of treadmill exercise testing. Although time-domain methods, especially the SDNN and RMSSD methods, can be used to investigate recordings of short durations, the frequency methods are usually able to provide more easily interpretable results in terms of physiological regulations. Frequency-domain methods should be preferred to the time-domain methods when investigating short-term recordings.[2] Despite the fact that it is generally assumed that HRV represents a global index of the autonomic derangement, an abnormality of the sinus node response could also be proposed as participating in the impaired chronotropic response to exercise.

Petretta, *et al* demonstrated that obese people showed a decline in cardiac sympatho-vagal activity, indicating that the body mass index was negatively correlated with the HRV.[27] They also found that LF power (reflecting a combination of sympathetic and parasympathetic control of heart rate) was slightly lower in the obese participants.[27] Generalized obesity (increased body mass index) but not that characterized by raised waist-hip ratio was also associated with increased perceived breathlessness during treadmill exercise testing.[28] Some studies showed that heart rate response was blunted in hypertensive patients with or without heart failure.[29] Our present study also demonstrated that the nondiagnostic group had higher BMI and more hypertension than the negative group.

Study limitations: First, our study was limited by a cross-sectional rather than a longitudinal design. However, resting short-term HRV measurements were still significantly associated with the nondiagnostic result in patients undergoing treadmill exercise testing. Second, we had a relatively small number of patients in the nondiagnostic group.

Conclusions: Cardiac autonomic indices derived from short-term HRV recordings are independent factors of nondiagnostic results of treadmill exercise testing. The short-term HRV might be a screening tool for treadmill exercise testing.

Final disclosure

The conduction of this study and preparation of the manuscript completely complied with modern ethical requirements as published in the International Journal of Cardiology.[30]

References

1. Heart rate variability for risk stratification of life-threatening arrhythmias. American College of Cardiology Cardiovascular Technology Assessment Committee. J Am Coll Cardiol 1993; 22: 948-50.
2. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043-65.
3. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213: 220-2.
4. Pomeranz B, Macaulay RJ, Caudill MA, *et al*. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985; 248: H151-3.
5. Gibbons RJ, Balady GJ, Beasley JW, *et al*. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997; 30: 260-311. (Review)
6. Gianrossi R, Detrano R, Mulvihill D, *et al*. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation 1989; 80: 87-98. (Review)
7. Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis 1989; 32: 173-206.
8. Ritchie JL, Bateman TM, Bonow RO, *et al*. Guidelines for clinical use of cardiac radionuclide imaging. Report of the

American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol 1995; 25: 521-47.
9. Fletcher GF, Balady GJ, Amsterdam EA, *et al*. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 2001; 104: 1694-740.
10. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. J Am Coll Cardiol 2002; 40: 251-6.
11. Gibbons RJ, Balady GJ, Bricker JT, *et al*. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002; 40: 1531-40.
12. Sánchez CD, Newby LK, Hasselblad V, *et al*. Comparison of 30-day outcome, resource use, and coronary artery disease severity in patients with suspected coronary artery disease with and without diabetes mellitus assigned to chest pain units. Am J Cardiol 2003; 91: 1228-30.
13. Robinson DJ, Woods PG, Snedeker CA, Lynch JH, Chambers K. A comparison trial for stratifying intermediate-risk chest pain: benefits of emergency department observation centers. Prev Cardiol 2002; 5: 23-30.
14. Chandra A, Rudraiah L, Zalenski RJ. Stress testing for risk stratification of patients with low to moderate probability of acute cardiac ischemia. Emerg Med Clin North Am 2001; 19: 87-103. (Review)
15. Finefrock S. Nuclear stress testing in an emergency department observation unit. J Emerg Nurs 2006; 32: 420-3.
16. Ramakrishna G, Milavetz JJ, Zinsmeister AR, *et al*. Effect of exercise treadmill testing and stress imaging on the triage of patients with chest pain: CHEER substudy. Mayo Clin Proc 2005; 80: 322-9.
17. Clark AL, Coats AJ. Chronotropic incompetence in chronic heart failure. Int J Cardiol 1995; 49: 225-31.
18. Kemp DL, Jennison SH, Stelken AM, Younis LT, Miller LW. Association of resting heart rate and chronotropic response. Am J Cardiol 1995; 75: 751-2.
19. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996; 93: 1520-6.
20. Colucci WS, Ribeiro JP, Rocco MB, *et al*. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. Circulation 1989; 80: 314-23.
21. Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?) Circulation 1996; 93: 1485-7.
22. Hammond HK, Froelicher VF. Normal and abnormal heart rate response to exercise. Prog Cardiovasc Dis 1985; 27: 271-96. (Review)
23. Routledge HC, Townend JN. Why does the heart rate response to exercise predict adverse cardiac events? Heart 2006; 92: 577-8.
24. Evrengul H, Tanriverdi H, Kose S, *et al*. The relationship between heart rate recovery and heart rate variability in coronary artery disease. Ann Noninvasive Electrocardiol 2006; 11: 154-62.
25. Fei L, Keeling PJ, Sadoul N, *et al*. Decreased heart rate variability in patients with congestive heart failure and chronotropic incompetence. Pacing Clin Electrophysiol 1996; 19: 477-83.
26. Roche F, Pichot V, Da Costa A, *et al*. Chronotropic incompetence response to exercise in congestive heart failure, relationship with the cardiac autonomic status. Clin Physiol 2001; 21: 335-42.
27. Petretta M, Bonaduce D, de Filippo E, *et al*. Assessment of cardiac autonomic control by heart period variability in patients with early-onset familial obesity. Eur J Clin Invest 1995; 25: 826-32.
28. Goyal D, Logie IM, Nadar SK, Lip GY, Macfadyen RJ. Generalized obesity but not that characterized by raised waist-hip ratio is associated with increased perceived breathlessness during treadmill exercise testing. Cardiovasc Ther 2009; 27: 10-6.
29. Yip GW, Fung JW, Tan YT, Sanderson JE. Hypertension and heart failure: a dysfunction of systole, diastole or both? J Hum Hypertens 2009; 23: 295-306. (Review)
30. Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009; 131: 149-50.