# A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction

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**Background** We evaluate a simple, bedside test that measures 1-minute heart rate variability in deep breathing as a predictor of death after myocardial infarction.

**Methods** Bedside heart rate variability was assessed in 185 consecutive patients 5.1 ± 2.5 days after a first myocardial infarction. Patients were instructed to take 6 deep respirations in 1 minute while changes in heart rate were measured and calculated by an electrocardiographic recorder. An abnormal test result was defined as a difference of less than 10 beats/min between the shortest and longest heart rate interval.

**Results** Heart rate variability <10 beats/min was found in 65 patients (35%) and was significantly lower (*P* < .05) in women, patients >60 years of age, patients with diabetes, patients with congestive heart failure, and patients taking angiotensin-converting enzyme inhibitors. Mean follow-up period was 16 months. Ten patients died during follow-up: 9 of cardiac causes and 1 of stroke. Nine of these 10 patients had heart rate variability <10 beats/min (*P* = .004). The sensitivity and specificity of this test for cardiovascular mortality is 90.0% and 68.0%, respectively. The negative predictive value is 99.2% and the relative risk is 16.6. Heart rate variability <10 beats/min remained a significant predictor of death after adjusting for clinical, demographic, and left ventricular function with an odds ratio of 1.38 (95% confidence interval, 1.13-1.63).

**Conclusions** This simple, brief bedside deep breathing test of heart rate variability in patients after myocardial infarction appears to be a good predictor for all-cause mortality and sudden death. It may be used as a clinical test for risk stratification after myocardial infarction. (Am Heart J 1999;138:32-8.)

Previous studies have demonstrated that both the sympathetic and the parasympathetic branches of the autonomic nervous system affect the frequency of sudden death and cardiovascular mortality after myocardial infarction.[1,2] Different methods for measuring autonomic nervous system activity in patients after myocardial infarction have been reported.[3-8] These methods include tests of heart rate variability measured by 24-hour Holter monitoring,[4-7] heart rate variability measurements over a briefer period of 2 to 15 minutes,[8] and assessment of baroreflex activity.[3] However, these tests require Holter monitoring with an elaborate analytic system, including computerized power spectral analysis or intravenous administration of phenylephrine with constant blood pressure and heart rate monitoring.

During deep breathing, changes in heart rate occur primarily because of alterations of vagal-cardiac activity.[9] An impairment of this system can lead to depressed heart rate variability.[10] In an era of sophisticated tests of the autonomic system, the purpose of this study was to evaluate prospectively a simple autonomic test (originally used to determine diabetic autonomic neuropathy) that measures changes in heart rate during deep breathing[11,12] as a clinical test for risk stratification of patients after myocardial infarction.

## Methods

### Deep breathing test

The deep breathing heart rate variability test was conducted 5.1 ± 2.5 days after a first myocardial infarction, with the patient in a supine position connected to the limb leads of a standard electrocardiogram (ECG). Patients had to be in stabilized condition and at least 1 day after ambulation had begun. All tests were performed in the morning in the patient's room after the patient had been in the supine position for 10 minutes. Before beginning the test, patients were taught to breathe at a rate of 6 respiration cycles per minute: 5 seconds for each inhalation and 5 seconds for each exhalation. All tests and measurements were per-

formed by a single examiner who raised her hand to signal the start of each inhalation and lowered it to signal the start of each exhalation. Lead II was then recorded continuously at a speed of 50 mm/sec for 60 seconds while the patient breathed as instructed. The heart rate variability interval (R-R intervals between adjacent QRS complexes resulting from sinus node depolarization) was measured manually with a scaled caliper. R-R intervals surrounding premature ventricular contractions were excluded from the analysis. The change in heart rate was calculated as the difference between the shortest and the longest R-R interval (Figure 1): Heart rate variability = [60,000/Short R-R interval (msec)] – [60,000/Long R-R interval (msec)], measured in beats per minute.

The 1-minute deep breathing heart rate variability test was chosen as a short bedside test based on the experience achieved in testing autonomic nervous control of the heart in patients with diabetes mellitus.[11,12] It has been shown that in patients with diabetes aged 18 to 60 years, deep breathing is a potent stimulus for heart rate.[12] The 1-minute deep breathing heart rate variability test was developed and tested in a diabetic population less than age 50 years.[11] In this population, when a cut-point of 10 beats/min was prespecified, the test provided quantitative bedside measurement of autonomic function. Although the myocardial infarction population differs from the original population for which the test was developed and analyzed, we decided to evaluate this simple test in patients after myocardial infarction. On the basis of this study,[11] a test result was prespecified as normal if there was a difference of 10 beats or more per minute between the slowest and the fastest heart rates.

## Study population

The study population was composed of 185 consecutive patients admitted with a first myocardial infarction to the Intensive Coronary Care Unit in the Soroka Medical Center in Beer-Sheva, Israel, between August 1990 and June 1992. Myocardial infarction was diagnosed in the presence of all the following criteria: typical ECG changes, including an ST elevation of at least 2 mm in 2 precordial leads or 1 mm in 2 limb leads; chest pain persisting for more than 30 minutes and not relieved by nitrates; a 2-fold or greater increase in serum creatine phosphokinase or creatine phosphokinase–MB levels. Exclusion criteria included (1) other heart disease (valvular heart disease or cardiomyopathy), (2) severe congestive heart failure (New York Heart Association class IV), (3) unstable angina, (4) coronary artery bypass graft surgery within 3 months of the infarction, (5) atrial flutter or atrial fibrillation, or multiple ventricular or atrial ectopy that precluded measurement of heart rate variability, (6) primary disturbance in sinus rhythm (sick sinus syndrome), (7) second- or third-degree atrioventricular block, (8) other diseases, such as malignancy, that were liable to shorten patient survival time, and (9) inability to undergo the breathing test because of either mechanical ventilation or because of language comprehension difficulties regarding instructions.

Clinical variables were recorded for each patient: age, comorbid factors (diabetes mellitus, hypertension, hyperlipidemia), location of myocardial infarction, thrombolytic therapy, dysrhythmias during the stay in the intensive care unit, congestive heart failure in the acute stage of myocardial

**Table I.** Patient characteristics

| Characteristic | No. of patients (%) (n = 185) |
|---|---|
| Sex | |
| Male | 146 (78.9) |
| Female | 39 (21.1) |
| Ethnic origin | |
| Jewish | 170 (91.9) |
| Bedouin | 15 (8.1) |
| Age (y) | |
| <60 | 98 (53.0) |
| ≥60 | 87 (47.0) |
| Comorbidity | |
| NIDDM | 30 (16.2) |
| IDDM | 3 (1.6) |
| Hypertension | 69 (37.3) |
| Site of myocardial infarction | |
| Anterior wall | 98 (53.0) |
| Inferior wall | 87 (47.0) |
| Thrombolytic therapy | |
| STK | 95 (51.4) |
| TPA | 13 (7.0) |
| STK and TPA | 11 (6.0) |
| CHF during ICCU hospitalization | 26 (14.1) |

*IDDM,* Insulin-dependent diabetes mellitus; *NIDDM,* non-insulin-dependent diabetes mellitus; *STK,* streptokinase; *TPA,* tissue plasminogen activator; *CHF,* congestive heart failure; *ICCU,* intensive coronary care unit.

infarction, and medications. During follow-up, the following data were recorded: recurrence of myocardial infarction, congestive heart failure, sudden death (defined as unexpected cardiac death occurring outside the hospital, preceded by no apparent symptoms or by symptoms of less than 1-hour duration),[13] and all-cause mortality. Data were gathered from patients' charts, telephone interviews, computerized hospital databases, and the Ministry of Health (population registry).

Left ventricular function, Holter recordings, and treadmill testing were not routinely performed on all patients after myocardial infarction in our institute during the study period, so these data are not included in the study. However, multivariate analysis was performed with all clinical variables.

## Statistical analysis

The chi-square test was used to evaluate the significance of the association between heart rate variability and other variables such as diabetes mellitus, morbidity (myocardial infarction, unstable angina, new congestive heart failure), and death. Means of continuous variables were compared by *t* tests. All results were expressed as mean ± SD with 95% confidence intervals (CI). Standard definitions of sensitivity, specificity, and positive and negative predictive values of the deep breathing test were used. Relative risk for outcome variables, sudden death, cardiac and all-cause mortality was defined as the event rate in patients with an abnormal heart rate variability divided by the event rate in patients with a normal heart rate variability. The association of heart rate variability and death after adjusting for age (older than 60 years), sex, diabetes mellitus, hypertension, site of myocardial infarction, thrombolytic therapy, congestive heart failure, basic heart rate >80 beats/min, and angiotensin-converting enzyme (ACE) inhibitor treatment was evaluated with a stepwise

**Table II.** Predictors of heart rate variability

| | HRV <10 beats/min (n = 65) | HRV ≥10 beats/min (n = 120) | Total | P value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 68% (44) | 85% (102) | 146 | .002 |
| Female | 32% (21) | 15% (18) | 39 | |
| Age (y) | | | | |
| Mean ± SD | 63 ± 7 | 54 ± 11 | 56 ± 11 | .001 |
| <60 | 41% (27) | 59% (71) | 98 | |
| ≥60 | 59% (38) | 41% (49) | 87 | |
| Heart rate during the test (beats/min) | | | | |
| Mean ± SD | | | 71 ± 14 | |
| <60 | 20% (13) | 14% (17) | | .006 |
| 60-79 | 46% (30) | 59% (71) | 30 | |
| ≥80 | 34% (22) | 27% (32) | 101 | |
| ACE inhibitor treatment | | | | |
| No | 46% (30) | 72% (86) | 116 | .022 |
| Yes | 54% (35) | 28% (34) | 69 | |
| β-Blocker treatment | | | | |
| No | 35% (23) | 28% (34) | 57 | .819 |
| Yes | 65% (42) | 72% (86) | 128 | |
| Diabetes mellitus | | | | |
| No | 71% (46) | 88% (105) | 151 | .014 |
| Yes | 29% (19) | 12% (15) | 34 | |
| Site of myocardial infarction | | | | |
| Anterior wall | 55% (36) | 52% (62) | 98 | .819 |
| Inferior wall | 45% (29) | 48% (58) | 87 | |
| Congestive heart failure | | | | |
| No | 82% (53) | 88% (106) | 159 | .050 |
| Yes | 18% (12) | 12% (14) | 26 | |

*HRV,* Heart rate variability.

**Table III.** The relation of heart rate variability to cardiac events

| | HRV <10 beats/min (n = 65) | HRV ≥10 beats/min (n = 120) | Total | P value |
|---|---|---|---|---|
| Cardiac event during follow-up (MI, CHF, angina, death) | | | | |
| No | 54% (35) | 72% (87) | 122 | .003 |
| Yes | 46% (30) | 28% (33) | 63 | |
| Recurrent myocardial infarction | | | | |
| No | 89% (58) | 95% (114) | 172 | .121 |
| Yes | 11% (7) | 5% (6) | 13 | |
| All-cause mortality | | | | |
| No | 86% (56) | 99% (119) | 175 | .004 |
| Yes | 14% (9) | 1% (1) | 10 | |

*HRV,* Heart rate variability; *MI,* myocardial infarction; *CHF,* congestive heart failure.

multivariate logistic regression. Odds ratio and 95% confidence intervals were computed for each variable.

## Results

Patient characteristics are summarized in Table I. Thrombolytic therapy was given to 64.4% of the patients, and 35.6% of the patients received conventional medical therapy given to patients with acute myocardial infarction on admission to the hospital: for example, aspirin, nitrates, and β-blockers. At the time of testing, 81% of the patients received aspirin, 69.7% received nitrates, 67.6% received β-blockers, 37.2% received ACE inhibitors (given at the time of the study only to patients with signs of congestive heart failure because class IV heart failure patients were excluded from this study), 13.5% received calcium-channel blockers, and 2.7% received antiarrhythmic medication. The follow-up period ranged from 7 to 26 months, the median was 14 months (mean 16 months), and 170 patients were followed

**Figure 1**
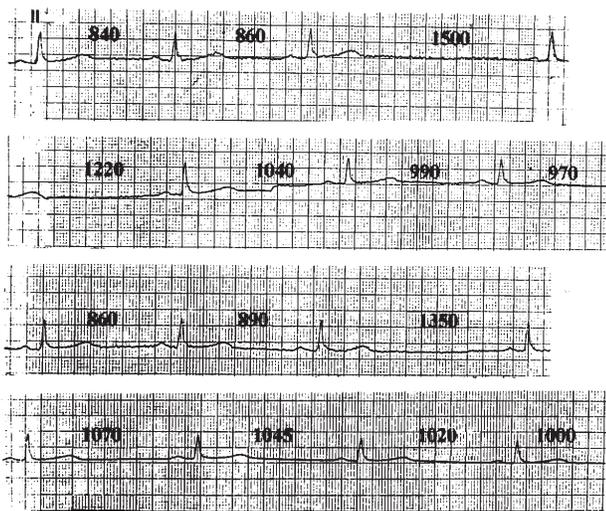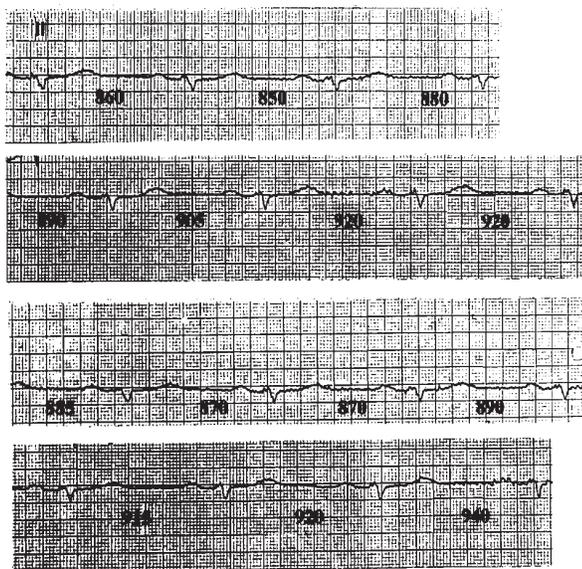


**A,** ECG of a patient with heart rate variability of 30 beats/min (paper speed 50 mm/sec). Fastest heart rate 60,000/860 = 70 beats min, slowest heart rate 60,000/1500 = 40 beats/min. The patient is currently alive. **B,** ECG of patient with heart rate variability of 6 beats/min (paper speed 50 mm/sec). Fastest heart rate 60,000/850 = 70 beats/min, slowest heart rate 60,000/940 = 64 beats/min. The patient died suddenly.

up for 1 year. During follow-up, 68.6% received aspirin, 64.3% received nitrates, 59.5% received β-blockers, 28.6% received ACE inhibitors, 23% received calcium-channel blockers, and 2.1% received antiarrhythmic medication.

**Figure 2**
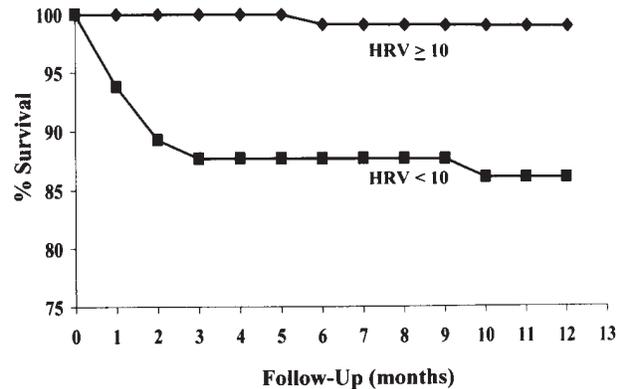


Survival curves for patients with heart rate variability ≥10 beats/min and <10 beats/min. Long-term survival was significantly worse in patients with variability <10 beats/min (*P* = .005).

**Table IV.** Heart rate variability calculated by mean ± SD of all R-R intervals measured during the 1-minute test: Comparison of patients who survived and patients who died

| Status | <50 msec (n = 90) | 50-100 msec (n = 40) | >100 msec (n = 55) | Total |
|--------|-------------------|----------------------|--------------------|-------|
| Alive | 89% (80) | 100% (40) | 100% (55) | 175 |
| Dead | 11% (10) | – | – | 10 |

### Heart rate variability and clinical variables

The heart rate variability of the entire group was 15 ± 9 beats/min. Heart rate variability was less than 10 beats/min in 35% of the patients, between 10 to 20 beats/min in 37%, and more than 20 beats/min in 28% (Table II). A heart rate variability lower than 10 beats/min was significantly more common in women, patients older than 60 years, patients with diabetes mellitus (both insulin-dependent and non-insulin-dependent), patients with congestive heart failure, and in patients treated with ACE inhibitors at the time of the test and during follow-up.

### Heart rate variability and cardiac events

Patients with heart rate variability <10 beats/min had a higher incidence of cardiac events during follow-up, including one or more of the following events: angina pectoris, congestive heart failure, recurrent myocardial infarction, or death (Table III). However, when each type of cardiac event was evaluated independently, recurrent myocardial infarction, acute ischemia, and congestive heart failure were not significantly correlated with heart rate variability <10 beats/min.

**Table V.** Independent clinical predictors of death

|  | Odds ratio | 95% CI | P value |
|---|---|---|---|
| Age >60 years | 1.04 | 0.93; 1.14 | .432 |
| Sex | 1.19 | 0.95; 1.49 | .789 |
| Diabetes mellitus | 1.23 | 0.64; 1.81 | .644 |
| Hypertension | 1.77 | 0.11; 3.33 | .476 |
| Site of myocardial infarction | 1.93 | 0.08; 3.78 | .093 |
| Thrombolytic therapy | 1.27 | 0.93; 1.62 | .255 |
| Congestive heart failure | 5.9 | 4.5; 7.3 | .016 |
| Basic heart rate >80 beats/min | 1.05 | 1.00; 1.10 | .079 |
| ACE inhibitor treatment | 1.59 | 0.47; 2.52 | .064 |
| HRV <10 beats/min | 1.38 | 1.13; 1.63 | .028 |

*HRV,* Heart rate variability.

### Heart rate variability and death

Ten patients (5.4%) died during follow-up. Four died suddenly, 2 with congestive heart failure, 3 of recurrent myocardial infarction, and 1 after a stroke. Age, presence of congestive heart failure, and heart rate variability <10 beats/min differed between the groups of patients who died and those who survived. Patients who died were older (61.6 ± 3.8 years vs 56.3 ± 5.6 years; *P* = .03), had a higher incidence of congestive heart failure (5 of 10 versus 21 of 175; *P* = .005), and had heart rate variability more frequently <10 beats/min (9 of 10 vs 56 of 175; *P* = .004). One-year survival rate for the patients with heart rate variability ≥10 beats/min and <10 beats/min was 99.2% and 86.1%, respectively (*P* < .05). Long-term cardiac survival (Figure 2) was significantly worse in the patients with heart rate variability <10 beats/min (*P* = .005). There was no difference between groups with variability ≥10 beats/min and variability <10 beats/min in terms of prevalence of hypertension, location of myocardial infarction, thrombolytic therapy, average heart rate, treatment with ACE inhibitors, or treatment with β-blockers. The sensitivity of the deep breathing test for detecting patients at high risk for death after myocardial infarction was 90%, and the specificity was 68.0%. The test's positive and negative predictive values were 13.8% and 99.2%, respectively. The relative risk for death during follow-up was 16.6 for patients with heart rate variability <10 beats/min.

The heart rate variability of the deep breathing test was also calculated by mean ± SD of all R-R intervals that were measured during the 1-minute test. This kind of analysis was performed in other studies during longer recording periods but was not done with the short deep breathing test. We found that 90 patients (48.9%) had an SD of less than 50 msec (Table IV). All the patients who died during follow-up were in this group. With this method of calculation, the sensitivity of the breathing test is 100%, its specificity is 53.7%, and its positive and negative predictive values are 11% and 100%, respectively.

Heart rate variability and congestive heart failure were the only clinical variables that maintained independent significance in the multivariate analysis (Table V). Basic heart rate was marginally correlated with the outcome. Congestive heart failure had the strongest correlation with increased mortality rate (odds ratio 5.9, 95% CI, 4.5-7.3), but heart rate variability <10 beats/min also correlated with increased mortality rate (odds ratio 1.38, 95% CI, 1.16-1.63).

## Discussion

Previous studies have shown that time and frequency domain measurements of heart rate variability are excellent predictors of death or arrhythmic events after myocardial infarction and that they are equivalent for this purpose.[4-7,14-20] In this study we evaluated a short, simple bedside method to measure heart rate variability and demonstrated that this test is a sensitive and independent predictor for all-cause mortality in patients after myocardial infarction.

The changes in heart rate associated with respiratory activity are mediated primarily by a combination of changing levels of efferent cardiac vagal and sympathetic activity and mechanically induced sinus node stretch with each respiration.[21] The degree of the contribution from each of these components is related to the frequency and amplitude of the respiratory signal, the mean level of vagal and sympathetic activity, and the mechanical state of the airways. In 1975, Katona and Jih[9] published observations showing the theoretical and experimental basis of respiratory sinus arrhythmia as the quantitative measurement of mean cardiac vagal efferent activity. Other previous investigations evaluated heart rate variability by time and frequency domain spectral analysis with Holter monitor technology[4-8,14-20] and found it to be a powerful predictor of both ventricular arrhythmia and death in patients surviving the acute phase of myocardial infarction.

There are no data concerning the predictive power of

heart rate variability in patients after myocardial infarction assessed from short-term ECG recordings obtained during controlled respiration. One method of controlled respiration is to test the heart rate variability during respiratory rate of 6 breaths/min, which expresses the maximal physiologic sinus arrhythmia.[21,22] Using this method, Bennet et al[12] and Mackay et al[11] demonstrated that heart rate variability during deep breathing proved to be a sensitive diagnostic test of autonomic nervous control of the heart in patients with diabetes mellitus. Patients with abnormally low vagal tone had reduced heart rate variability as measured during deep breathing,[12] or quantitatively heart rate variability <10 beats/min during 6 deep respirations.[11] Of note, patients with diabetic autonomic neuropathy and reduced vagal tone were seen to have a higher incidence of cardiac mortality.[23,24] Vagal tone may be antiarrhythmic by prolonging ventricular refractoriness[25] and altering excitability of myocardial cells.[2,26]

In our study using similar methodology, we showed that this test was also useful for patients after myocardial infarction. Patients with heart rate variability ≥10 beats/min were found to be at minimal risk for cardiac death. On the basis of multivariate analyses, congestive heart failure was the strongest risk factor for death after myocardial infarction. Heart rate variability <10 beats/min with this bedside test was also an independent predictor of death in these patients.

### Limitations

The deep breathing test used in our study does require cooperation because the patient has to inhale and exhale for 5-second periods. Patients with severe congestive heart failure or pulmonary edema are in respiratory distress or are even ventilated mechanically and thus cannot perform the test; they were therefore excluded from the study. Other patients who cannot be tested by deep breathing are those with certain arrhythmias that preclude accurate R-R measurements.

This analysis is limited by the small number of total deaths (n = 10), which affects the analysis of a multivariable model. Therefore the power to preclude that the predictive information in this variable is independent of other important variables is limited. The power to determine whether the relation between heart rate variability and outcome is continuous and the nature of the relation across the spectrum of various values is likewise limited.

In our institution at the time of the study, left ventricular function tests and Holter recordings were not routinely performed on all patients after myocardial infarction because of lack of resources. Therefore this study could not address any possible additive value of these tests to the predictive value of heart rate variability. Clinical end points such as adverse outcome, death, stroke, reinfarction, and congestive heart fail-

ure may be useful in detecting diagnostic and therapeutic benefit in patients with acute myocardial infarction in the reperfusion era.[27] Regardless, heart rate variability measurement by our method was an independent predictor of death in patients after myocardial infarction.

### Conclusions

This prospective study analyzed a simple, inexpensive bedside test for evaluating heart rate variability. It was found to be sensitive, and its predictive value could be used to identify a subgroup of patients after myocardial infarction who are at high risk for cardiovascular death. Further studies will be needed to evaluate its role in a broader group of patients after myocardial infarction.

## References

1. Eckberg DL. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. Am J Physiol 1980; 239:H581-H593.
2. Malliani A, Schwartz PJ, Zanchetti A. Neural mechanism in life threatening arrhythmias. Am Heart J 1980;100:705-14.
3. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. Circulation 1988;78:816-24.
4. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256-62.
5. Cripps TR, Malik M, Farrell T, Camm AJ. Prognostic value of reduced heart rate variability after myocardial infarction, clinical evaluation of a new analysis method. Br Heart J 1991;65:14-9.
6. Malik M, Farrell Y, Cripps TR, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction, selection of optimal processing techniques. Eur Heart J 1989;10:1060-74.
7. Bigger JT, Fleiss JL, Steinman RC, Rolinitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164-71.
8. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993;88:927-34.
9. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol 1975;39:801-5.
10. Van Ravenswaaij-Arls CA, Kollee LA, Hopman JC, Stoelinga GB, Van Geijn HP. Heart rate variability. Ann Intern Med 1993; 118:436-47.
11. Mackay JD, Page MM, Cambridge J, Watkins PJ. Diabetic autonomic neuropathy. The diagnostic value of heart rate monitoring. Diabetologia 1980;18:471-8.
12. Bennett T, Farquhar IK, Hosking DJ, Hampton JR. Assessment of methods for estimating autonomic nervous control of the heart in patients with diabetes mellitus. Diabetes 1978;27:1167-74.
13. Kuller LH. Sudden death: definition and epidemiological considerations. Prog Cardiovasc Dis 1980;23:1-12.
14. Lombardi F, Sandrone G, Pernpruner S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. Am J Cardiol 1987;60:1239-45.
15. Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. Med J Australia 1978;2:52-3.
16. Casolo GC, Stroder P, Signorini C, et al. Heart rate variability during

the acute phase of myocardial infarction. Circulation 1992; 85:2073-9.

17. Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. Am J Cardiol 1990; 66:1049-54.

18. Rich MW, Saini JS, Kleiger RE, Carney RM, Velde A, Freedland KE. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. Am J Cardiol 1988;62:714-7.

19. Odemuyiwa O, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm AJ. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic event and sudden death after acute myocardial infarction. Am J Cardiol 1991;68:434-9.

20. Fei L, Statters DJ, Anderson MH, Malik M, Camm AJ. Relationship between short- and long-term measurement of heart rate variability in patients at risk of sudden cardiac death. PACE 1994;17:2194-200.

21. Hirsch JA, Bishop B. Respiratory sinus arrhythmia in humans: How breathing patterns modulate heart rate. Am J Physiol 1981;10:H620-H629.

22. Mehisen J, Pagh K, Nielsen JS, Sestoft L, Nielsen SL. Heart rate response to breathing dependency upon breathing pattern. Clin Physiol 1987;7:115-24.

23. Ewing DJ, Campbell IW, Clarke BF. Mortality in diabetic autonomic neuropathy. Lancet 1976;I:601-3.

24. Page M, Watkins PJ. Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1978;I:14-6.

25. Prystowsky EN, Jackman WN, Rinkenberger RL, Heger JJ, Zipes AP. Effect of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in humans. Circ Res 1981;49:511-8.

26. Lown B, Verrier RL. Neural activity and ventricular fibrillation. N Engl J Med 1976;294:1165-70.

27. Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation 1990;82:1847-53.