Heart Rate Variability From 24-Hour Electrocardiography and the 2-Year Risk for Sudden Death

Ale Algra, MD, PhD; Jan G.P. Tijssen, PhD; Jos R.T.C. Roelandt, MD, PhD; Jan Pool, MD, PhD; and Jacobus Lubsen, PhD

Background. Low heart rate variability has been implicated as a risk factor for sudden death. However, no large epidemiological studies using sudden death as an outcome event have been reported.

Methods and Results. A total of 6,693 consecutive patients who underwent 24-hour ambulatory ECG were followed up for 2 years; of these, 245 patients died suddenly. Clinical data at the time of 24-hour ambulatory ECG were collected for all patients who died suddenly and for a random sample of 268 patients from the study cohort. In all patients in sinus rhythm with or without occasional supraventricular arrhythmias at the 24-hour ECG (193 patients who died suddenly and 230 patients from the sample), heart rate variability parameters were derived. Patients with low short-term RR interval variability (mean during 24 hours of per-minute standard deviations [SD] of RR intervals <25 msec) had a 4.1-fold higher risk (95% confidence interval [CI], 2.6, 8.1) for sudden death than patients with high short-term variability (≥40 msec); after adjustment for age, evidence of cardiac dysfunction, and history of myocardial infarction, the relative risk was 2.6 (95% CI, 1.4, 5.1). The crude relative risk of long-term RR interval variability (SD during 24 hours of per-minute means of RR intervals <8 msec) was 4.4 (95% CI, 2.6, 7.7); after adjustment for the same risk factors, it was 2.2 (95% CI, 1.2, 4.1). Patients with a minimum heart rate ≥65 beats per minute had a double risk of sudden death compared with those with a minimum heart rate <65 beats per minute (adjusted relative risk, 2.1; 95% CI, 1.3, 3.6).

Conclusions. These findings support the theory that patients with low parasympathetic activity (low short-term RR interval variability) have an increased risk for sudden death independent of other risk factors. (Circulation 1993;88:180-185)

Key Words • autonomic nervous system • heart rate • risk factors

Although evidence from several sources suggests that disturbance of autonomic nervous system activity is accompanied by an elevated risk for sudden death, no large epidemiological studies in this field have been published.1 Task Force 4 on nonpharmacological interventions in sudden cardiac death set up at the 1985 American Heart Association Conference on Behavioral Medicine and Cardiovascular Disease recommended such studies.2 Moreover, several studies on heart rate variability used all-cause mortality as outcome event; studies on sudden death generally have series of limited size.

Data from experimental research indicate that reduced parasympathetic nervous system activity increases the likelihood of ventricular fibrillation during myocardial ischemia, especially when sympathetic hyperactivity coexists.3-6 In a clinical study, attenuated baroreceptor reflexes, which are an expression of enhanced sympathetic and reduced parasympathetic activity, were more common in patients who died suddenly after myocardial infarction than in survivors.7 The Multicenter Post-Infarction Research Group reported that low heart rate variability, corresponding to reduced parasympathetic tone, was associated with 5.3-fold higher all-cause mortality than high levels of heart rate variability.8 Also, enhanced activity of the sympathetic nervous system can cause (or, more prudently, is associated with) sudden death; e.g., pooled data from long-term β-blocker trials yield a reduction of the incidence of sudden death of 32%,9 and recently it was demonstrated that selective cardiac sympathetic denervation can reduce the risk of sudden death.10

The hypothesis underlying our study is that sudden death may be precipitated by a disturbance of autonomic nervous system activity. Early disturbances may characterize patients with an elevated risk for sudden death. Therefore, we studied the risk implications of heart rate variability with regard to the occurrence of sudden death in patients in sinus rhythm with or without occasional supraventricular arrhythmias originating...
from a cohort of 6,693 consecutive patients who under-
went 24-hour ambulatory ECG.

Methods

Study Cohort

All 6,693 consecutive patients who had 24-hour ECG in one of the four participating Rotterdam hospitals between August 1, 1980, and December 31, 1984, were included in this study. Indications for 24-hour ECG were the evaluation of symptoms potentially related to cardiac arrhythmias (palpitations, dizziness, syncope, angina) (65%), of the effect of antiarrhythmic therapy (8%), and of risk after myocardial infarction (10%), or the search for a cardiac cause of transient ischemic attacks or strokes (7%). Most 24-hour ECGs were recorded in outpatients (75%).

Follow-up

Patients were followed for mortality until 2 years after 24-hour ambulatory ECG. Follow-up was complete in 99.5% of the patients; 716 patients had died (10.7%). Cause and circumstances of death were determined from the records of general practitioners and hospitals. Patients were considered to have died suddenly if death was observed and had occurred within 1 hour after new or more serious symptoms and if its probable cause was cardiovascular. Also, patients who died unexpectedly during sleep or died while unobserved were considered to have died suddenly if circum-
stantial evidence pointed to sudden death from cardio-
vascular causes. All cases of sudden death were independently verified by two senior cardiologists. Thus, a total of 245 cases of sudden death were identified, of which 66 cases (27%) occurred in the hospital.

Collection of Baseline Data

Baseline characteristics were retrospectively collected for all patients who died suddenly and a random sample of 268 patients from the complete study cohort. Information on the following patient characteristics at the time of 24-hour ECG was collected from the medical records: known cardiovascular risk indicators, cardio-
vascular history, cardiovascular function tests if avail-
able, routine laboratory studies, current drug use, and a resting 12-lead ECG. Evidence of cardiac dysfunction was considered to be present if there had been a history of symptoms of pump failure (e.g., shortness of breath or treatment with digitalis) or an ejection fraction <40% at cineangiographic or radionuclide ventriculog-
raphy. Details on data from the resting 12-lead ECG have been published previously.11

RR Interval Measurements and Parameters

A stream of all RR intervals was obtained during computer-aided analysis of the 24-hour ECGs.12 The parameters of RR interval duration and variation are shown in Table 1. For the calculation of the RR parameters, only RR intervals between QRS complexes of supraventricular origin were used. Intervals whose duration was <80% or >120% of that of the running RR average were excluded to eliminate intervals related to premature supraventricular complexes and ven-
tricular arrests (pragmatically defined as an RR interval >2 seconds). Also excluded were the intervals after a

<table>
<thead>
<tr>
<th>TABLE 1. Parameters of RR Duration and Variability During 24-Hour Electrocardiography and Their Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>RR interval/heart rate</td>
</tr>
<tr>
<td>Maximum heart rate</td>
</tr>
<tr>
<td>Minimum heart rate</td>
</tr>
<tr>
<td>Interval differences &gt;50 msec</td>
</tr>
<tr>
<td>Short-term variation RR</td>
</tr>
<tr>
<td>Long-term variation RR</td>
</tr>
</tbody>
</table>

All parameters were calculated over a period of 24 hours unless indicated otherwise.

short interval (presumably related to a premature supraventricular complex), because these intervals tend to be prolonged as partially compensatory pause.

Data Analysis

Four patients with unanalyzable 24-hour ECGs were excluded, as well as patients with frequent supraventricular rhythms other than sinus rhythm at the 24-hour ECG, leaving 193 cases of sudden death and 230 patients from the random sample.

The effect of an ECG characteristic, e.g., high heart rate variability, on the risk for sudden death was expressed as the relative risk, which is equal to the risk for sudden death among patients with the characteristic divided by that among patients without the characteristic. The risk for sudden death among patients with the characteristic was obtained as the number of sudden deaths with the characteristic divided by the (estimated) total number of patients with the characteristic. The latter was obtained by extrapolating the heart rate variability findings in the sample to the whole study cohort; i.e., the total number of patients with the characteristic was obtained by multiplying the number of patients with the characteristic in the sample by 6,693/268, which was the inverse of the sampling fraction. In this calculation, a correction factor of 241/245 was used to compensate for the exclusion of four cases. The risk for sudden death among patients with the property absent was obtained analogously. The 95% confidence interval (CI) of the odds ratio was used and calculated from the data laid out for a case–control study.13

All RR interval parameters mentioned in Table 1 were divided into thirds. If the absolute risks for sudden death in two adjacent categories were essentially the same, these categories were joined into one category in later analyses.

We used stratified analysis and multiple logistic re-
gression to calculate adjusted relative risks to assess the influences of independent risk factors of sudden death.
Table 2. Patient Characteristics at the Time of 24-Hour Electrocardiography in the Sudden Death Patients and the Patients From the Random Sample of the Study Cohort Selected for the Heart Rate Variability Data Analysis

<table>
<thead>
<tr>
<th></th>
<th>Sudden deaths</th>
<th>Referents</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n)</td>
<td>193</td>
<td>230</td>
</tr>
<tr>
<td>Outpatients (%)</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td>Men (%)</td>
<td>78</td>
<td>64</td>
</tr>
<tr>
<td>Age &gt;60 years (%)</td>
<td>68</td>
<td>49</td>
</tr>
<tr>
<td>Evidence of cardiac dysfunction* (%)</td>
<td>50</td>
<td>17</td>
</tr>
</tbody>
</table>

History (%)

- Angina: 60
- Myocardial infarction: 68
- Supraventricular arrhythmias: 48
- Ventricular arrhythmias: 55
- Atrioventricular conduction defects: 15
- Palpitations: 30
- Dizziness: 44
- Syncope: 25
- Coronary bypass surgery: 9
- Transient ischemic attack or stroke: 19
- Intermittent claudication: 12
- Diabetes mellitus: 18
- Cigarette smoking: 34
- Systolic blood pressure >140 mm Hg (%): 45
- Diastolic blood pressure >80 mm Hg (%): 36
- Cholesterol >6 mmol/L† (%): 57

Drug use (%)

- Digitalis: 46
- β-Blockers: 34
- Diuretics: 54

Antiarrhythmic drugs

Class 1: 17
Class 3: 8
Class 4: 5

*Defined as a history of symptoms and/or signs of pump failure or an ejection fraction <40% at cineangiographic or radionuclide ventriculography.
†Data available in only about one third of the patients.

unequally distributed between patients with and without a specific ECG characteristic.

Results

The distribution of baseline characteristics of all the 193 sudden death patients and the 230 patients from the random sample selected for the heart rate variability data analysis is shown in Table 2. Risk factors of sudden death are more prevalent among the sudden death patients, e.g., age, evidence of cardiac dysfunction, and a history of myocardial infarction. Also, patients from the random sample less frequently used any of the drugs listed in Table 2.

In Table 3, the occurrence of sudden death in relation to several heart rate parameters is shown. Crude analysis (unadjusted relative risks) reveals that mean heart rates <70 and ≥80 beats per minute are related to a slightly increased risk for sudden death. The lower the maximum heart rate is, the higher the risk for sudden death, whereas a high minimum heart rate (≥65 beats per minute) relates to an increased risk. A low percentage of interval differences >50 msec also exhibits an elevated risk. Patients with low short-term and long-term variation have a risk four times higher than patients with high variation. During the assessment of the influence of other risk factors for sudden death on the crude relative risk estimates, we found that the combination of age, evidence of cardiac dysfunction, and history of myocardial infarction altered the estimates (Table 3, middle column); addition of other patient characteristics, including drug use, to the logistic models yielded no further relevant changes. Adjusted relative risk estimates were lower for maximum heart rate <100 beats per minute (1.4 versus 2.5), short-term variation <25 msec (2.6 versus 4.1), and long-term variation <8 msec (2.2 versus 4.4). When the age-adjusted, myocardial infarction–adjusted, and cardiac dysfunction–adjusted relative risks are adjusted additionally for the other heart rate parameters, the relative risk estimates are essentially the same (Table 3, right column).

If the analysis was restricted to the sudden death patients who died in the hospital, the crude relative risks for short-term and long-term variation of the RR
Table 3. Sudden Death in Relation to Several Parameters of RR Interval Duration and Variability in the 24-Hour ECG

<table>
<thead>
<tr>
<th>Mean heart rate (bpm)</th>
<th>%SD*</th>
<th>RRcr†</th>
<th>95% CI‡</th>
<th>RRadj§</th>
<th>95% CI‡</th>
<th>RRadj§</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>4.1</td>
<td>1.6</td>
<td>0.9, 2.6</td>
<td>1.4</td>
<td>0.8, 2.4</td>
<td>1.0</td>
<td>0.5, 2.1</td>
</tr>
<tr>
<td>70–80</td>
<td>2.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>≥80</td>
<td>3.5</td>
<td>1.3</td>
<td>0.8, 2.1</td>
<td>1.4</td>
<td>0.8, 2.5</td>
<td>0.8</td>
<td>0.3, 1.9</td>
</tr>
<tr>
<td>Maximum heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>5.6</td>
<td>2.5</td>
<td>1.5, 4.3</td>
<td>1.4</td>
<td>0.7, 2.7</td>
<td>1.6</td>
<td>0.5, 5.3</td>
</tr>
<tr>
<td>100–125</td>
<td>3.5</td>
<td>1.6</td>
<td>1.0, 2.5</td>
<td>0.9</td>
<td>0.5, 1.5</td>
<td>0.7</td>
<td>0.3, 1.4</td>
</tr>
<tr>
<td>≥125</td>
<td>2.3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Minimum heart rate (bpm)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>2.7</td>
<td>2.7</td>
<td>1.4, 3.8</td>
<td>2.1</td>
<td>1.3, 3.6</td>
<td>1.7</td>
<td>0.9, 3.5</td>
</tr>
<tr>
<td>≥65</td>
<td>6.2</td>
<td>4.8</td>
<td>1.8, 2.8</td>
<td>1.5</td>
<td>0.9, 2.4</td>
<td>0.9</td>
<td>0.5, 1.6</td>
</tr>
<tr>
<td>Interval differences &gt;50 msec (%)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>4.8</td>
<td>1.8</td>
<td>1.2, 2.8</td>
<td>1.5</td>
<td>0.9, 2.4</td>
<td>0.9</td>
<td>0.5, 1.6</td>
</tr>
<tr>
<td>≥3</td>
<td>2.7</td>
<td>...</td>
<td>...</td>
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<td>...</td>
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<tr>
<td>Short-term variation RR interval (msec)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>7.0</td>
<td>4.1</td>
<td>2.6, 8.1</td>
<td>2.6</td>
<td>1.4, 5.1</td>
<td>2.6</td>
<td>0.9, 7.6</td>
</tr>
<tr>
<td>25–40</td>
<td>2.7</td>
<td>1.6</td>
<td>1.0, 2.9</td>
<td>1.2</td>
<td>0.6, 2.3</td>
<td>1.4</td>
<td>0.7, 2.8</td>
</tr>
<tr>
<td>≥40</td>
<td>1.7</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
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<tr>
<td>Long-term variation RR interval (msec)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>6.4</td>
<td>4.4</td>
<td>2.6, 7.7</td>
<td>2.2</td>
<td>1.2, 4.1</td>
<td>1.9</td>
<td>0.7, 5.4</td>
</tr>
<tr>
<td>8–12</td>
<td>3.4</td>
<td>2.3</td>
<td>1.5, 4.2</td>
<td>1.6</td>
<td>0.9, 2.9</td>
<td>1.3</td>
<td>0.6, 2.7</td>
</tr>
<tr>
<td>≥12</td>
<td>1.5</td>
<td>...</td>
<td>...</td>
<td>...</td>
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</tr>
</tbody>
</table>

%SD, 2-year sudden death rate; RRcr, crude relative risk; CI, confidence interval; RRadj, relative risk adjusted for age, evidence of cardiac dysfunction, and history of myocardial infarction; RRadj2, relative risk adjusted for age, evidence of cardiac dysfunction, history of myocardial infarction, and all RR interval parameters; bpm, beats per minute.

*The denominator was estimated as the number of patients from the random sample multiplied by the inverse of the sampling fraction, 6,693/268, and corrected by 241/245 because of the exclusion of four cases of sudden death.

†Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference.

§Calculated as the 95% CI for the odds ratio.

||
|Discussion||
|Heart Rate Variability (RR Interval Variability)|
|Patients with low parasympathetic activity as expressed by 50-msec interval differences <3% had a risk for sudden death approximately double that of those with high parasympathetic activity (interval differences ≥3%). Patients with low levels of short-term variation (<25 msec) had a fourfold risk for sudden death compared with patients with high levels (≥40 msec). After adjustment for other risk factors, low short-term variation independently increases the risk for sudden death by a factor of 2.6. These observations are probably in accordance with each other because both parameters are interpreted at least partly as measures of parasympathetic activity. The inverse relation of long-term RR interval variation with the occurrence of sudden death (adjusted relative risk, 2.2) may also be explained in part by parasympathetic activity.

The decrease of some of the relative risk estimates after adjustment (Table 3, middle column) has to be attributed to the relation between the sudden death risk factors age, evidence of cardiac dysfunction, and history of myocardial infarction (see Table 1) and the heart rate parameters. For example, among the patients from the random sample, 32% with low short-term variation (<25 msec) had evidence of cardiac dysfunction compared with 10% with high short-term variation (≥40 msec). Likewise, the patients with low short-term variation were older (75% >60 years old) and more often had a history of myocardial infarction (41%) than those with high short-term variation (24% >60 years old and 24% with a history of myocardial infarction). Adjustment in addition to the clinical parameters for the other heart rate parameters (Table 3, right column) hardly changes the effect of estimates of main interest, i.e., those for short-term and long-term variability. Hence, we conclude that there is no confounding by the other heart rate parameters.

The percentage of successive intervals that differed more than 50 msec was taken as a measure of parasympathetic activity.14 This index is sensitive primarily to frequency components of the heart rate spectrum between 0.15 and 0.50 Hz15 and comprises the peak of variations around 0.25 Hz, which corresponds to the respiratory frequency modulated by the parasympathetic nervous system.16,17 Short-term variation according to our definition is sensitive to spectral components between approximately 0.05 and 0.50 Hz,13 containing not only respiratory frequencies but also those attrib-
uted to the baroreceptor reflex, which is influenced by both the sympathetic and parasympathetic nervous systems. Long-term variation corresponds with low-frequency components of the heart rate spectrum, around frequencies of 0.02–0.05 Hz, 15 enclosing the peak that probably originates from fluctuations in peripheral vasomotor tone associated with thermoregulation.18

Our findings correspond well with those from the Multicenter Post-Infarction Project, in which heart rate variability (taken as the standard deviation of all normal RR intervals in a 24-hour ECG and comparable to our definition of short-term heart rate variability) <50 msec was related to a 5.3-fold higher all-cause mortality than heart rate variability >100 msec.1 These findings were confirmed in more detailed analyses of heart rate variability (including frequency domain analysis) of the same group of patients also if other risk factors were taken into account.18,20 In a comparison of heart rate variability parameters similar to the ones we used, six survivors of documented ventricular fibrillation had clearly lower levels of variability as assessed by all parameters than a comparison group of six volunteers without evidence of heart disease.15 Also, in two survivors of ventricular fibrillation without coronary heart disease, depressed vagal reflexes (baroreflex sensitivity) were observed.21

Heart Rate (RR Interval Duration)

Mean heart rate over a period of 24 hours exhibited no clear relation with the occurrence of sudden death; this was also the case in the patient groups not taking β-blockers and without evidence of cardiac dysfunction. Actually, the average of all mean heart rates over a period of 24 hours in our study did not differ from that reported for a group of healthy male subjects (77 versus 74 beats per minute).22 Apparently, prognostic information with regard to sudden death is lost by taking the 24-hour average, because the other parameters of heart rate had prognostic implications and also because reports on heart rate as taken from standard 12-lead ECGs showed that sudden death rates increased progressively with heart rate.23,24

A maximum heart rate <100 beats per minute yielded a crude relative risk of 2.5; after adjustment for age, evidence of cardiac dysfunction, and history of myocardial infarction, the relative risk dropped to 1.4. This finding may be compared with that from exercise testing, in which inability to raise heart rate is related to a poor prognosis.25 Conversely, in comparison with healthy subjects, patients with angiographically proven coronary artery disease reached lower maximum heart rates.26 Thus, low maximum heart rate may be interpreted as a correlate of low exercise capacity.

In both crude and adjusted analyses, a minimum heart rate ≥65 beats per minute more than doubled the risk for sudden death; this certainly fits with reduced vagal tone. High minimum heart rate may be the reflection of many conditions, some of which are impaired myocardial function, autonomic imbalance, poor physical fitness, or any combination of these. The role of the first factor may be confirmed by our data: minimum heart rate was higher in patients with evidence of cardiac dysfunction than in those without (difference, 5.2 beats per minute; 95% CI, 2.9, 7.5).

Implications

Heart rate variability may be useful in clinical practice because this parameter is easily obtained from 24-hour ECG and has a strong relation with the occurrence of sudden death. Moreover, since low variability is linked to low parasympathetic activity, heart rate variability may give direction to therapeutic interventions. Insofar as low parasympathetic activity is related to high sympathetic activity, β-blockers may be efficacious drugs. This would be in agreement with pooled observations from long-term β-blocker trials that yield a 32% reduction of the incidence of sudden death.23 Direct stimulation of parasympathetic activity may be an alternative, because recent intervention studies in dogs after myocardial infarction indicate that direct vagal stimulation and muscarinic receptor agonists reduce the incidence of ventricular fibrillation27,28; however, the efficacy of drugs that modify vagal tone in patients still has to be demonstrated.29,30

In the estimation of the risk of sudden death (prediction, as opposed to understanding of pathophysiology), however, heart rate parameters hardly increase the efficiency of the prediction compared with that based on history, a standard 12-lead ECG, and routine analysis of a 24-hour ECG only.31

Limitations of the Study

The criteria used for classification of the cases of sudden death were pragmatic, because information on cause and circumstances of death had to be obtained between 1 and 4 years after death. Actually, stricter criteria can be used in a prospective study, because details are not lost with time.

Our findings apply to a group of patients selected because they had one of several indications for 24-hour ECG and were in sinus rhythm with only occasional supraventricular arrhythmias. Hence, the study group was heterogeneous, but because our findings are in keeping with those from the literature, we consider the heterogeneity a strong point rather than a limitation of the study.

The occurrence of sudden death in the cohort was conditional on the interventions that took place since 24-hour ECG. Therefore, the findings during routine analysis of the 24-hour ECGs may have influenced intervention strategies. This would jeopardize the validity of the estimation of the effect of ECG parameters on sudden death. However, during the study period, heart rate variability was not generally used in clinical practice. Thus, it is unlikely that the validity of the estimation of relative risk is influenced by the findings on the 24-hour ECGs.

Conclusions

The data from our study indicate that patients with either low short-term or low long-term variation have a risk more than double that of patients with high variation independently of other risk factors. Patients with a minimum heart rate ≥65 beats per minute have a twofold risk for sudden death compared with those with a minimum heart rate <65 beats per minute. Patients with <3% RR interval differences >50 msec tend to have a somewhat higher risk for sudden death than those with ≥3% RR interval differences >50 msec.
Further attention to the several parameters that provide information on autonomic activity in studies of the identification of patients at high risk for sudden death is indicated.32

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