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Heart rate variability in relation to prognosis after myocardial infarction: Selection of optimal processing techniques

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Automatic analysis of heart rate variability from Holter recordings may be invalidated by beat recognition errors and recording artefact, necessitating filtering and editing of the computer-recognized RR interval sequence. Two new methods for heart rate variability analysis have been developed, based on an estimation of the width of the main peak of the frequency distribution curve of the computer-recognized normal-to-normal beat sequence. These methods are independent of a low level of recognition error and artefact, thus removing the need for operator-dependent, time-consuming editing. The value of the new methods (heart variability indices 1 and 2) in identifying patients with serious events (death and symptomatic, sustained documented ventricular tachycardia) during a 6-month follow-up after acute myocardial infarction was assessed in a case-control study comparing 20 patients who had experienced such events (Group I) with 20 patients who, following admission with acute myocardial infarction, had remained free of complications for >6 months after discharge (Group II). Group II was selected to match Group I with regard to age, sex, infarct site, ejection fraction, and β-blocker treatment.

Analysis of the unfiltered computer-recognized normal-to-normal interval sequence showed that heart rate variability indices 1 and 2 were significantly lower ($P < 0.005$, $P < 0.002$) in those who had experienced events compared with those free from complications. Two other methods of expressing heart rate variability, including the standard deviation method, in combination with four different data-filtering techniques, gave less significant distinction between those with and without events during follow-up. It is concluded that using the methods described, reduced heart rate variability in patients at risk from death or sustained ventricular tachycardia after acute myocardial infarction can be detected automatically from unfiltered Holter tape recordings even in the presence of a low level of beat recognition error and recording artefact.

Introduction

Investigation of heart rate variability and its relation to different clinical phenomena has been the subject of several previous studies[1–6]. In particular, attention has been paid to heart rate variability in coronary artery disease and after acute myocardial infarction[7–9].

Recently, it has been reported[1] that reduction in heart rate variability, determined from Holter recordings made prior to discharge after acute myocardial infarction, can be used to predict long-term mortality. The Holter recordings were digitized off-line and reanalysed using a standard computer algorithm[10] identifying each normal QRS complex. The obtained sequence of intervals between successive normal complexes (called the NN intervals) was further analysed and the standard deviation of the durations of NN intervals was used to express the variability of the heart rate in numerical terms.

However, in many patients, continuous electrocardiographic records are imperfect, containing noise and artefacts of both biological and environmental origin. The voltage and morphology of the QRS complexes may vary enough to make the computer recognition algorithms incapable of recognizing all normal beats. Since the electrocardiographic morphology of atrial or nodal ectopic beats is not usually distinguishable from normal QRS complexes, such ectopic beats are also a source of artefact in the computer-recognized sequence of NN intervals.

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For these reasons, it is assumed that prior to quantification of heart rate variability, artefacts within the sequence of NN intervals should be excluded. In one of the studies mentioned above[1], the rate variability computation considered only those NN intervals which differed in duration by less than ±20% from the previous interval. Such filtering was clearly not effective in removing all artefacts, hence visual checking and manual correction of the computer-recognized and filtered NN interval sequence was also required.

The need for visual checking and manual editing is time consuming and subject to observer bias. The objective of our present study was to investigate if it was possible to develop an alternative, fully automatic method to measure heart rate variability, which was of equivalent prognostic power in acute myocardial infarction patients to the previously described, operator-dependent method.

Patients and methods

PATIENTS

During the period of the study, May 1986 to January 1989, 320 patients who were admitted to the hospital with acute myocardial infarction survived to discharge. Myocardial infarction was defined as the presence of two of the three criteria, ischaemic-type chest pain lasting ⩾20 min, elevation of aspartate transaminase, β-hydroxybutyrate dehydrogenase and/or creatine phosphokinase to at least twice the upper limit of the reference range for our laboratory, and the development of new pathological Q waves or persistent ST/T changes. During the first 6 months of follow-up, 20 patients had serious events, either death or documented, symptomatic sustained ventricular tachycardia. Twelve of these were deaths, all but one of which were sudden; eight patients experienced sustained ventricular tachycardia. From the remaining patients, 20 were selected for a case-control study to determine the optimum method for analysis of heart rate variability, in order to distinguish between those with and without events. The control group was selected to match with the positive group with regard to sex, age, infarct site, ejection fraction and administration of β-blockers during hospitalization. The group was selected by a computer search, and absolute correspondence with respect to sex, infarct site and β-blocker treatment was required. As it was not possible to achieve an absolute correspondence in respect of the two remaining parameters, patients with near values were selected. Statistically (paired Student's *t*-test), there are no differences between the groups regarding age (64·20 years ± 6·29 for the positive group, and 63·75 ± 6·33 for the negative group) and ejection fraction (48·80 ± 13·12 and 49·30 ± 14·50 respectively). The clinical features of the 40 patients analysed are shown in Table 1.

HOLTER RECORDING TECHNIQUE

Two channel recordings (modified lead III and CM5) were made using a Tracker recorder (Reynolds Medical Ltd, Hertford, U.K.). A commercially available long-term ECG analysis system (Pathfinder III, Mk 2, Reynolds Medical Ltd) was used to obtain the NN interval sequence for each patient. Using this equipment, the durations of NN intervals were measured on a discrete time-scale with the time unit of (1/128) s (≅ 8 ms).

FILTERING OF THE SEQUENCE OF NN INTERVALS

The NN interval sequence filtering suggested by Kleiger *et al.*[1] is based on the assumption that the physiologic mechanisms controlling heart rate do not result in sudden changes in rate on a beat-to-beat basis. Therefore, any computer-determined NN interval which differs remarkably in duration from the previous or succeeding interval is unlikely to be a real NN interval.

It is debatable whether the duration of each interval should be compared with the length of the previous or next interval and what is the highest acceptable difference between neighbouring intervals. Therefore, we tested different filtering algorithms, each of which depended on a variable parameter that expressed the maximum acceptable beat-to-beat change. Filter *a* accepted an NN interval if the ratio between its length and the length of the previous interval was acceptable (the difference was lower than the threshold specified by the parameter). Filter *b* required each interval to differ acceptably from *either* the previous *or* the next interval; and filter *c* required an acceptable difference from *both* the previous *and* the next intervals.

However, a filter based on a ratio between the durations of neighbouring NN intervals fails when a misinterpreted abnormality is repeated during long-term ECG recording. For example, ectopic bigeminal beats may not be recognized by the analysis algorithm. Then, the corresponding part of the computer-generated NN interval sequence consists of 'normal-ectopic-normal' intervals. Furthermore, such incorrectly identified intervals may

Table 1 Clinical summary of all patients included in the study

Patient	Sex	Age (years)	Infarct site	Ejection fraction (%)	β-blocker treatment	Event	Event time (days)
P1	M	57	INF Q	45	no	SD	21
N1	M	57	INF Q	63	no		
P2	M	59	INF Q	52	no	VT	95
N2	M	58	INF Q	54	no		
P3	M	73	ANT Q	35	no	SD	27
N3	M	71	ANT Q	30	no		
P4	M	70	ANT Q	22	no	VT	7
N4	M	70	ANT Q	30	no		
P5	F	72	INF NQ	45	no	SD	53
N5	F	72	INF NQ	18	no		
P6	M	69	ANT Q	55	no	VF	32
N6	M	70	ANT Q	35	no		
P7	M	64	ANT Q	52	no	SD	27
N7	M	64	ANT Q	57	no		
P8	M	56	ANT Q	56	yes	VT	18
N8	M	56	ANT Q	64	yes		
P9	M	69	INF Q	49	no	VT	60
N9	M	69	INF Q	57	no		
P10	M	66	ANT Q	35	no	SD	93
N10	M	65	ANT Q	42	no		
P11	F	68	ANT NQ	68	yes	SD	28
N11	F	65	ANT NQ	70	yes		
P12	F	62	ANT NQ	39	no	SD	7
N12	F	59	ANT NQ	49	no		
P13	M	53	INF Q	52	no	SD	27
N13	M	52	INF Q	63	no		
P14	M	56	INF Q	60	no	VT	12
N14	M	56	INF Q	57	no		
P15	M	72	ANT Q	20	no	SD	73
N15	M	70	ANT Q	30	no		
P16	M	64	INF Q	62	no	VT	91
N16	M	63	INF Q	63	no		
P17	M	57	INF Q	66	no	VT	23
N17	M	58	INF Q	52	no		
P18	F	66	ANT NQ	57	no	SD	14
N18	F	68	ANT NQ	61	no		
P19	F	70	INF Q	49	no	SD	22
N19	F	72	INF Q	40	no		
P20	M	60	INF Q	57	yes	HFD	9
N20	M	60	INF Q	51	yes		

The patients in the positive group are identified as *P1, P2, . . ., P20*; those in the negative group are identified as *N1, N2, . . ., N20*. For the positive group, the events which complicated the course are listed. SD: sudden death, HFD: heart failure death, VT: symptomatic sustained ventricular tachycardia. Event time: time interval between infarction and end-point event in days.

differ from each other only slightly in length, making the beat-to-beat filters incapable of excluding them.

To overcome this problem, we suggested an alternative filtering method, in which the length of each filtered interval is compared with the duration of the last interval accepted by the filter. However, such a filter is very sensitive to its own failures. Once it has accepted an artefactual interval, it will omit a large series of correct intervals by comparison with the artefact. Therefore, in method *d*, each NN interval is related to the latest accepted interval and to the mean length of all computer recognized intervals. More exactly, filter *d* requires each interval to differ within the given range from *either* the previously accepted interval *or* the mean length of all intervals.

In summary, the study reported here involved four different filtering algorithms. Each of them used a real parameter $R(0 < R \leq 1)$ specifying the acceptable difference between the compared intervals. The exact descriptions of the filtering algorithms employed are presented in the Appendix.

THE NUMERICAL EXPRESSION OF HEART RATE VARIABILITY

Once the original NN interval sequence has been filtered, it can be used to express heart rate variability numerically. The usual method of expressing heart rate variability is the standard deviation of the filtered interval sequence[1,11], but this is not the only possibility. Since no method for removing the incorrectly recognized NN intervals can be guaranteed, we designed five other methods less dependent upon the accuracy of the original or filtered interval sequence.

Hence, we compared the following six methods for numerical expression of the rate variability (see Appendix for exact formulae): *A*: the standard deviation of the filtered NN interval sequence; *B*: the baseline width of the main peak of the frequency distribution curve, computed as the width of the frequency distribution curve at the level of 5% of its maximum value; *C*: since method *B* may not be able to distinguish such different situations as our cases *P6* and *N10* (Figs 1 and 2), we used a method expressing the rate variability as a ratio of the total number of filtered intervals to the maximum number of computer-recognized intervals of the same length; *D*: in cases with a higher level of recording noise, the results of method *C* may still be affected. Therefore, this method modified method *C* and used its formula with a fictional density distribution curve, the values of which were equal to the squares of the values of the original empiric density distribution; *E*: the baseline width of the main peak of the frequency distribution curve computed as the baseline width of its triangular interpolation (minimum square difference); *F*: the top angle of the triangular interpolation (minimum square difference) of the main peak of the frequency distribution curve.

NORMALIZATION OF HEART RATE VARIABILITY

The obvious question arises of whether the variability of heart rate is related to heart rate itself. Reported studies[1] show that heart rate and its variability provide independent prognostic factors after myocardial infarction. At the same time, these parameters are most likely to be correlated. When a pathological process shortens the NN intervals, it would be surprising if it does not reduce the differences between individual NN intervals. In formal words, a linear modification of the stochastic process affects not only its mean but also its deviation.

To overcome the interdependence between heart rate and its variability, we also introduced the normalized HRV as the ratio between the measured HRV and the mean length of NN intervals (see Appendix). This normalized HRV excludes the simple mathematical influence of mean heart rate.

ORGANIZATION OF EXPERIMENTS

The methods for filtering the NN sequences were combined with the suggested methods of numerical expressions of heart rate variability and compared in terms of their ability to distinguish statistically between the negative and positive groups of patients.

In order to perform such a comparison, each of the four filters *a–d* was evaluated with 100 different values of the parameter *R*: $R = 0{\cdot}01, 0{\cdot}02, 0{\cdot}03, \ldots, 0{\cdot}99, 1{\cdot}00$; i.e. the acceptable difference between the durations of compared intervals was consecutively set to $\pm 1\%$, $\pm 2\%$, $\pm 3\%$, , ..., $\pm 99\%$, and $\pm 100\%$. This resulted in 400 filtering possibilities, each of which was combined with the variability expression methods *A*, *B*, *C*, *D*, *E* and *F*. Thus, 2400 combinations were evaluated. Each of these combinations resulted in a set of numerical values expressing the heart rate variability for all patients. For each such set of values, the paired Student's *t*-test was employed to distinguish between the positive and negative groups of patients.

A standard configuration of a *Compaq 386/25* personal computer was used in all computations.

Results

UNFILTERED DATA

Fig. 1 shows the sample frequency distributions of durations of NN intervals recorded in both groups of patients. Visually, the difference between the two groups is obvious. Narrow patterns of distribution plots are seen in several patients in the positive group while most patients of the negative group are characterized by a broader frequency distribution curve. However, Fig. 2 displays the same frequency distributions in a quadratic logarithmic scale on the vertical axis: the noise and inaccuracies of the recognition algorithm are now more clearly visible.

Table 2 shows the standard deviations of NN interval durations computed from original unfiltered sequences for all 40 patients. Note the effect of artefact, for example in cases *P8* and *P10*. Note also that for instance, the approximate same values were found for patients *P18* and *N8*. (Compare the numbers in Table 2 with the patterns in Fig. 1). Statistical evaluation of standard deviations of both groups suggest that there is no significant difference between the groups ($P > 0{\cdot}85$); this is clearly incorrect, as we can see from the Figs. Hence, when using unfiltered data to compute rate variability from the standard deviation of the durations of NN sequences, the two groups cannot be distinguished.

RESULTS OF FILTERING AND HEART RATE VARIABILITY ANALYSIS

Fig. 3 shows the results of the statistical tests comparing our positive and negative groups using different combinations of filtering algorithms and heart rate variability expression methods.

It can be seen that apart from the extreme values (R near to 0, or R near to 1), each filter operates nearly independently of its parameter R. When comparing the filtering algorithms *a, b, c* and *d*, the only important difference between them was observed when combining them with the method *A* (standard deviation of the filtered sequence) and partly with the method *B* (the width of the distribution curve at 5% of its maximum value). Both these methods are sensitive to noise and artefact. In the case of method *A* (Fig. 3A), filter *d* offers a more significant distinction between the two groups of patients than the other filters (with the exception of the extreme values of the parameter R).

The difference between the filters disappears when combining them with the other methods of numerical expression of heart rate variability. In general, method *B* offers a more marked distinction between the positive and negative groups than method *A*, and similarly, methods *C, D*, and *E*, are more efficient than methods *B* and *F*. Table 3 summarizes the results obtained when applying methods *C, D*, and *E*, together with unfiltered data, to distinguish between our two groups of patients. We can see in Table 3 that the difference between the groups is highly significant (compare with Table 2).

RESULTS OF NORMALIZING THE HEART RATE VARIABILITY

We can also see in Table 3 that the maximum significance of distinguishing between the groups of patients was obtained when simply using their mean heart rates. This is not surprising because the heart rate is, for instance, known to reflect the size of myocardial infarct.

To show that HRV is an independent prognostic factor, the normalized values of the data presented in Table 3 were also computed. The results of this normalization are shown in Table 4.

Surprisingly, the results differ for methods *C* and *E*, for which the normalized values of HRV show a significant difference between the groups of patients (Fig. 4), and for the method *D*, in which case the difference between the groups disappeared.

To establish to what extent the process of normalization of HRV removes the influence of the mean heart rate, we also computed the correlations between the mean NN intervals and not-normalized and normalized HRV values assessed by methods *C* and *E* (Fig. 5). The correlation coefficients obtained are presented in Table 5. We can see that in the group of positive patients, the normalized values of HRV still correlate with the mean duration of NN intervals, while in the negative group of patients, the normalized values of HRV and the mean heart rate are mutually independent.

Discussion

The results of this study have important implications for clinical use of heart rate variability to predict serious events after myocardial infarction. However, the limitations of the study and their impact on the interpretation of its results should first be considered.

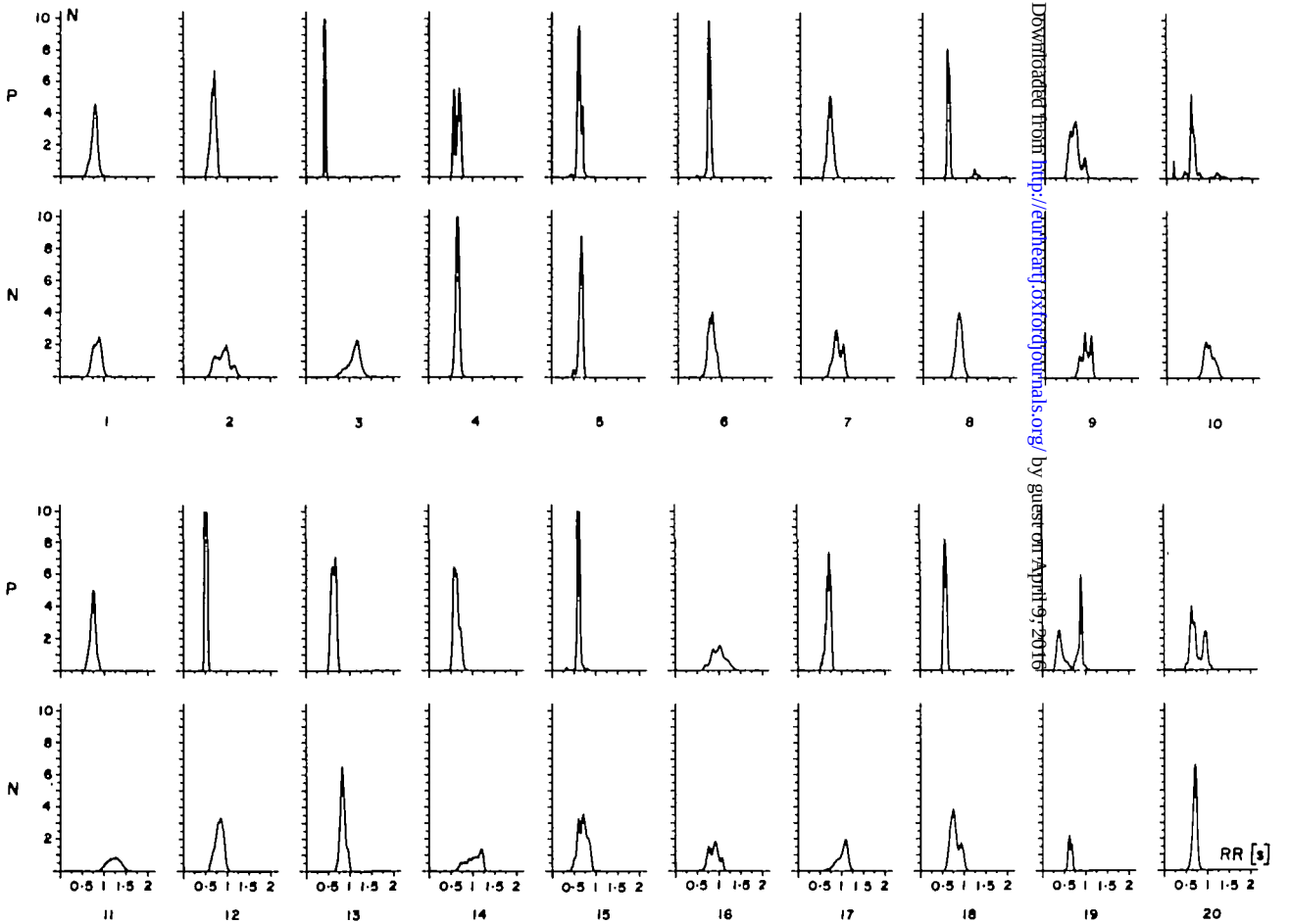

Figure 1 The plots represent the frequency distributions of durations of computer-recognized NN sequences for the patients in both groups. The presented 20 pairs correspond to the 20 matching pairs of patients (see text for details). In each of presented pairs, the top curve (P) belongs to the patient of the positive group, the bottom curve (N) to the patient of the negative group. The numbering 1, 2, . . ., 20 corresponds to the identification of patients in the text.

The horizontal axes RR represent the duration of NN intervals in seconds, the vertical axes N represent the total number (scaling in thousands) of recognized NN intervals with the same length (measured in discrete units of 1/128 s).

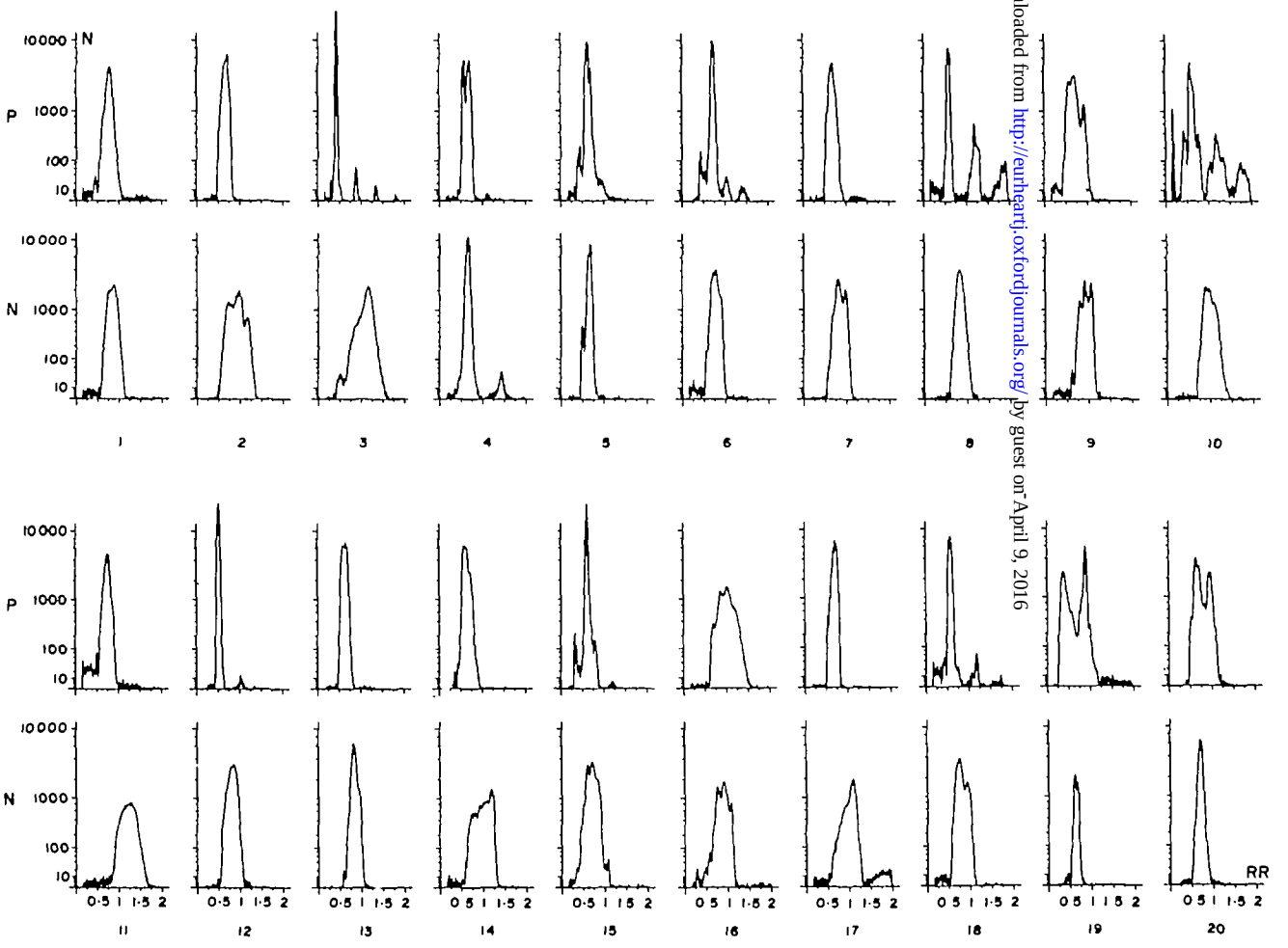

Figure 2 The same frequency distributions as in Fig. 1 plotted in a quadratic logarithmic scale on the vertical axes N. Note the noise and artefact in cases *P3*, *P6*, *P8*, *P10*, *N4*, etc.

Table 2 Standard deviations of durations of NN intervals computed from unfiltered computer-recognized sequences of intervals

Patient number	Positive group	Negative group	Difference
1	10·740	12·261	1·521
2	7·914	20·724	12·809
3	4·621	20·033	15·412
4	8·863	8·697	−0·166
5	7·469	6·213	−1·255
6	7·600	10·690	3·090
7	8·482	13·317	4·835
8	30·383	9·478	−20·905
9	15·584	14·402	−1·182
10	36·080	14·719	−21·360
11	10·598	20·118	9·520
12	3·628	11·911	8·282
13	7·027	8·201	1·174
14	8·732	22·327	13·595
15	5·647	14·196	8·549
16	20·455	16·096	−4·358
17	7·323	20·084	12·761
18	9·052	14·053	5·000
19	30·887	5·558	−25·328
20	19·429	6·509	−12·920
mean	13·026	13·479	0·454
SD	9·476	5·202	12·059

For each matched pair of patients, the difference is also shown (no significant difference between both groups has been found). *Mean*: mean of the presented data, *SD*: standard deviation of the presented data. The values were computed with a higher precision and they are rounded in the Table. Therefore, the presented values of differences may not exactly correspond to the differences of the data tabulated for the positive and negative groups.

LIMITATIONS AND TECHNICAL RESTRICTIONS OF THE STUDY

Firstly, the value of the different data-processing methods was assessed by their ability to distinguish between the same two groups of patients using a statistical test. It is not certain that the same results would be obtained with other groups of positive and negative cases. In this study, only a few parameters were used to match the two groups of patients while their other characteristics such as the presence of old myocardial infarction, results of exercise tests, signal average electrocardiograms, etc. were not taken into consideration. Nevertheless, useful conclusions can be drawn regarding the sensitivity of different methods to their parameters and to the effect of noise and artefact in the original computer-recognized sequences of NN intervals.

Secondly, the filtering algorithms and mathematical formulae expressing heart rate variability examined in this study represent only a narrow selection from many different data-processing possibilities. For instance, Parer *et al.*[12] examined 22 formulae designed to quantify foetal heart rate variability. However, in order to test the formulae, their study employed artificially generated sequences of numbers with known variability. Our use of natural data necessitated investigation of only a selection of evaluation methods. If many more methods were tested, the computational demands would have become unacceptable. Also, our study concentrated only on elaboration of frequency distributions of filtered NN sequences. Power spectral analysis[13–16] and beat-to-beat analysis (i.e. the analysis[17,18] of differences between durations of neighbouring NN intervals) were not included. The way in which we examined the accuracy of filtering methods was also restricted. Certainly, a much more appropriate approach would be to check the result of each filter visually in order to establish and compare, for different filters and their different parameters, how many intervals between normal cardiac beats are excluded and how many RR intervals involving an ectopic beat are not filtered out. Such a visual evaluation of all records in 40 patients would not be easy to perform. In this study which copes specifically with problems of automated measurement of HRV, the visual evaluation of filtering algorithms was not included because the results showed that for an assessment of heart rate variability, the use of an NN sequence filter is pointless, providing the method which expresses HRV numerically is robust against the recording noise and recognition artefact.

Thirdly, the selection of a control group the same size as the positive group enables each positive case to be compared with its matching control, but does not permit other important parameters to be computed, such as the sensitivity and specificity of differently established not-normalized and normalized HRV. We also do not see any reasons why the normalized values of HRV assessed by method *D* fail to distinguish between positive and negative cases. It is possible that this result is related to the restricted number of patients involved in our study and that it will not be confirmed when larger populations are studied. On the other hand, this also means that our results with normalized values of methods *C* and *E* can also be artificial. Nevertheless, the values obtained by not-normalized methods *C*, *D* and *E* correspond to a visual

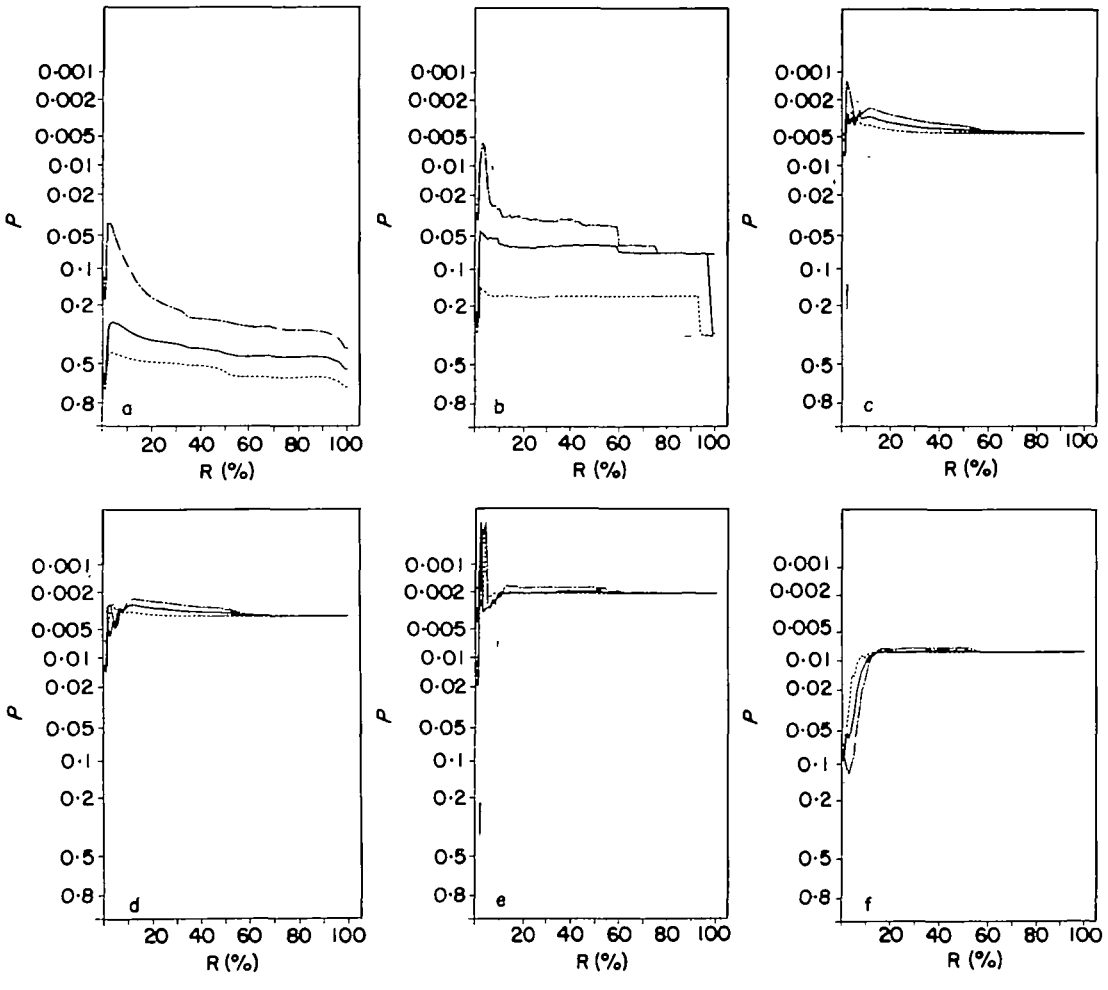

Figure 3 Statistical evaluation of the different combinations of NN sequence filters in combination with the methods for numerical expression of heart rate variability.

Cases A–F correspond to the combinations of different filters with the rate variability expression methods *A–F*, respectively. In each part of the figure, each curve corresponds to a combination of one filtering algorithm with the particular variability expression method and shows the probability level (vertical axes *P*), at which the positive and negative groups of patients can be distinguished dependent upon the parameter of the filter (horizontal axes R).

The full lines correspond to filter *a*, the dashed lines to filter *b*, the semi-interrupted lines to filter *c*, and finally, the dotted lines to filter *d*. In each case, the bold arrow at the right margin of the plot indicates the probability level at which both groups of patients were distinguished when applying the corresponding method for HRV expression to the unfiltered sequences of NN intervals.

Note the oscillations of the results corresponding to filter *d* with small values of its parameter (the negative values in the plot F correspond to the situation when a more restricted HRV was established in the negative group).

judgement of the frequency distribution curves of NN intervals (compare Fig. 1 and Table 3). Hence, the technical conclusion that automatic methods can express the HRV independently of low-level recording noise and recognition artefact, is not controversial.

Finally, application of the paired Student's *t*-test requires that differences between the statistically compared samples are normally distributed. This assumption was not verified for our data because it is known[19] that departures from this condition do not greatly influence the results of the test.

Table 3 Results of applying HRV expression methods C, D *and* E *to the unfiltered NN interval sequences in all patients*

Patient	Mean NN (ms)	M	num	HRV *C*	HRV *D*	HRV *E* (ms)
P1	773	4590	94 468	20·58	3·644	304
N1	844	2489	75 833	30·46	4·656	460
dif	71			9·88	1·011	156
P2	680	6751	120 221	17·80	3·387	281
N2	911	2028	89 899	44·32	5·194	718
dif	231			26·52	1·807	437
P3	434	62 712	201 326	3·21	1·486	46
N3	1102	2328	81 892	35·17	4·505	523
dif	668			31·96	3·019	476
P4	652	5627	107 631	19·12	3·698	312
N4	662	11 074	139 366	12·58	2·895	187
dif	10			−6·54	−0·803	−125
P5	638	9596	124 189	12·94	2·907	203
N5	666	8875	109 934	12·38	2·893	179
dif	10			−0·55	−0·014	−023
P6	724	9938	102 773	10·34	2·678	148
N6	771	4108	102 812	25·02	4·149	382
dif	48			14·68	1·471	234
P7	687	5150	96 497	18·73	3·525	281
N7	853	3005	87 305	29·05	4·291	468
dif	166			10·31	0·766	187
P8	665	8186	86 956	10·62	2·692	132
N8	835	4099	94 422	23·03	4·009	335
dif	179			12·41	1·317	203
P9	697	3577	118 529	33·13	4·696	429
N9	944	2875	79 195	27·54	4·075	468
dif	247			−5·59	−0·621	39
P10	683	5332	79 868	14·97	2·669	171
N10	987	2259	80 126	35·46	4·966	531
dif	304			20·49	2·297	359
P11	737	5008	95 919	19·15	3·522	281
N11	1217	859	42 104	49·01	5·907	726
dif	480			29·86	2·384	445
P12	523	22 037	171 746	7·79	2·327	117
N12	815	3331	102 121	30·65	4·706	453
dif	292			22·86	2·379	335
P13	633	7121	139 998	19·65	3·909	281
N13	835	6538	111 330	17·02	3·256	257
dif	202			−2·63	−0·653	−023
P14	632	6469	136 051	21·03	3·889	312
N14	1012	1394	58 585	42·02	4·963	703
dif	380			20·99	1·074	390
P15	610	21 296	141 978	6·66	2·011	93
N15	699	3575	123 551	34·55	4·883	531
dif	89			27·89	2·872	437
P16	996	1577	71 873	45·57	5·387	718
N16	877	1841	62 671	34·04	4·689	539
dif	−119			−11·53	−0·697	−179
P17	705	7413	114 802	15·48	3·157	234
N17	1020	1965	57 227	29·12	4·081	437
dif	315			13·63	0·923	203
P18	582	8226	99 315	12·07	2·978	171
N18	790	3893	113 321	29·10	4·263	476
dif	208			17·03	1·284	304
P19	669	5953	115 951	19·47	2·875	125
N19	636	2195	28 489	12·97	3·024	195
dif	−34			−6·49	0·149	70
P20	770	4030	118 267	29·34	4·074	515
N20	702	6612	94 372	14·27	3·104	210
dif	−67			−15·07	−0·969	−304
mean	184			10·50	0·950	181
SD	193			14·70	1·283	228
P<	0·001			0·008	0·005	0·002

mean NN: mean length of unfiltered NN intervals; M: maximum number of intervals with the same duration according to the discrete scale of measurement; num: number of computer-recognized NN intervals; *HRV*: heart rate variability assessed by methods *C*, *D* and *E*.

For each pair of patients, the differences in mean NN interval duration and in the HRV values are also listed (*dif*). At the bottom of the table, the mean (*mean*) and standard deviation (*SD*) of these differences are shown. The last line (*P<*) shows the significances of paired *t*-tests distinguishing between the groups of patients. The values were computed with a higher precision and they are rounded in the Table. Therefore, the presented values of differences may not exactly correspond to the differences of the data tabulated for the positive and negative groups.

In spite of all these omissions and simplifications, the reported study has important implications for the clinical use of the predictive value of heart rate variability in post-myocardial infarction patients.

CLINICAL RELEVANCE OF RESULTS

First, we can conclude that appropriate filtering of the computer-recognized NN interval sequence is highly individual. On average, none of the filtering methods (whatever the value of the parameter) was significantly more powerful than the others.

Secondly, evaluation of different combinations of the NN sequence filters and the heart rate variability expression methods suggest that methods *C* and *E*, which are resistant to noise and artefact within the original NN interval sequence and which

Table 4 Results of applying normalized HRV expression methods C, D *and* E *to the unfiltered NN interval sequences in all patients*

Patient number	$HRV_C n$			$HRV_D n$			$HRV_E n$		
	POS	NEG	dif	POS	NEG	dif	POS	NEG	dif
1	26·62	36·11	9·48	4·71	5·51	0·80	394	546	152
2	26·19	48·65	22·45	4·98	5·70	0·71	413	788	375
3	7·39	31·92	24·53	3·42	4·08	0·66	107	475	367
4	29·34	19·01	−10·33	5·67	4·37	−1·30	479	283	−196
5	20·27	18·59	−1·67	4·55	4·34	−0·21	318	269	−48
6	14·29	32·46	18·16	3·70	5·38	1·68	205	496	291
7	27·28	34·04	6·76	5·13	5·02	−0·10	409	549	139
8	15·96	27·58	11·61	4·04	4·80	0·75	199	402	202
9	47·52	29·17	−18·34	6·73	4·31	−2·41	616	496	−119
10	21·93	35·94	14·01	3·90	3·03	1·12	251	538	286
11	25·99	40·27	14·27	4·78	4·85	0·07	381	597	215
12	14·91	37·63	22·72	4·45	5·77	1·32	224	556	332
13	31·03	20·38	−10·65	6·17	3·89	−2·27	444	308	−135
14	33·26	41·51	8·24	6·15	4·90	−1·24	494	694	200
15	10·92	49·41	38·48	3·29	6·98	3·68	153	759	605
16	45·74	38·81	−6·93	5·40	5·34	−0·06	721	614	−106
17	21·95	28·54	6·58	4·47	4·00	−0·47	332	428	96
18	20·73	36·84	16·11	5·11	5·39	0·28	295	603	308
19	29·10	20·41	−8·68	4·29	4·75	0·46	186	307	120
20	38·12	20·32	−17·80	5·29	4·42	−0·87	669	300	−369
mean			6·95			0·13			136
SD			15·41			1·40			236
P<			0·06			NS			0·02

For each pair of patients, the Table shows the values obtained for the patient of the positive group (*POS*), the values obtained for the patient of the negative group (*NEG*) and their differences (*dif*). *Mean* and *SD*: mean difference and standard deviation of differences between the patients of the positive and negative group. The last line (*P<*) shows the significances of paired *t*-tests distinguishing between the groups of patients (*NS*: no significant difference). The values were computed with a higher precision and they are rounded in the Table. Therefore, the presented values of differences may not exactly correspond to the differences of the data tabulated for the positive and negative groups.

(when normalized) are of additional value to the mean heart rate, can distinguish between the positive and negative cases better than the previously published method *A*, and even when it is combined with sophisticated and complex filtering.

The fact that even the normalized values of HRV correlate with mean heart rate in the positive group of patients is not surprising. The positive group included patients with very severe infarction, in which both the heart rate and its variability were greatly affected (for instance, see cases *P3, P12* and *P15* in Fig. 1). On the other hand, the circumstance that the normalized values of HRV do not correlate with the mean heart rate in the negative group agrees well with previously published observations that both these phenomena provide independent prognostic information.

We have observed (Cripps *et al.*, unpublished observation) that in a larger group of patients, method *C* applied to unfiltered data is a powerful tool for identifying those post-myocardial infarction patients who later suffer sudden death or sustained ventricular tachycardia. At the same time, this method does not require any sophisticated computing. Providing the long-term ECG analysis equipment produces the total number of recognized NN intervals and the maximum count of equally long intervals, method *C* expresses heart rate variability as the ratio of these two numbers, and can easily be calculated.

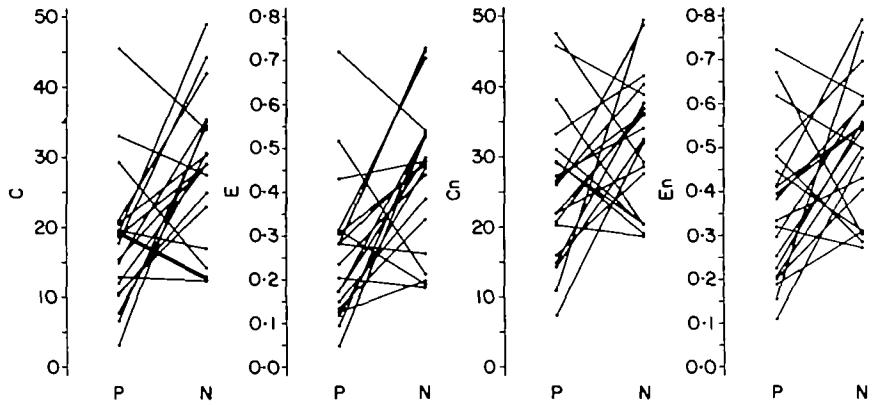

Figure 4 Diagrams showing how the patients of the positive (P) and negative (N) groups are distinguished by methods *C* and *E* applied to the unfiltered sequences of NN intervals. Plots C and E correspond to non-normalized values of these methods, plots Cn and En to their normalized values.

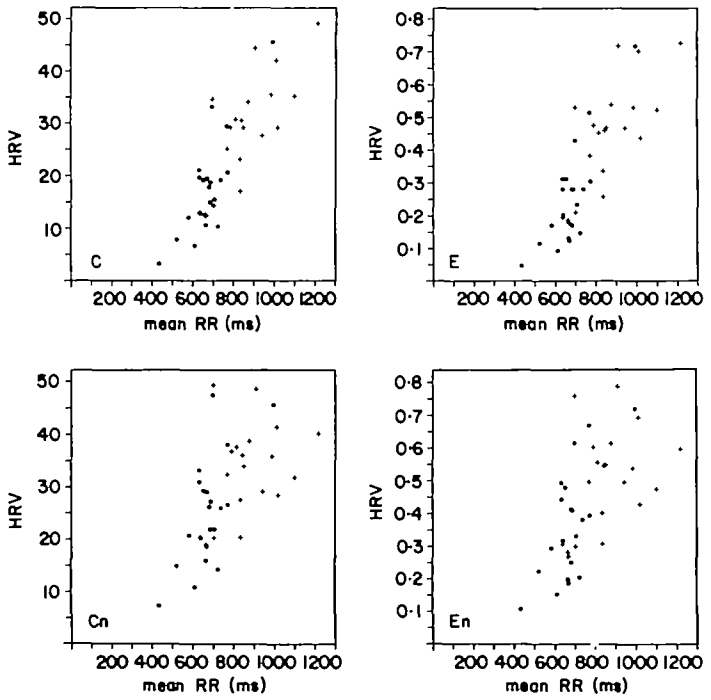

Figure 5 The plots show the correspondence between mean durations of NN intervals (horizontal axes mean RR: scaling in ms) and the values of HRV (vertical axes) assessed by methods *C* and *E* applied to the unfiltered sequences of NN intervals. The plots C and E correspond to non-normalized values of these methods, the plots Cn and En to their normalized values.

Dots indicate the data corresponding to the patients of the positive group, crosses indicate the data of patients of the negative group.

Table 5 Correlation coefficients between the mean duration of all computer-recognized NN intervals and not-normalized and normalized values of HRV assessed by applying methods C *and* E *to the unfiltered sequences of NN intervals*

	Positive group	*Negative group*
HRV_C	0·798 ($P<0·01$)	0·779 ($P<0·01$)
HRV_E	0·808 ($P<0·01$)	0·749 ($P<0·01$)
HRV_{C_n}	0·635 ($P<0·01$)	0·419 (NS)
HRV_{E_n}	0·670 ($P<0·01$)	0·404 (NS)

Significant correlation ($P<$) has been found in all cases but when normalizing the HRV of the patients of the negative group.

Naturally, other retrospective and prospective studies also applying methods *D* and *E* to large groups of patients are necessary to suggest the most appropriate way for standard expression of heart rate variability. Nevertheless, our methods permit automated measurement of HRV in Holter tapes and can make the assessment of HRV widely clinically useful, especially when combined with other factors of post-myocardial infarction prognosis, such as baroreflex sensitivity[20,21], signal-averaged ECG[22], left ventricular dysfunction[23,24] etc.

In conclusion, our results suggest that use of fully automated methods that are independent of a low level of recording noise and beat misrecognition artefact, provide clinically useful information obtained from the analysis of heart rate variability in patients with recent myocardial infarction. Method *C* is computationally trivial, being merely the ratio between the total number of computer-recognized normal-to-normal intervals and the number of the most frequently observed interval duration. Method *E* needs computer support, but it can easily be implemented on the average personal computer.

Skilled visual editing is unnecessary and the analysis process becomes rapid, reproducible, and operator independent. The methods are therefore accessible to any clinical unit equipped with a simple personal computer and commercially available facilities for 24-h ECG analysis.

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Appendix

FILTERING ALGORITHMS

Each of four filters used a real parameter R ($0 < R \leq 1$) specifying the acceptable difference between the compared intervals. In the following description of the filters, I(i) represents the ith interval in the computer-recognized succession ($1 < i < n$; where n is the total number of all intervals); d_J represents the length of the interval J; L represents the last interval accepted by the given filter; and U is the mean length of all intervals.

Filter a

for i = 2 to n:
  I(i) is accepted if
    $1 - R < (d_{I(i)}/d_{I(i-1)}) < 1 + R$.

Filter b

for i = 2 to $n-1$:
  I(i) is accepted if
    $1 - R < (d_{I(i)}/d_{I(i-1)}) < 1 + R$
    or
    $1 - R < (d_{I(i)}/d_{I(i+1)}) < 1 + R$.

Filter c

for i = 2 to $n-1$:
  I(i) is accepted if
    $1 - R < (d_{I(i)}/d_{I(i-1)}) < 1 + R$
    and
    $1 - R < (d_{I(i)}/d_{I(i+1)}) < 1 + R$.

Filter d

for i = 1 to n:
  if L is not defined {no interval has been accepted yet} then
    I(i) is accepted if
      $1 - R < (d_{I(i)}/\mathrm{U}) < 1 + R$
  else
    I(i) is accepted if
      $1 - R < (d_{I(i)}/d_{\mathrm{L}}) < 1 + R$
      or
      $1 - R < (d_{I(i)}/\mathrm{U}) < 1 + R$.

METHODS FOR NUMERICALLY QUANTIFYING THE RATE VARIABILITY

In the following description, S represents the discrete scale in which the computer recognition measures the duration of intervals; f represents the frequency distribution of the filtered interval sequence, i.e., for $s \varepsilon \mathrm{S}$, $f(\mathrm{s})$ is the number of intervals with the length s within the filtered sequence; n is the total number of filtered intervals; M is the maximum value of f; and m is such a value from the scale S, that $f(\mathrm{m}) = \mathrm{M}$.

Method A

Standard deviation of the filtered NN interval sequence:

$$\mathrm{HRV}_A = [(1/\mathrm{n})(\sum_{s \varepsilon \mathrm{S}} s^2 f(s)) - (1/\mathrm{n})(\sum_{s \varepsilon \mathrm{S}} s f(s))^2]^{\frac{1}{2}}.$$

Method B

Baseline width of the main peak of frequency distribution curve.

$$\mathrm{HRV}_B = X - x,$$

where

$$X = \min \{s \varepsilon \mathrm{S};\ (s > \mathrm{m}) \text{ and } (f(s) < e\mathrm{M})\}$$

and

$$x = \max \{s \varepsilon \mathrm{S};\ (s > \mathrm{m}) \text{ and } (f(s) < e\mathrm{M})\},$$

where $e (e \ll 1)$ is a parameter of the method.

As with the filtering algorithms, this method depends on the variable e and should be tested with its different values. However, to keep the computing demands of the study under description at a reasonable level, we used only one value $e = 0{\cdot}05$.

Method C

$$\mathrm{HRV}_C = \mathrm{n}/\mathrm{M}.$$

Method D

$$HRV_D = \{_{\pi S}[f(s)]^2/M^2\}^{\frac{1}{2}}.$$

Method E

Baseline width of the main peak of frequency distribution curve computed by the means of its triangular interpolation.

$$HRV_E = Y - y,$$

where $y < Y$, and the triangular, partially linear function g such that $g(Y) = g(y) = 0, g(m) = M$, is the best minimum square difference triangular interpolation of the function f.

Method F

Top angle of the triangular interpolation of the frequency distribution curve, i.e. the top angle in the triangle between the points [y,0], [m,M], [Y,0], where y and Y are as in the description of method *E*. For computation, the following formula was used:

$$HRV_F = \arctan((Y - m)/M) + \arctan((m - y)/M).$$

NORMALIZED VALUES OF HEART RATE VARIABILITY

Let HRV_Z be the value of the HRV assessed by any of the above methods *A–F*. Then its normalized value $HRV_Z n$ is given by the formula

$$HRV_Z n = HRZ_Z/U,$$

where U is the mean length of NN intervals. (In this study, the normalized HRV was only computed for the HRV obtained from unfiltered sequences of NN intervals.)