Time Course of Recovery of Heart Period Variability After Myocardial Infarction

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Four components of the heart period power spectrum—ultra low frequency (<0.0033 Hz), very low frequency (0.0033 to <0.04 Hz), low frequency (0.04 to <0.15 Hz) and high frequency power (0.15 to 0.40 Hz)—plus total power (1.157×10^{-5} to 0.4 Hz for a 24-h electrocardiographic [ECG] recording) all predict mortality after myocardial infarction. To determine the time course and magnitude of recovery for these measures of heart period variability, 68 patients in the Cardiac Arrhythmia Pilot Study (CAPS) placebo group who had 24-h ECG recordings at baseline, 3, 6 and 12 months after myocardial infarction were studied. The 24-h power spectral density was computed with use of fast Fourier transforms and divided into the four components listed previously. The values for the five frequency domain measures of heart period variability in the CAPS patients were similar to those found in 715 patients who participated in the Multicenter Post Infarction Program (MPIP), indicating that the CAPS sample is generally representative of postinfarction patients with respect to these measures. The values for the five measures were one third to one half of those found in 95 normal persons of similar age and gender. There was a substantial increase in all measures of heart period variability between the baseline 24-h ECG recording and the 3-month recording ($t_4 < 0.001$). Between 3 and 12 months, the values were quite stable for the group as a whole, as well as for individual patients (intraclass correlation coefficients ≥0.66). However, even at 12 months after infarction, values for the five measures of heart period variability were one half to two thirds the values found in the sample of 95 normal persons.

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The standard deviation of normal RR (NN) intervals over a 24-h period (1 ± 3 days after myocardial infarction is a strong predictor of mortality during the subsequent 3 years (1) and power spectra of heart rate or heart period variability have been used to predict sudden cardiac death (2). The intrinsic sinus rate is modulated by autonomic nervous system activity producing cyclic variation in normal RR intervals. Power spectral analysis can resolve the frequency modulation into physiologically meaningful components that provide insight into autonomic nervous activity in intact men and women. Also, low (0.04 to 0.15 Hz) and high (0.15 to 0.4 Hz) frequency information in heart rate or heart period power spectra have been used to evaluate the autonomic nervous system under various conditions (3,4). High frequency power is modulated by parasympathetic nervous system activity while low frequency power is modulated by both parasympathetic and sympathetic nervous system activity (3–5).

The purpose of this study was to determine the time course and extent of recovery for total power and for four components of the heart period power spectrum during 1 year of follow-up after acute myocardial infarction. To accomplish these aims, we studied the placebo-treated group from the Cardiac Arrhythmia Pilot Study (CAPS) (6,7).

Methods

Study subjects. To evaluate the time course of recovery after myocardial infarction, we determined the values for five frequency domain measures of heart period variability in the Cardiac Arrhythmia Pilot Study placebo group. The CAPS protocol called for a baseline 24-h ECG recording to be made 6 to 60 days after myocardial infarction, a variable number of tapes to be recorded during "drug" titration and follow-up tapes to be recorded 3, 6, 9 and 12 months after enrollment. The baseline tapes were recorded 25 ± 17 days after myocardial infarction. To determine whether the CAPS patients (a group selected for the presence of arrhythmias) were similar to an unselected, representative sample of patients after myocardial infarction, we compared the CAPS placebo group with the Multicenter Post Infarction Program

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(MPIP) sample (8,9). To evaluate the time course of recovery of the four measures of heart period variability, we analyzed tapes from the 68 patients in the CAPS placebo group who had 24-h recordings available at baseline as well as at 3, 6 and 12 months after enrollment. To determine values in normal persons with ages similar to those of patients in the CAPS sample, we studied normal subjects at our medical center as well as those having annual checkups in occupational health facilities.

Analysis of 24-h recordings. The 24-h recordings were digitized by a Marquette 8000 scanner and submitted to the standard Marquette algorithms for QRS labeling and editing (version 5.7 software). Then, the data files were transferred by high speed link from the Marquette scanner to a Sun workstation where a second stage of editing was done, using algorithms developed at Columbia University, to find and correct any remaining errors in QRS labeling that adversely affect measurement of heart period variability. For a tape to be eligible for this study, we required it to have ≥12 h of analyzable data and have at least half of the nighttime (midnight to 5:00 AM) and daytime (7:30 AM to 9:30 PM) periods analyzable. Also, at least half the daytime and nighttime data had to be recorded during sinus rhythm. Patients with atrial flutter or fibrillation or any other sustained rhythm disturbance were excluded. These rules excluded seven patients in the CAPS placebo group.

Time series analysis of normal RR intervals. After the second stage of editing and review of the results by a cardiologist, the heart period power spectrum was computed over a 24-h interval using a method first described by Albrecht and Cohen (10). Our adaptation of the method was described by Rottman et al. (11). First, a regularly spaced time series was derived from the RR intervals by sampling the irregularly spaced series defined by the succession of normal RR intervals. For each 24-h ECG recording, 2^{18} points were sampled. A "boxcar" low pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines, removing their effect on measurement of heart period variability (10,11). A fast Fourier transform was computed and the resulting power spectrum was corrected for the attenuating effects of both the filter and the sampling.

Frequency domain measures of heart period variability. Finally, frequency domain components of heart period variability were computed by integrating within selected frequency bands. We used frequency domain variables in this study because they comprise a mutually exclusive, all inclusive categorization of heart period variability. From 24-h heart period power spectra, we calculated power within four frequency bands: 1) <0.0033 Hz, ultra low frequency power; 2) 0.0033 to <0.04 Hz, very low frequency power, which has been shown to be increased in patients with congestive heart failure (12) and is the lowest frequency band that can be estimated by our 5-min method (11); 3) 0.04 to <0.15 Hz, low frequency power, which reflects increased sympathetic or parasympathetic tone modulated substantially by baroreflex activity (13,14); and 4) 0.15 to 0.4 Hz, high frequency power, a specific measure of vagal tone, modulated primarily by breathing (15,16).

Statistical methods. Independent sample *t* tests were used to test for the significance of mean baseline differences in heart period variability between patients from the CAPS and MPIP samples, and between the CAPS sample at 12 months and the sample of normal persons. A repeated measurements analysis of variance (17) was performed for each measure to test for changes over time in average level of variability. To determine the stability over time of measures of heart period variability within individuals, intraclass correlation coefficients were computed for each measure (18). Because the distributions of the frequency domain measures of heart period variability are extremely skewed, the log transformation of each measure—which produces distributions that are nearly normal—was applied before statistical analyses were performed. All analyses of changes over time in the mean logarithms used the residual mean square from the analysis of variance as the error term (17). The Bonferroni criterion for adjusting for multiple comparisons was applied when testing for significant differences between pairs of means (17). Because there are six pairwise comparisons involving the four time points, each was tested at the 0.05/6 (that is, the 0.0083) level to keep the overall type I error rate at 0.05.

Results

Is the Cardiac Arrhythmia Pilot Study (CAPS) sample representative? Table 1 compares the CAPS placebo group at baseline with the Multicenter Post Infarction Program (MPIP) sample. There was only one significant difference between the two groups for any measure of heart period variability, a small but significant difference between the two samples for high frequency power (*t* ratio for unpaired data 2.88, df 803, $p < 0.01$). Part of this difference may be real, but part can be explained by a technical feature of our analytical software and by the difference in the frequency of ventricular arrhythmias between the two samples (average ventricular premature depolarizations/h was 138 for CAPS and 0.8 for MPIP). On average, a greater percent of the CAPS than of the MPIP 24-h ECG recordings were splined because of ectopic complexes (12.6% vs. 3.2%). Linear splining causes a small, selective reduction of power in the high frequency region of the heart period power spectrum (10,11) and accounts for some of the difference between the samples for this one variable. Overall, the placebo group from CAPS seems representative of patients after myocardial infarction with respect to heart period variability and we considered it a suitable group in which to pursue our aims.

Time course of recovery of heart period variability after myocardial infarction (Table 2). The standard deviations of the logarithms of each measure of variability were more similar over time than were the standard deviations of the untransformed values. Further, for each measure, the cor-

Table 1. Comparison of the Baseline Recordings From the CAPS Placebo Group With the 24-Hour ECG Recordings from MPIP

	CAPS (n = 90)	MPIP (n = 7)
Normal RR intervals (ms)	780 ± 143	855 ± 138*
Ultra low frequency power (<0.0033 Hz) (ms^2)	6,528 ± 5,062	6,281 ± 5,090
(Ln ultra low frequency power)	(8.46 ± 0.91	(8.45 ± 0.81
Very low frequency power (0.0033–0.04 Hz) (ms^2)	846 ± 849	899 ± 856
(Ln very low frequency power)	(6.15 ± 1.31	(6.36 ± 1.03)
Low frequency power (0.04–0.15 Hz) (ms^2)	302 ± 472	304 ± 374
(Ln low frequency power)	(4.89 ± 1.42)	(5.08 ± 1.22)
High frequency power (0.15–0.4 Hz) (ms^2)	116 ± 230	139 ± 213*
(Ln high frequency power)	(3.97 ± 1.25)	(4.33 ± 1.09)
Total power (<0.4 Hz) (ms^2)	7,793 ± 5,949	7,623 ± 6,050
(Ln total power)	(8.63 ± 0.92)	(8.65 ± 0.8)

Values are mean values ± SD. *$p < 0.001$; †$p < 0.01$ (probably due to pooling; see text). CAPS = Cardiac Arrhythmia Pilot Study, baseline recordings made 25 ± 17 days after myocardial infarction; MPIP = Multicenter Post Infarction Program, recordings made 11 ± 3 days after myocardial infarction; Ln = natural logarithm

relations between the logarithms of measurements made at different time points were similar to each other. (For the logarithms of total power, for example, the minimal correlation was 0.48, between the measurements made at baseline and 6 months, and the maximal was 0.68, between the measurements made at 3 and 6 months.) These findings indicate that theoretic requirements for the validity of a repeated measurements analysis of variance (comparable standard deviations and comparable correlations) were satisfied.

All four measures of heart period variability showed a substantial and statistically highly significant increase between the tapes obtained at baseline and at 3 months (Table 2). Each paired-sample t ratio between data acquired at 3 months or beyond and baseline values exceeded 4.00 ($p < 0.001$). No significant differences were found between the means of the 3-, 6- and 12-month tapes; that is, on average, recovery was complete by 3 months. The changes in the mean logarithms for high frequency power from 3 months to 12 months were, however, of borderline significance (F ratio = 2.70, df = 2 and 201, $p < 0.10$).

Furthermore, the intraclass correlation coefficients in Table 2 (all ≥ 0.66) indicate good to excellent stability for individual patients over time (17). Not only do the group means for 3, 6 and 12 months remain fairly stable, so do the values for individual patients. Figure 1 shows that, between the baseline 24-h ECG recording and the recording made 12 months after enrollment, the distributions for measures of heart period variability shifted to the right and became narrower at the base.

Extent of recovery of heart period variability after myocardial infarction (Table 3). To evaluate the extent of recovery of heart period variability after myocardial infarction, we compared the 83 patients in the CAPS placebo group who had a 24-h recording at 12 months after enrollment with 95 normal persons of similar age and gender. In the CAPS sample, all four measures of heart period variability were substantially and significantly lower 12 months after enroll-

Table 2. Recovery of Heart Period (Normal RR Intervals) and Heart Period Variability After Myocardial Infarction (n = 68)*

	Baseline (25 ± 17d)‡	3 Months (124 ± 21d)‡	6 Months (215 ± 19d)‡	12 Months (394 ± 19d)‡	Residual Mean Square	Intraclass Correlation Coefficient
Normal RR intervals (ms)	780 ± 137	826 ± 122	843 ± 120	845 ± 120	5,190	0.78
Ultra low frequency power (<0.0033 Hz) (ms^2)	6,674 ± 5,307	9,635 ± 6,130	10,306 ± 6,153	11,040 ± 7,223		
(Ln ultra low frequency power)	(8.48 ± 0.89)	(8.95 ± 0.74)	(9.01 ± 0.78)	(9.08 ± 0.73)	(0.263)	(0.66)
Very low frequency power (0.0033–0.04 Hz) (ms^2)	847 ± 759	1,225 ± 965	1,272 ± 955	1,443 ± 1,475		
(Ln very low frequency power)	(6.19 ± 1.29)	6.81 ± 0.83	(6.84 ± 0.88)	(6.89 ± 0.91)	(0.429)	(0.78)
Low frequency power (0.04–0.15 Hz) (ms^2)	280 ± 302	443 ± 519	444 ± 419	539 ± 724		
(Ln low frequency power)	(4.94 ± 1.35)	(5.54 ± 1.15)	(5.62 ± 1.11)	(5.64 ± 1.22)	(0.526)	(0.78)
High frequency power (0.15–0.4 Hz) (ms^2)	100 ± 105	171 ± 238	181 ± 195	229 ± 327		
(Ln high frequency power)	(4.01 ± 1.18)	(4.49 ± 1.19)	(4.70 ± 1.06)	(4.75 ± 1.16)	(0.479)	(0.75)
Total power (<0.4 Hz)† (ms^2)	7,902 ± 5,995	11,475 ± 7,036	12,204 ± 6,908	13,250 ± 8,651		
(Ln total power)	(8.65 ± 0.9)	(9.14 ± 0.72)	(9.19 ± 0.77)	(9.26 ± 0.73)	(0.253)	(0.67)

Values are mean values ± SD. *Analysis restricted to the patients who had recordings in all four periods. †1.157×10^{-5} for a 24-h electrocardiographic (ECG) recording. ‡Days after myocardial infarction. For the normal RR interval values and for the power spectral measures of heart period variability, all the 3-, 6- and 12-month values are significantly different from the baseline values at the $p < 0.001$ level; there are no significant differences among the 3-, 6- and 12-month values.

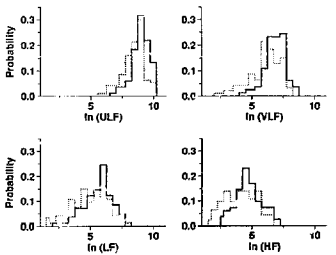

Figure 1. Frequency distributions for the natural logarithms of ultra low frequency (ULF), very low frequency (VLF), low frequency (LF) and high frequency (HF) power for 24-h electrocardiographic recordings made in the CAPS placebo group at baseline and 12 months. The natural logarithms (ln) were used because the distributions are skewed to the right. The frequency distribution shifts to the right between baseline (25 ± 17 days) and 12 months (394 ± 19 days) after myocardial infarction. Total power is not plotted because it strongly resembles the plot for ultra low frequency power; ultra low frequency power represents ≥84% of total power at baseline and at 12 months. Baseline = **dotted line**; 12 months = **solid line**.

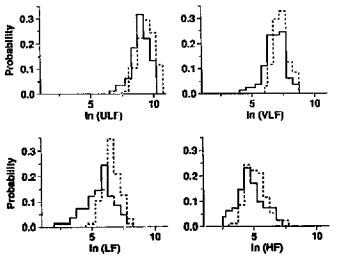

Figure 2. Frequency distributions for the natural logarithms of ultra low frequency (ULF), very low frequency (VLF), low frequency (LF) and high frequency (HF) power for 24-h electrocardiographic recordings made in the CAPS placebo group at 12 months compared with normal subjects matched for age and gender. The natural logarithms (ln) were used because the distributions are skewed to the right. Notice that the frequency distribution for normal persons (**dotted line**) is considerably to the right of the distribution after full recovery after a myocardial infarction (**solid line**).

ment than the values found in the normal group. Figure 2 compares the distributions of measures of heart period variability 12 months after myocardial infarction in the CAPS sample with those in the sample of normal middle-aged persons. The distribution for the postinfarction sample is further to the left and has a broader base than does the distribution for the normal group. Figure 3 compares the CAPS results during the year after myocardial infarction (four bars on the left) with the normal sample (bar on the right). Because the distributions are skewed to the right, the medians are plotted. Throughout the year after infarction, all measures of heart period variability have appreciably lower median values in the postinfarction sample than in the sample of normal persons. Despite the greater high frequency power in the normal group, the average of normal RR intervals was lower in this group than in the CAPS group 1 year after myocardial infarction (Table 3).

Discussion

The present study shows that all four components of the heart period power spectrum, plus total power, were markedly reduced after myocardial infarction. Despite the selec-

Table 3. Comparison of CAPS Placebo Group at 12 Months After Myocardial Infarction Compared with Age- and Gender-Matched Normal Persons

	CAPS (n = 82)	Normal Persons (n = 95)
Age (yr)	59 ± 10	52 ± 10
Percent male	80	89
Normal RR intervals (ms)	841 ± 120	797 ± 100*
Ultra low frequency power (<0.0033 Hz) (ms^2)	10,796 ± 6,965	16,592 ± 10,525‡
(Ln ultra low frequency power)	(9.07 ± 0.7)	(9.54 ± 0.61)‡
Very low frequency power (0.0033–0.04 Hz) (ms^2)	1,360 ± 1,321	1,913 ± 1,328
(Ln very low frequency power)	(6.89 ± 0.84)	(7.37 ± 0.6)‡
Low frequency power (0.04–0.15 Hz) (ms^2)	504 ± 669	913 ± 719
(Ln low frequency power)	(5.65 ± 1.14)	(6.58 ± 0.7)‡
High frequency power (0.15–0.4 Hz) (ms^2)	216 ± 305	291 ± 454
(Ln high frequency power)	(4.74 ± 1.12)	(5.19 ± 0.88)†
Total power (<0.4 Hz) (ms^2)	12,877 ± 8,187	19,710 ± 12,248
(Ln total power)	(9.25 ± 0.69)	(9.72 ± 0.58)‡

Values are mean values ± SD. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.

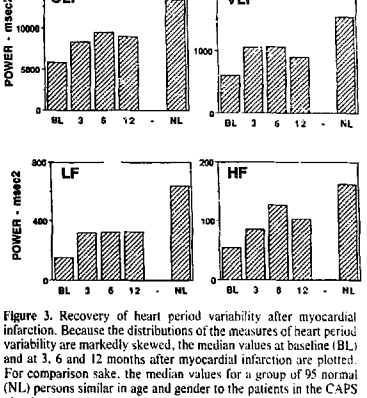

Figure 3. Recovery of heart period variability after myocardial infarction. Because the distributions of the measures of heart period variability are markedly skewed, the median values at baseline (BL) and at 3, 6 and 12 months after myocardial infarction are plotted. For comparison sake, the median values for a group of 95 normal (NL) persons similar in age and gender to the patients in the CAPS placebo group are plotted. Abbreviations as in Figure 1.

tion of patients in the upper quintile for ventricular arrhythmias, the Cardiac Arrhythmia Pilot Study (CAPS) sample was representative of the postmyocardial infarction population with respect to heart period variability. Heart period variability recovered appreciably by 3 months and remained at approximately the same level for the rest of the year. However, after a full year for recovery, the values in the CAPS group remained substantially lower than values found in normal subjects of similar age and gender.

Previous study of heart period variability. Lombardi et al. (5) previously studied heart period variability in 70 patients 2 weeks after myocardial infarction using short (about 7 to 8 min) recordings to measure the mean RR interval and RR variance. Also, they used an autoregressive method to estimate high and low frequency normalized power. They found no change in the average RR interval or the RR variance between 2 weeks and 12 months after myocardial infarction. They also found a decrease in normalized high frequency power and an increase in normalized low frequency power 2 weeks after myocardial infarction. Unlike our results, however, values for these variables in their patients 12 months after infarction were almost identical to those of their group of 26 normal control subjects. In agreement with Lombardi et al. (5), we found a decrease, relative to normal persons, in high frequency power within 1 month of myocardial infarction. In contrast to their study (5), we found a decrease in low frequency power and a decrease in total variance early after infarction. Again, in contrast to their study (5), we found a substantial increase from baseline in the total variance (total power) during the year after infarction.

The difference in our findings and those of Lombardi et al. (5) for total variance (or its equivalent, total power) is most likely due to the difference in length of the recordings used in the two studies, that is, 7 to 8 min in their study versus 24 h in ours. The difference for low frequency power between the two studies, however, is probably attributable to signal processing. The autoregressive method as implemented by Lombardi et al. (5) is complex, selecting portions of the data in a power spectral range, particularly in the low frequency region, and "normalizing" the selected data (4,19). Our fast Fourier transform method retains all of the power spectrum below 0.4 Hz and we do not normalize the data (11). If the autoregressive method is used without selection of portions of the data and without normalization, it gives results virtually identical to those obtained with our fast Fourier transform method. Therefore, the differences seen between our results and those of Lombardi et al. (5) are most likely attributable to signal-processing procedures. Another difference between the two studies is the brief recording periods they used (512 RR intervals) versus our 24-h recording periods: 24-h heart period power spectra are very reproducible from day to day in normal subjects and in patients with heart failure (20,21). In striking contrast to the remarkable reproducibility of 24-h heart period power spectra, there is marked variability between adjacent 5-min intervals throughout the day.

Lombardi et al. (5) also performed a preliminary evaluation of the time course of recovery of heart period variability, specifically of the total RR variance and the low and high frequency normalized power in 7- to 8-min segments of RR intervals. Total RR variance decreased only 10% at 2 weeks after myocardial infarction compared with the values found in recordings made 12 months after infarction or with values from normal control subjects. By 12, but not by 6, months after myocardial infarction, they found recovery of low frequency and high frequency normalized power to levels not significantly different from those of normal control subjects. Measured over a 24-h period, and compared with normal control values, total power (total RR variance) in our study was reduced by 61% and all components of total power were markedly reduced. We also found considerable recovery toward normal by 3 months after myocardial infarction with little, if any, additional recovery by 12 months. Furthermore, 1 year after infarction, we found that values for our four measures of heart period variability were still far below those found in normal persons of similar age and gender. The comparison made by Lombardi et al. (5) was not optimal: they compared 70 baseline recordings with 33 6-month and 29 12-month recordings. Such multiple unpaired comparisons can give a false impression of the recovery process as a result of selection bias; that is, the patients who have 6- and 12-month recordings may not be representative of the entire group that had baseline recordings. For example, sicker patients are more likely than other

patients to have an incomplete set of recordings because of deaths and dropouts. To avoid this bias, we studied a group of patients that had a complete set of recordings at regular intervals during the year after infarction. We found that Lombardi et al. (5) were correct that heart period variability recovers substantially during the year after myocardial infarction. In this study, we improved the time resolution of recovery by showing that the recovery process was virtually complete by 3 months. So far as the timing of our recordings permits, all four components seemed to recover with a similar time course; that is, all recovered by 3 months. We did not have a standardized set of tapes recorded between the baseline recording (25 ± 17 days after infarction) and 3 months (124 ± 21 days after infarction). Future studies that obtain several recordings over the 1st 3 months after myocardial infarction may show differences among the four measures of heart period variability with respect to recovery between infarction and 3 months.

Recovery of heart period variability and mortality rates. It is intriguing that the recovery of heart period variability after myocardial infarction is completed at about the same time that the mortality rate is dropping to a stable value. Of course, the association between these two phenomena may be coincidental rather than causal.

Stability of heart period variability after recovery. From 3 to 12 months after myocardial infarction, measures of heart period variability were quite stable within individual patients; that is, the intraclass correlation coefficients were quite high (median = 0.75). This remarkable stability over the period from 3 to 12 months after enrollment in CAPS is congruent with our previous finding (20) that these same measures are quite stable in normal subjects. We obtained a pair of 24-h ECG recordings an average of 18 days apart in 14 normal subjects, aged 32 ± 7 years, and found that, within an individual, values for measures of heart period variability between the two recordings were exceedingly stable (20). This stability of measures of heart period variability makes it easier to detect changes in the measures due to disease or drug therapy than for variables that show orders of magnitude greater spontaneous variability, e.g., ventricular arrhythmias or episodes of ST segment depression.

Heart period variability does not fully recover after infarction. The steady state recovery values for total power of heart period variability and its four components are substantially lower than the values found in normal age- and gender-matched persons. Figure 2 shows that the distributions of heart period variability variables are still shifted to the left 12 months after myocardial infarction. The distributions in the CAPS sample are broader than those for the normal persons; that is, some patients have values for heart period variability after myocardial infarction that are near the upper end of the distribution of normal values; others have values well below the lower extreme of that distribution. Very few normal middle-aged persons have values for measures of heart period variability that are in the range we have used to identify high risk patients after myocardial infarction (22). It will be interesting to determine in the future if low recovery values for measures of heart period variability will predict subsequent mortality, conditional on surviving for 3 to 12 months after myocardial infarction.

Mechanism of reduced heart period variability after infarction. The present study does not establish the mechanism responsible for the reduction in total power of heart period variability and its four components early after myocardial infarction. We hypothesized previously (23) that increased afferent sympathetic nerve traffic from the heart to the brain stem would reduce high frequency power by decreasing efferent traffic on the vagus nerves. The reduction of average 24-h low frequency power suggests that this variable is strongly affected by tonic vagal activity as well. If low frequency power averaged over 24 h predominantly reflected sympathetic nervous system activity, low frequency power would have increased. In normal subjects also, low frequency power averaged over 24 h predominantly reflects parasympathetic nervous system activity (24). The presence of the sympathetic nervous system component of low frequency power usually can be demonstrated by measuring low frequency power in both the supine and standing positions or in the supine position and during head-up tilt to ≥60° (3,4). It may be that the signal-processing methods of Pagani and Baselli et al. (4,19) used by Lombardi et al. (5) increase the proportional contribution of the sympathetic nervous system to the signal selected from the low frequency power region. This possibility should be pursued.

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