Effects of *Verapamil* on Indexes of Heart Rate Variability After Acute Myocardial Infarction

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In patients with previous myocardial infarction (MI), depressed heart rate variability (HRV) may reflect a reduction in vagal activity and lead to cardiac electrical instability. Interventions designed to increase HRV may be of clinical interest. Data on the effects of calcium antagonists on HRV in post-MI patients are very limited. The aim of our study was to assess the effects of verapamil on HRV and on the sympathovagal balance after MI. Fifty consecutive patients with a first MI, stable sinus rhythm, and left ventricular ejection fraction >0.40 were studied. Each patient underwent two 24-hour Holter recordings, 1 at baseline and another after 4 days of treatment with verapamil retard (180 mg 2 times daily). Time and frequency domain parameters of HRV were analyzed. All time domain measurements increased significantly after verapamil: the standard deviation of all NN intervals (SDNN) from 87.1 ± 31.4 to 98.1 ± 30.3 ms ($p < 0.05$) and the log-transformed percentage of pairs of adjacent NN intervals that differ >50 ms (pNN50) from 0.57 ± 0.42 to 0.76 ± 0.45 ($p < 0.01$). The standard deviation of the averages of RR interevals (SDANN) (75.9 ± 30.1 vs 86.3 ± 29.4 ms, $p < 0.05$), root-mean-square of successive differences between RR intervals (rMSSD) (23.0 ± 11.7 and 28.1 ± 13.1 ms, $p < 0.01$), and the triangular HRV index (28.3 ± 9.6 vs 23.4 ± 8.6, $p < 0.001$) also increased. A significant inverse correlation was found between improvement in HRV indexes induced by verapamil and baseline values. Spectral analysis showed a significant increase in high-frequency power of 58.5% without changes in low and very low components. With normalized units, significant reductions in low-frequency power and low- to high-frequency ratio were observed. Diabetic patients did not show any significant changes in HRV on administration of verapamil. These findings indicate that verapamil, administered during the subacute phase of MI, improves both global and short-period indexes of HRV and induces a shift in the sympathetic-parasympathetic interaction toward vagal predominance. This effect may contribute to an explanation of the beneficial effects of verapamil that have been reported in post-MI patients. ©1998 by Excerpta Medica, Inc.

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Verapamil has been shown to decrease the number of major events after myocardial infarction (MI).[1,2] Specifically, some experimental[3,4] and clinical data[5] suggest the positive effect of verapamil on ventricular arrhythmias after MI. A close relation between output of the autonomic nervous system, a propensity for arrhythmic events and sudden cardiac death has been demonstrated.[6] Sympathetic activation has been related to the occurrence of life-threatening cardiac arrhythmias in post-MI patients,[7] whereas high vagal activity seems to have a protective effect.[8] Verapamil has been shown to have antisympathetic properties,[9] which provide the basis for an eventual antiarrhythmic action. Heart rate variability (HRV) is a reliable indicator of cardiac autonomic tone[10] and it is a powerful predictor of arrhythmic events and mortality in post-MI patients.[11,12] Moreover, the balance between sympathetic and parasympathetic activities can be assessed by spectral analysis of variations in heart period.[13] Only limited data relating to the effects of verapamil on HRV and its spectral components after MI are available.[14] The goal of this study was to determine the influence of verapamil on indexes of HRV and to examine the specific effects of the drug on both sympathetic and parasympathetic limbs of the autonomic nervous system in patients during the subacute phase of MI.

METHODS

Patient population: Fifty consecutive patients with a first MI were included in the study (39 men and 11 women; mean age 62 years, range 37 to 81). Exclusion criteria were left ventricular ejection fraction (LVEF) <0.40, as assessed by echocardiography, congestive heart failure, early postinfarction angina, significant valvular disease or cardiomyopathy, atrial fibrillation or abnormal sinus node function, severe noncardiac disease (including hepatic and renal failure), and concomitant administration of digitalis, β blockers, angiotensin-converting enzyme inhibitors, antiarrhythmic agents, or other calcium channel blockers. Heparin, aspirin, and nitrates were allowed during the study. Patients undergoing percutaneous or surgical coronary revascularization were also excluded.

Study protocol: The study protocol was approved by the local ethics committee, and informed consent
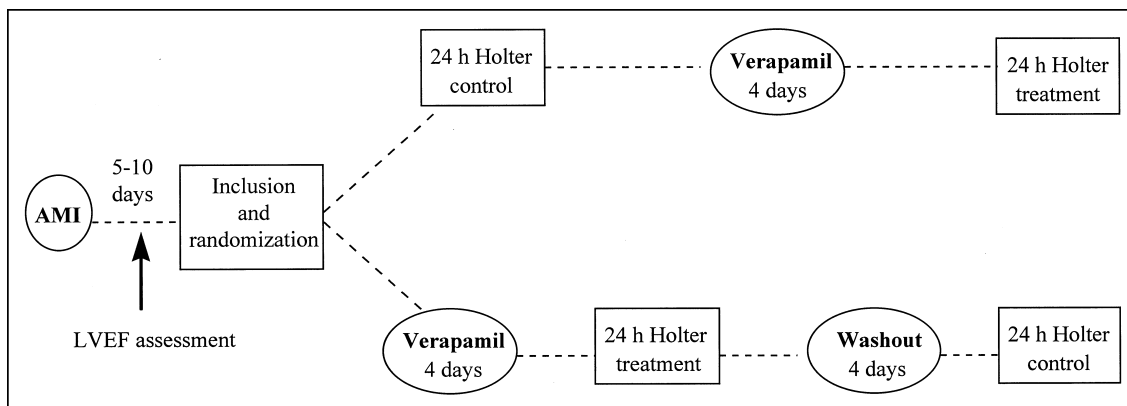
FIGURE 1. Flowchart of study.

was obtained from every patient. Between 5 and 10 days after acute MI, all patients underwent two 24-hour Holter recordings in random order (Figure 1). One recording was performed after 4 days of treatment with verapamil retard (180 mg twice daily) and the other was performed under baseline conditions, either before the start of administration of verapamil or after a drug-free period of ≥4 days. Nitrates and heparin were administered to patients with appropriate clinical indications, but such drugs and dosages were not changed during the entire study period to minimize possible differential effects on both Holter recordings.

Processing of 24-hour recordings and time domain measurements of HRV: The 24-hour recordings were digitized by a Holter scanner (model 563; Del Mar, Irvine, California) and submitted to its arrhythmia analysis program for QRS labeling and editing (version AV-PUB 94-4 software). A direct review by eye of each abnormal beat or artifact was made to limit any potential misclassification by the system. Tapes were processed without knowledge of patients' characteristics and ≥20 hours of analyzable data were required for eligibility in the study. After editing was completed, each RR interval was labeled with a code number that identified its normality or its class of abnormality and the annotated sequence was stored in a computer file. Time domain measurements of HRV were obtained with the standard Del Mar algorithms.[15] The HRV index, not provided by the system, was calculated as the total number of normal-to-normal RR intervals divided by the maximum count of equally long intervals.[16]

Frequency domain analysis: The power spectrum of RR intervals was computed by an adaptation of a previously reported segmental method.[17] In brief, each 24-hour recording was divided into consecutive, nonoverlapping 5-minute segments. Intervals with artifacts or abnormal beats at a level of >10% were excluded. For each 5-minute segment, an instantaneous heart period function was sampled at 1-second intervals, and gaps in the time series that resulted from noise or ectopic beats were filled in by linear interpolation. After removal of baseline and trend components, a fast-Fourier transform was computed using

128 data point segments, a Hanning window, and 50% overlap between adjacent segments. The spectral power was computed for each 5-minute epoch within 3 frequency bands: (1) <0.04 Hz, very low frequency power; (2) 0.04 to <0.15 Hz, low-frequency power; and (3) 0.15 to 0.40 Hz, high-frequency power. In addition, we calculated the ratio of low- to high-frequency power, and the normalized low- and high-frequency components as the value of each power component relative to the total power minus the very low-frequency component. The resulting values were finally averaged for the 24-hour period.

Statistical analysis: Statistical analysis was performed using the SPSS statistical package (SPSS Inc., Chicago, Illinois). Distributions of the proportion of adjacent RR intervals differing by >50 ms (pNN50) and absolute power variables were right-skewed. Thus, log transformation was performed and the log-transformed data were used for summaries and for comparisons of means. Continuous data were expressed as mean ± SD. Mean values with and without treatment were compared by Student's t test for paired data. The increment in each parameter of HRV (difference between the measurement after treatment and at baseline) was correlated with baseline values using Pearson's r coefficient. Mean differences were considered significant when a 2-tailed p value <0.05 was obtained. For correlation analysis, a p value <0.01 was required.

RESULTS

Study population: Seventeen patients (34%) presented with anterior MI, 30 (60 %) received thrombolytic therapy, and 35 (70%) underwent coronary angiography. One-, 2-, and 3-vessel disease was found in 13, 11, and 8 patients, respectively. Three patients had nonsignificant coronary obstructions. The mean LVEF was 0.53 ± 0.06 (range 0.40 to 0.66).

Effects of verapamil on heart rate variability: Heart rate was reduced by 7.6% after administration of verapamil. The effects of the drug on the indexes of HRV are shown in Table I. All time domain measurements analyzed were found to have increased significantly after treatment with verapamil. The relative sizes of the increases ranged between 12.6% for the

TABLE I Time Domain and Frequency Domain Parameters of Heart Rate Variability at Baseline and after Administration of Verapamil

	Control	Verapamil	p Value
Time Domain Analysis			
Mean NN interval (ms)	836.3 ± 123.1	903.8 ± 130.2	<0.001
SDNN (ms)	87.1 ± 31.4	98.1 ± 30.3	<0.05
SDANN (ms)	75.9 ± 30.1	86.3 ± 29.4	<0.05
RMSSD (ms)	23.0 ± 11.7	28.1 ± 13.1	<0.01
L_{10} pNN50	0.57 ± 0.42	0.76 ± 0.45	<0.01
HRV index	23.4 ± 8.6	28.3 ± 9.6	<0.001
Frequency Domain Analysis			
L_{10} VLF (ms²)	4.6 ± 0.4	4.6 ± 0.3	NS
L_{10} LF (ms²)	4.2 ± 0.5	4.2 ± 0.4	NS
LF norm (nu)	73.6 ± 14.8	65.1 ± 14.8	<0.001
L_{10} HF (ms²)	3.7 ± 0.4	3.9 ± 0.4	<0.01
HF norm (nu)	26.1 ± 14.7	34.8 ± 14.7	<0.001
LF/HF	3.9 ± 2.4	2.5 ± 1.7	<0.001

HF = high frequency; LF = low frequency; LF/HF = low- to high-frequency ratio; LF (HF) norm = normalized LF (HF); L_{10} = log-transformed values; nu = normalized units; NN = normal RR intervals; pNN50 = percentage of pairs of adjacent NN intervals that differ by <50 ms; RMSSD = root-mean-square successive difference; SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the averages of NN intervals in all 5-minute segments; VLF = very low frequency.

standard deviation of all NN intervals (SDNN) and 58.9% for pNN50. Frequency domain analysis revealed a significant increase in the absolute high-frequency power of 58.5% after administration of verapamil, whereas the low- and the very low-frequency content of the spectrum did not change significantly (Table I). Using normalized units, we confirmed the increase in high-frequency power and a significant reduction in low-frequency power due to verapamil became evident (65.1 ± 14.8 vs 73.6 ± 14.8 at baseline, p <0.001). Consequently, a significant decrease in the low- to high-frequency ratio was recognized after the active treatment period (2.5 ± 1.7 vs 3.9 ± 2.4 at baseline, p <0.001).

Effects of verapamil in patients with diabetes: Heart rate and time domain measurements of HRV did not change significantly on administration of verapamil in diabetic patients (n = 21). Changes in SDNN (87.3 ± 28.0 after verapamil vs 83.9 ± 31.7 at baseline), the standard deviation of the averages of RR intervals (SDANN) (76.7 ± 28.4 vs 73.1 ± 29.1), rMSSD (24.0 ± 10.3 vs 23.7 ± 12.6), and pNN50 (5.9 ± 6.2 vs. 5.2 ± 6.7) were all nonsignificant. Frequency domain indexes also remained unchanged.

Correlation between the increases in parameters of HRV and HRV at baseline: A significant inverse correlation was recognized between the changes induced by verapamil in the time domain parameters of HRV and parameters of HRV at baseline (Figure 2). For example, SDNN increased by 41.4% in patients with baseline SDNN ≤80 ms (n = 23) but remained virtually unchanged in the subgroup with baseline SDNN >80 ms. We obtained qualitatively similar results when we

analyzed values of rMSSD, pNN50, and heart rate. The decrease induced by verapamil in the low- to high-frequency ratio, considered to be a marker of sympathetic activity, was inversely and strongly correlated with its baseline value (r = −0.73, p <0.001).

DISCUSSION

This study revealed that verapamil at clinical doses induced a significant increase in parameters of HRV in patients with recent MI. The effect was due primarily to enhancement of the power of the high-frequency peak, since no significant changes were found in low- and very low-frequency power. Using normalized instead of absolute units, we noted that the low-frequency content decreased significantly after administration of verapamil and, consequently, the low- to high-frequency ratio was significantly reduced by the drug.

Verapamil and HRV after myocardial infarction: Abnormal autonomic function may be an important factor in the development of potentially lethal arrhythmias and sudden death in clinical and experimental situations.[6,7] HRV is a useful index of autonomic activity and has been used as a noninvasive marker of risk in patients with MI because depressed HRV is a strong independent predictor of both total deaths and sudden death.[11,18] Data about the effects of verapamil on HRV after MI are limited. Our results suggest a clear improvement in time domain parameters of HRV after administration of verapamil in the subacute phase of MI. Qualitatively similar findings were reported recently by Bonaduce et al.[14] In their study, SDNN, RMSSD, and pNN50 increased by 21%, 61%, and 145%, respectively, after administration of verapamil. The lower mean age and the exclusion of diabetic patients from this earlier series may explain the higher relative increments compared with our results. The effect of verapamil on HRV in diabetic post-MI patients has not previously been evaluated, but according to our results, changes in HRV induced by the drug could be small or absent in this subgroup. To our knowledge, a negative relation between the increment in HRV obtained with verapamil and the baseline value has not previously been reported. This observation may be of clinical interest since high-risk patients are those with the lowest indexes of HRV and this subgroup seems to gain the greatest benefit from the drug.

Frequency domain analysis: As reported previously,[14] verapamil induced a significant increase in high-frequency power in our series, and this result suggests the enhancement of parasympathetic activity by the drug. Data on the effects of verapamil on the low-frequency band are more controversial. Bonaduce et al[14] found a significant increase of approximately 20% in the low-frequency component on administration of verapamil to post-MI patients. By contrast, enhanced fluctuations in the low-frequency band of 0.05 to 0.09 Hz, as seen in patients with migraine, were significantly reduced after administration of verapamil.[19] Our results did not reveal any significant change in the absolute low-frequency power in response to vera-
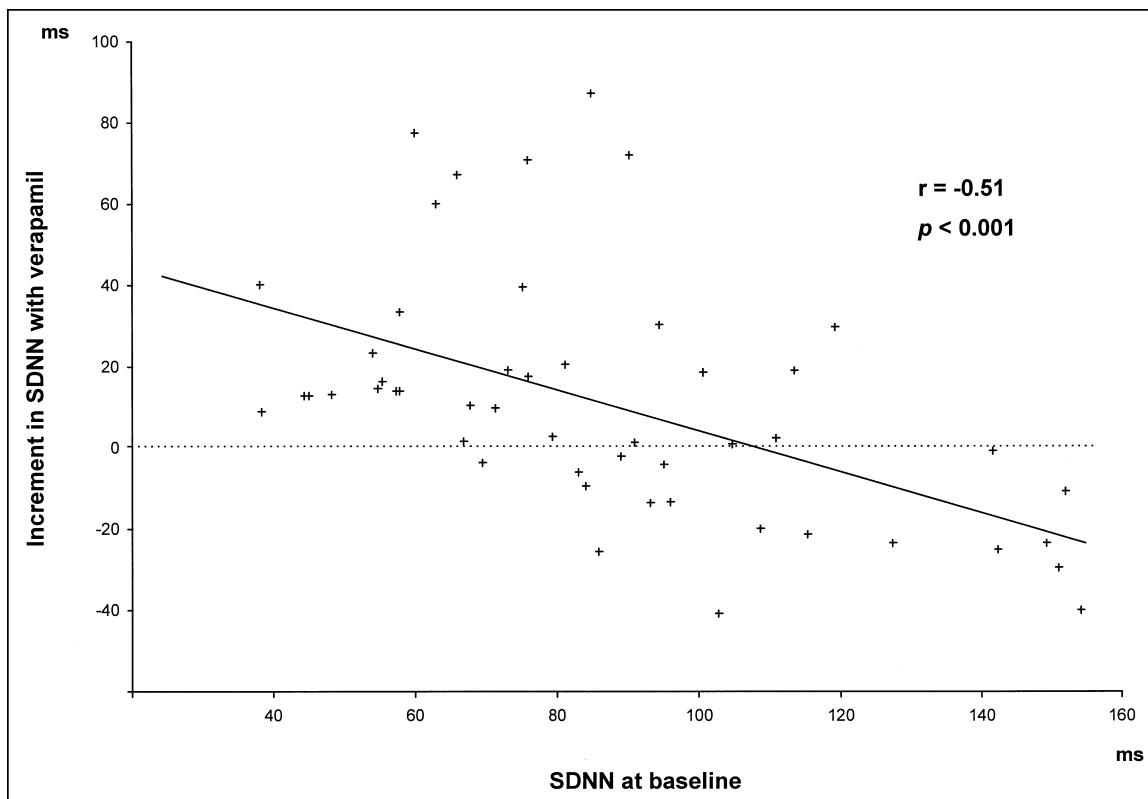
FIGURE 2. Correlation between SDNN at baseline and the increase in SDNN after administration of verapamil.

pamil. However, using normalized units, we unmasked a significant reduction in the relative contribution of this frequency band. A similar effect was observed with the low- to high-frequency ratio, in agreement with previous data.[14] The mechanisms by which verapamil influences components of HRV have not been clearly elucidated, but they are probably related to specific properties of the drug that have a suppressive effect on the sympathetic outflow of catecholamines, including depletion of vesicular stores of catecholamines[20,21] and inhibition of noradrenergic neurotransmission.[9,22] The increment in high-frequency content may be an indirect result of the reduction in sympathetic outflow induced by verapamil,[23] because a high adrenergic drive induces the release of renin,[24] which is thought to have vagolytic effects.[25,26]

Study limitations: Patients with severe depression of LVEF were not included in the study because verapamil might have further impaired left ventricular function in these patients.[27] The effects of the drug in this high-risk subgroup may be different and remain to be elucidated. Another potential limitation is that the spectral measurements were obtained from 5-minute segments averaged over the entire 24-hour period. This method has several computational advantages[28] but may be less accurate for assessing very low-frequency power[12] and our results regarding this band of the spectrum should be interpreted with caution.

Conclusions and clinical implications: We have shown that verapamil improves HRV in post-MI patients, inducing a shift in the sympathovagal balance toward a parasympathetic predominance. The influence of verapamil on HRV may have clinical consequences. Depressed HRV after MI may reflect decreased vagal activity with predominance of the sympathetic tone, leading to electrical instability and sudden death.[7,12] The drug-induced increase in indexes of HRV and of high-frequency power, as a marker of vagal activity, may contribute to the explanation of the reported beneficial effects of verapamil.[29] The hypothesis that this positive effect could be greater in nondiabetic patients with low baseline indexes of HRV merits further investigation.

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