Effects of *Propranolol* on Recovery of Heart Rate Variability Following Acute Myocardial Infarction and Relation to Outcome in the Beta-Blocker Heart Attack Trial

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This study evaluated the effects of propranolol on recovery of heart rate variability (HRV) after acute myocardial infarction and its relation to outcome in the Beta-blocker Heart Attack Trial (BHAT). Beta blockers improve mortality after acute myocardial infarction, but through an unknown mechanism. Depressed HRV, a measure of autonomic tone, predicts mortality after acute myocardial infarction. Whether β blockers influence recovery of HRV after acute myocardial infarction, and thereby improve outcome, is unknown. We compared 24-hour HRV parameters at 1 week after acute myocardial infarction and after 6 weeks of treatment with propanolol (n = 88) or placebo (n = 96). The relation between 25-month outcome (death/acute myocardial infarction/congestive heart failure), propranolol treatment, and HRV was further analyzed. After 6 weeks, high-frequency (HF) power (log-normalized), an index of vagal tone, increased more in propranolol-treated patients (4.28 ± 0.1 to 5.17 ± 0.09 ms^2) than in placebo-treated patients (4.26 ± 0.09 to 4.77 ± 0.1 ms^2, p <0.05). Sympathovagal balance measured by the low-frequency (LF) to HF ratio increased in placebo-treated patients (3.55 ± 0.24 to 3.86 ± 0.24) but decreased in those treated with propranolol (3.76 ± 0.29 to 3.17 ± 0.23, p <0.01). Other frequency-domain parameters increased over time but were not affected by propranolol. Propranolol blunted the morning increase in the LF/HF ratio. Recovery of HF, the strongest HRV predictor of outcome, and propranolol therapy independently predicted outcome. In summary, after acute myocardial infarction, propranolol therapy improves recovery of parasympathetic tone, which correlates with improved outcome, and decreases morning sympathetic predominance. These findings may elucidate the mechanisms by which β blockers decrease mortality and reduce the early morning risk of sudden death after acute myocardial infarction. ©2003 by Excerpta Medica, Inc.

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Whether β blockers alter the extent or timing of recovery of heart rate variability (HRV), a predictor of mortality in patients after acute myocardial infarction,[1–3] has not been well studied. Several studies have shown an effect of β blockers on altering indexes of HRV, a measure of changing sympathetic and parasympathetic activity transmitted to the sinoatrial node,[4,5] in normal subjects[5,6] and in patients with coronary artery disease.[7–9] Similar effects have been suggested in patients after they have had acute myocardial infarction,[10–14] in small or nonrandomized studies. The inter-relation of β blockers, HRV, and outcome has not been evaluated in a single study. To assess these effects, we analyzed HRV from ambulatory electrocardiographic (Holter) recordings in a subset of patients enrolled in the Beta-Blocker Heart Attack Trial (BHAT), a large randomized, placebo-controlled study of propranolol versus placebo in patients with acute myocardial infarction, whose demonstrated reduction in mortality, from 9.8% in the placebo-treated group to 7.2% in the propranolol-treated group,[15,16] continues to guide therapy after acute myocardial infarction.

METHODS

Study population: The BHAT study population included 3,837 patients between age 30 and 69 years (mean 54; 85% male) hospitalized with an acute myocardial infarction from June 6, 1978 to October 2, 1980 (from 134 hospitals in 31 United States and Canadian centers). Acute myocardial infarction was documented by symptoms, electrocardiograms, and enzymes. Patients were excluded from the study if they had contraindications to β blockade, such as bradycardia, severe congestive heart failure, or asthma; other life-threatening illness; were likely to undergo cardiac surgery; or if they were already taking β blockers. Patients were randomized to receive propranolol or placebo in a double-blind manner during the initial hospitalization, 5 to 21 days after admission. Treated patients received propanolol at a dose of 180 or 240 mg/day based on blood levels. Twenty-four-

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hour ambulatory electrocardiographic (Holter) monitoring was not mandatory but was obtained at the time of randomization before initiation of therapy in 3,279 patients and 6 weeks later in a random sample of 25% (419 propranolol and 407 placebo-treated patients). Details of the BHAT study design and results have been previously described.[15,16]

The present study population was drawn from a subset of the BHAT cohort enrolled in the Health Insurance Plan substudy, which included 2320 male patients (60% of the entire BHAT study group). As in the overall group, 25% of the Health Insurance Plan patients were randomly assigned to undergo 6-week follow-up Holter monitoring (approximately 580 patients). Of these patients, 325 had baseline and 6-week Holter recordings available for scanning. Less than 5% of the recordings could not be scanned because of tape deterioration. Within this group, 88 propanolol-treated and 96 placebo-treated patients had baseline and 6-week follow-up Holter recordings of sufficient length and without excess ectopics and/or noise (see the following). These 184 patients comprised the study population of this investigation.

Processing of Holter recordings: Holter reel-to-reel recordings generated on Delmar Avionics recorders (Irvine, California) were digitally sampled (128 Hz) and analyzed using a Zymed system (Oxnard, California). Each tape was manually processed and edited to ensure accurate identification of QRS complexes. A list of RR intervals with annotations denoting normal beats, types of ectopics, and noise was saved and later transferred to a Sun workstation (Santa Clara, California) for further processing and analysis with customized software.

Frequency-domain analysis: Before spectral analysis, the RR interval data file was first edited to remove ectopics and noise. The gaps resulting from edits were filled in by interpolated linear splines.[17] Holter recordings of patients with >20% interpolated RR intervals or <18 total recorded hours were excluded from further analysis. The RR interval time series was sampled using a boxcar window[18] to give 1,024 samples/5 minutes (3.41333 Hz) to generate a uniformly spaced instantaneous heart rate time series. The heart rate spectrum was computed using a fast-Fourier transform with a Parzen window. The fast-Fourier transform was performed on sequential 1-hour segments and on the entire RR interval file (18 to 24 hours). Because the fast-Fourier transform routines were optimized for sequences with lengths equal to multiples of small primes,[2,3,5] considerable flexibility was available in processing patient files of differing duration. The power spectrum was corrected for attenuation due to windowing and sampling.[19] For both the 1- and 24-hour analyses, the power spectrum was integrated over 5 discrete frequency bands as defined by Bigger et al[1,20]: ultra LF <0.0033 Hz; very LF 0.0033 to <0.04 Hz; LF 0.04 to <0.15 Hz; HF 0.15 to 0.40 Hz, and total power. The ratio of LF to HF power was measured as an index of sympathovagal balance.[5] For analysis of circadian patterns, results from the analysis of 1-hour segments were averaged over four 6-hour time blocks: midnight to 6 A.M. (MN), 6A.M. to noon (AM), noon to 6 P.M. (Noon), and 6 P.M. to midnight (PM), respectively.

Time-domain analysis: Three conventional time-domain indexes of HRV were computed for the entire Holter recording and for consecutive 1-hour segments: (1) percent of adjacent normal to normal (NN) intervals differing by >50 ms (pNN50), (2) the root-mean-square of differences in successive NN intervals (rMSSD), and (3) the SD of NN intervals (SDNN). As in the frequency-domain analysis, 1-hour measurements were aggregated into the four 6-hour time blocks—MN, AM, Noon, and PM for analysis of circadian patterns.

Follow-up: Mean follow-up in the BHAT was 25 months. BHAT end points of death, acute myocardial infarction, or congestive heart failure were combined into a composite end point for analysis of outcome in the present study.

Statistical analyses: For univariate analysis, unpaired *t* test or chi-square test were used. All HRV parameters except SDNN were highly skewed, and therefore, log-transformed for statistical analysis.[1] A repeated measures 2-way analysis of variance was used to study the effects of time (baseline to follow-up) and the interaction of time and treatment on HRV measurements. A significant interaction effect was taken to indicate that propranolol influenced measured HRV parameters apart from any effects of time. A repeated measures 2-way analysis of variance was also employed to study whether propranolol treatment at follow-up had a differential effect when compared with placebo on the circadian variation of HRV parameters. Circadian variation was defined by the pattern of HRV parameter changes over the 4 time periods of the day (MN, AM, Noon, PM). Analysis of variance with repeated measures was performed using the standard least-squares regression and the multivariate analysis of variance platforms. Stratified analysis of effects of propranolol on HRV parameters was performed based on presence or absence of "mechanical complications," including pulmonary edema, cardiogenic shock, hypotension, rales, or symptoms and/or signs of congestive heart failure, as defined in previous BHAT analyses.[21] Evaluation of effects of propranolol and HRV parameters on outcome was performed with multiple logistic regression. Clinical variables were controlled for age, diabetes, hypertension, New York Heart Association class at enrollment, presence of rales, and ventricular arrhythmia (defined in BHAT as ≥3 successive premature ventricular contractions or ventricular fibrillation.) All statistics were computed using JMP software (SAS Institute, Inc., Version 3.1.6, Cary, North Carolina). A p value of <0.05 was considered significant.

RESULTS

Patient population: Demographic variables for the propranolol and placebo groups are listed in Table 1. All patients in this subset were male. Overall, baseline characteristics were similar in this subgroup to the

TABLE 1 Baseline Characteristics

	Propranolol (n = 88)	Placebo (n = 96)
Age (yrs)	54 ± 9	54 ± 9
Caucasian	80 (91%)	85 (88%)
Systemic hypertension	29 (33%)	33 (34%)
Diabetes mellitus	11 (12%)	10 (10%)
Healed myocardial infarction	11 (12%)	18 (19%)
Tobacco use	80 (91%)	82 (85%)
AMI location		
Anterior	29 (33%)	31 (32%)
Inferior	29 (33%)	36 (37%)
Non–Q-wave	30 (34%)	29 (30%)
Post-AMI complications		
"Mechanical complications"*	16 (18%)	16 (17%)
Any arrhythmia†	30 (34%)	44 (46%)
Ventricular arrhythmia	25 (28%)	36 (37%)
Baseline New York Heart Association		
Class I	44 (50%)	56 (58%)
Class ≥II	44 (50%)	39 (41%)
Baseline		
SBP (mm Hg)	110 ± 10	111 ± 10
DSP (mm Hg)	71 ± 9	72 ± 8
HR (beats/min)	75 ± 10	76 ± 12

*Defined in text.

†Including complete or incomplete atrioventricular block, atrial tachyarrhythmias, or ventricular arrhythmia (defined as ≥3 premature ventricular contractions or fibrillation). All comparisons are nonsignificant.

Values are mean ± SD or number (percentage).

AMI = acute myocardial infarction; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

TABLE 2 Heart Rate Variability Parameters

	Baseline ± SE*	6 wks ± SE	p Value
RR interval			<0.01
Propranolol	854 ± 12	991 ± 14	
Placebo	830 ± 12	829 ± 14	
Frequency domain			
Ln HF (ms^2)			<0.05
Propranolol	4.28 ± 0.11	5.17 ± 0.09	
Placebo	4.26 ± 0.09	4.77 ± 0.1	
Ln LF (ms^2)			NS
Propranolol	5.37 ± 0.1	6.13 ± 0.09	
Placebo	5.3 ± 0.09	5.94 ± 0.1	
Ln very LF (ms^2)			NS
Propranolol	6.75 ± 0.08	7.4 ± 0.07	
Placebo	6.6 ± 0.08	7.06 ± 0.08	
Ln ultra LF (ms^2)			NS
Propranolol	8.51 ± 0.08	8.99 ± 0.07	
Placebo	8.6 ± 0.08	9.08 ± 0.08	
Ln total power (ms^2)			NS
Propranolol	8.74 ± 0.08	9.27 ± 0.06	
Placebo	8.8 ± 0.07	9.28 ± 0.07	
Ln LF/HF (ms^2)			<0.01
Propranolol	1.09 ± 0.07	0.96 ± 0.07	
Placebo	1.04 ± 0.07	1.17 ± 0.06	
Time domain			
Ln pRR50			<0.01
Propranolol	0.19 ± 0.14	1.18 ± 0.14	
Placebo	0.27 ± 0.14	0.92 ± 0.14	
Ln rMSSD			<0.01
Propranolol	2.94 ± 0.04	3.38 ± 0.04	
Placebo	2.93 ± 0.03	3.10 ± 0.03	
SD			NS
Propranolol	86.25 ± 3.01	114.76 ± 3.71	
Placebo	88.78 ± 2.75	117.07 ± 3.94	

*No parameter differed at baseline between treated (n = 88) and placebo (n = 96) groups.

The p value shown reflects the differential effect of propranolol beyond that of time alone.

larger BHAT population, with the exception of gender.[15,16]

Frequency-domain measures of heart rate variability: Twenty-four-hour frequency-domain measures of HRV (log-normalized) at baseline and at 6 weeks in β-blocker and placebo groups are listed in Table 2. As seen in Figure 1, HF power increased significantly in both groups at 6 weeks; however, there was a significantly greater increase in propranolol-treated patients (21% in propranolol-treated vs 12% in placebo-treated, p = 0.02 for propranolol effect above the effects of time). LF, very LF, ultra LF, and total power increased in both groups at 6 weeks but were not affected by β-blocker treatment. At 6 weeks, the LF/HF ratio in placebo-treated patients was greater than at baseline but had decreased in the β-blocker treated patients (p <0.01) (Figure 2).

Time-domain measures of heart rate variability: All time-domain measures increased significantly from baseline to 6-week follow-up (p <0.01). There was a significantly greater increase in pNN50 and rMSSD (p <0.01 for propranolol effect above the effect of time), but not SDNN, in the treated patients.

Circadian variation of heart rate variability measures: At 6 weeks, the placebo group showed an expected circadian variation in the LF/HF ratio, with an abrupt increase in the morning, high levels throughout the day, and decreasing at night, which was not seen in the propranolol-treated patients (Figure 3). The pattern of circadian variation differed significantly between groups (p <0.05). Both HF and LF showed circadian variation with power higher at night and decreasing in the morning, but this pattern was not significantly changed with propranolol therapy. In the time domain, the morning decrease in pNN50 and rMSSD was significantly blunted by propranolol (p <0.01).

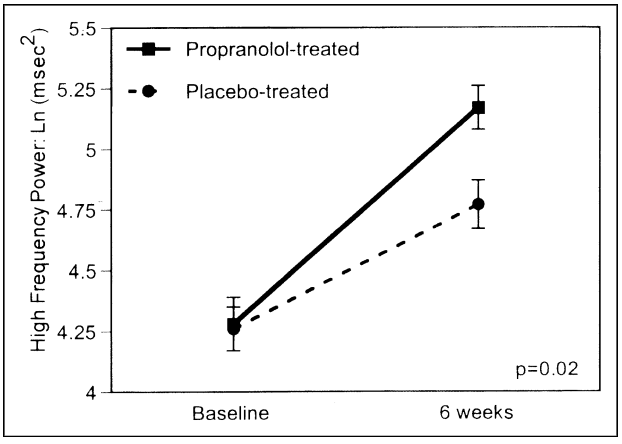

FIGURE 1. Effect of propranolol compared with placebo on recovery of HF power (0.15 to 0.40Hz). Power has been log-normalized. Groups did not differ at baseline. p = 0.02 for the significance of treatment-effect over the effect of time alone. p <0.01 for the effect of time.

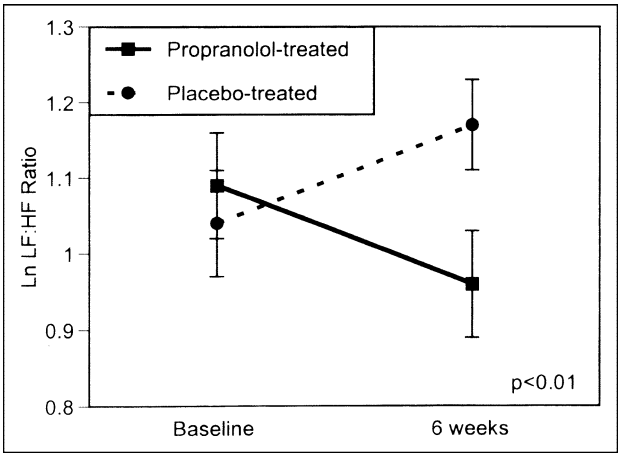

FIGURE 2. Effect of propranolol compared with placebo on recovery of LF/HF ratio (p = 0.008).

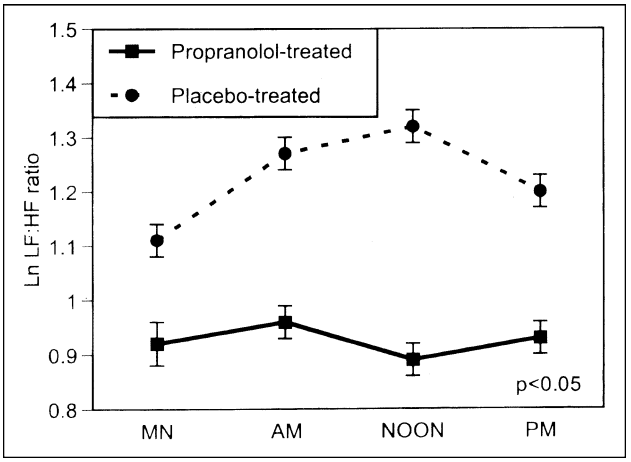

FIGURE 3. Effect of propranolol compared with placebo on circadian variation of LF/HF ratio at 6 weeks. p <0.05 for the effect of treatment on the pattern of variation.

Correlations with outcome: Similar to the results of the overall BHAT, propranolol in this subgroup improved outcome. The combined outcome of death, myocardial infarction, or congestive heart failure (used in all further analyses), occurred in 23% of the untreated patients, compared with a 9% incidence in the patients who received β blockers (p = 0.02). Death occurred in 9.4% of placebo and 4.5% of treated patients (p = NS). In this population, HRV at 6 weeks predicted outcome. Although ultra LF, very LF, LF, and HF predicted outcome in univariate analysis, only HF power remained significant in multivariable regression. Similarly, in the time domain, SD, pNN50, and rMSSD were univariate predictors, but pNN50 was the only independent predictor. RR interval did not significantly predict outcome in the univariate or multivariate analyses.

HF power was then dichotomized at the first quartile for further analysis. Death, acute myocardial infarction, or congestive heart failure occurred in 2% of those in the highest quartile, compared with 21% of those in the lower quartiles (p <0.01). In multivariable analysis, propranolol and high HF power exerted

TABLE 3 Inter-relationship of Propranolol, High-frequency power (HF), and Outcome

		n	Death/AMI/CHF	Relative Risk	p Value†
High HF*	Treated	28	0%	0	<0.01
High HF	Placebo	20	5%	0.18	0.04
Low HF	Treated	60	13%	0.48	0.04
Low HF	Placebo	76	27%	1.00	

*Normalized HF power dichotomized at first quartile.
†p Values reflect comparison with the highest risk group.

TABLE 4 High-frequency Power (log-normalized) Stratified by Presence of Mechanical Complications (ms^2)

	Baseline ± SE*	6 wks ± SE	p Value
Mechanical complications present			<0.03
Propranolol	3.96 ± 0.22	5.56 ± 0.26	
Placebo	4.06 ± 0.22	4.65 ± 0.26	
Mechanical complications absent			0.17
Propranolol	4.35 ± 0.11	5.08 ± 0.11	
Placebo	4.30 ± 0.10	4.79 ± 0.10	

significant and independent effects. To further evaluate the inter-relation between propranolol, HF power, and outcome, event rates were compared by treatment and HF status, as shown in Table 3. Patients with high HF power, whether achieved through treatment with propranolol (60% of those in the highest quartile of HF) or spontaneously in those patients given placebo, had excellent outcomes. In patients with low HF despite treatment with propranolol, relative risk was still improved over placebo-treated patients with similar HF power.

Stratified analysis of propranolol effects on autonomic parameters based on presence of mechanical complications: Patients with mechanical complications had a higher incidence of cardiovascular events than did those without complications (28% vs 13%, p <0.05), and the impact of β blockers on event rate was significant only in those with mechanical complications. As shown in Table 4, propranolol significantly improved HF power in those with, but not those without, mechanical complications.

DISCUSSION

This analysis shows that propranolol increases the recovery of parasympathetic tone in patients with acute myocardial infarction, as measured by HF power, pNN50, and rMSSD; it also alters autonomic balance at 6 weeks, as measured by the LF/HF ratio. Improvement in vagal tone was further correlated with improvement in outcome, suggesting that propranolol effects are mediated in part through this effect. Propranolol blunted the early morning increase in sympathetic dominance of autonomic balance, the time period of maximum cardiovascular events.[22–24]

Recovery of HRV after acute myocardial infarction: The randomized, placebo-controlled BHAT population is well-suited to investigate the effect of propran-

olol on recovery of HRV and the inter-relation with outcome. The study design included a first Holter recording in-hospital before randomization and a second 6 weeks after administration of placebo or β blocker, or about 8 weeks after acute myocardial infarction, close to the previously described 6- to 12-week plateau of HRV recovery in untreated patients.[25,26] In these studies of untreated patients, recovery of HRV did not reach that of age and gender-matched normal controls. In the present study, while HF power in the untreated group at 6 weeks (8 weeks post-acute myocardial infarction) was similar to that described in 12-week post-acute myocardial infarction patients by Bigger et al,[25] the recovery level of HF in the β-blocked group was similar to that of the normal controls.

Effect of propranolol on autonomic function as measured by HRV: Evaluation of the effects of propranolol on HRV may help elucidate mechanisms by which propranolol exerts its beneficial effects. Consistent with the previously described studies, recovery of HRV from its initial post-acute myocardial infarction nadir was seen in placebo- and propranolol-treated patients. Propranolol, however, significantly improved the recovery of HF power over time. HF power is abolished by parasympathetic blockade[4] and thus provides a marker of parasympathetic activity. That HF increased after 6 weeks of propanolol treatment implies that this drug acts to increase parasympathetic tone. Previous studies have shown a similar effect on HF power in normal subjects,[5,6] (with 1 exception[9]) and in patients with coronary artery disease.[7,8] Although previous smaller studies in patients with acute myocardial infarction have suggested an increase in HRV parameters with β blockade,[10–14] these trials were either not controlled[13,14] or crossover[12]; the study size was not stated in 1[10] and 1 randomized only 25 patients to therapy.[11]

With propranolol therapy, there was no enhanced recovery of LF power, which reflects sympathetic, parasympathetic, and possibly other neurohormonal influences. However, there was a dramatic differential treatment effect on the LF/HF ratio, with this parameter increasing after 6 weeks in placebo-treated patients but decreasing in the β-blocker treated group. Most data suggest this ratio is an index of sympathetic predominance. Although the LF/HF ratio has not been shown to correlate with cardiac norepinephrine spillover,[27] LF/HF increases with orthostatic challenge,[5] and shows circadian variations similar to those of plasma catecholamines.[28,29] The increase in LF/HF over time in placebo-treated patients in this study may reflect an increase in sympathetic activity, due to the resumption of upright posture with daily activities by the time of the follow-up outpatient Holter monitoring, which was blocked by propranolol.

Interaction of congestive heart failure and effects of propranolol on autonomic parameters: As in previous analyses of BHAT,[21,30] in this subpopulation, evidence of congestive heart failure as manifested by "mechanical complications" was associated with an increased event rate, and it was these patients in whom propranolol treatment most improved outcome. Interestingly, it was in these sickest patients that propranolol increased vagal tone as measured by HF power, suggesting that this action may in part mediate propranolol's beneficial effects in this population.

Study limitations: Ambulatory electrocardiograms were recorded reel-to-reel in 1978 to 1980, using technology that did not include a time-track or calibration signals, which would have confirmed the accuracy and lack of deterioration of the tapes after storage. The original reel-to-reel recordings were scanned without a phase-lock loop system, which may have introduced a very small amount of HF distortion.[1,18] However, any contamination of the data by noise or technical imprecision should be similar for both groups, and HRV values for the immediate post-acute myocardial infarction and the 2-month placebo-treated patients are similar to those previously published,[25] suggesting technical accuracy was within an adequate range. Results of this study are limited by the subpopulation studied, which included only men (85% of the original BHAT group). Whether these results can be extrapolated to women requires further investigation. Left ventricular function was not measured in the BHAT trial, and thus possible differential effects of propranolol among patients based on left ventricular function cannot be determined. The number of cardiovascular outcomes experienced by the patients in this group was limited by the relatively short duration of follow-up in BHAT (25 months).

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