Lipophilic versus hydrophilic β_1 blockers and the cardiac sympatho-vagal balance during stress and daily activity in patients after acute myocardial infarction

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Abstract

Objective—To compare the effects of a lipophilic and a hydrophilic β_1 blocker on cardiac sympatho-vagal balance during daytime activity and stress in patients four to six weeks after myocardial infarction.

Design—Randomised, double blind, crossover study comparing the effect of atenolol (50 mg once daily) with metoprolol CR (100 mg once daily) with treatment periods of four weeks.

Setting—Large teaching hospital.

Patients—50 patients (45 male, 5 female, age range 40 to 75 years), four to six weeks after an acute myocardial infarction.

Methods—At the end of each treatment period the 24 hour heart rate variability, heart rate variability power spectra during head up tilt and mental stress, baroreflex sensitivity, and exercise performance were evaluated.

Results—During daytime activity and during orthostatic and mental stress, both heart rate and the ratio between the low and high frequency spectral components of the heart rate variability were significantly lower with atenolol. Conversely, there was no difference between treatments in baroreflex sensitivity and resting plasma catecholamines. Exercise duration and peak oxygen consumption did not differ between treatments, but the heart rate during submaximal and peak exercise was significantly lower with atenolol.

Conclusions—At the doses used in this study, atenolol achieved greater β_1 adrenergic blockade than metoprolol CR and this was associated with significant inhibition of vagal withdrawal during stress. This suggests that peripheral blockade of β_1 adrenergic receptors may be more important than central blockade in preventing stress induced vagal withdrawal in patients after myocardial infarction.

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Keywords: adrenergic receptors; myocardial infarction; stress; baroreceptors

It is now well established that long term β adrenoceptor blockade is effective in lowering mortality in patients surviving myocardial infarction.¹ Several β blockers have been shown to have a protective effect in patients after myocardial infarction; however, the largest

trials have all been carried out with lipophilic agents.¹

Theoretically there are several reasons why lipophilicity might be advantageous. Lipophilic β blockers can readily pass the blood-brain barrier and effectively block β receptors in the brain.² This has been associated with an anti-fibrillatory effect in animal models of stress induced arrhythmias during acute ischaemia.³ Furthermore, it has been suggested that β blockade in the CNS might exert part of its antiarrhythmic effect by counteracting stress induced vagal withdrawal⁴ and by reducing the level of sympathetic efferent discharge.⁵ Treatment with hydrophilic β_1 blockers such as atenolol, however, has also been found to increase indices of vagal tone in man^{6,7} and to cause a reduction in sympathetic outflow,⁸ suggesting that these effects might be a result of peripheral β adrenergic blockade. Consistent with this, Tuininga *et al*⁹ have shown no significant differences between treatments with the hydrophilic β_1 receptor blocker atenolol (100 mg once daily) and the lipophilic metoprolol CR (200 mg once daily) in the autonomic response to mental tasks and to exercise in patients three to 12 months after myocardial infarction. At this late stage, however, the alterations in cardiac sympatho-vagal balance that follow myocardial infarction would have substantially recovered^{10,11} and the patients would be at lower risk of arrhythmic death.

Our present study aimed to compare the effects of metoprolol CR (100 mg once daily) and atenolol (50 mg once daily) on the cardiac sympatho-vagal balance during exercise and orthostatic and mental stress in patients enrolled four to six weeks after an acute myocardial infarct. The effect of the two agents on the sensitivity of the arterial baroreflex (an index of reflex vagal activity) was also evaluated.

Methods

STUDY DESIGN

The study was a double blind, crossover comparison of the effects of treatment with atenolol (50 mg once daily) and metoprolol CR (100 mg once daily) (fig 1) in 50 patients (45 male, 5 female, age range 40 to 75 years), four to six weeks after an acute myocardial infarct. Heart failure (New York Heart Association class > II), moderate to severe angina, diabetes mellitus, atrial fibrillation, cardiac conduction abnormalities, chronic obstructive lung disease, and liver or kidney failure were exclusion criteria. At entry patients were familiarised

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Figure 1 Study protocol. Patients were familiarised with the procedures (with the exception of the mental stress test) before randomisation and were tested at the end of each four week period (arrows).

with the procedures (with the exception of the mental stress test) and randomised to receive one of the two β_1 blockers for a four week period (period I). They were then crossed over to receive the other β blocker for two further periods of four weeks (periods II and III).

At the end of each of the three four week periods the patients came to the cardiovascular laboratory, where the electrocardiogram (ECG) and breathing rate (derived from changes in chest impedance) were recorded while they were resting in the supine position, and during 60° head up tilt and mental stress. After 30 minutes in the supine position a venous blood sample was taken for the measurement of plasma catecholamines and the baroreflex sensitivity was assessed by the phenylephrine technique.¹² Patients were then asked to perform an incremental exercise test until exhaustion, during which ventilation ($\dot{V}_i$), oxygen uptake ($\dot{V}_{O_2}$), CO_2 production ($\dot{V}_{CO_2}$), and heart rate were measured. After 15 minutes of rest, they were fitted with an ambulatory ECG recorder for 24 hours.

Patients were instructed to take their tablets between 0700 and 0800; laboratory tests were consistently performed between 1100 and 1300 in 24 patients, and between 1600 and 1800 in 26 patients.

A questionnaire evaluating CNS related symptoms¹³ was completed by the patients on the last morning of each treatment period.

Data from periods I and II were used for comparing the effects of the two β blockers, while data from period I, II, and III, irrespective of treatment, were used for the assessment of time effects after myocardial infarction.

The study was performed according to the Declaration of Helsinki and the protocol was approved by the central Oxford research ethics committee. Written informed consent was obtained from each patient before entry into the study.

24 HOUR RR INTERVAL VARIABILITY

The ECG recordings were digitised at 256 samples per second and submitted to standard algorithms for QRS labelling (Biomedical Systems Corporation, St Louis, Missouri, USA). Measurement of the RR intervals were taken from the zero crossing point of the first derivative of the signal. The appropriateness of automated QRS triggering and labelling was then checked visually by superimposing the QRS complexes classified in each of the bins by their trigger point. Finally, we plotted the frequency histogram of all normal RR and of the ratio

between adjacent RR; the ECG strips containing the beats forming the tails of the distribution curve were then disclosed and, when necessary, re-edited. Tachogram files were then automatically created for the whole 24 hours. Irregularly spaced time series were used, defined by the succession of normal RR.¹⁴ Gaps in the tachograms resulting from noise or ectopic beats were interpolated, taking into account the prevailing RR immediately before and after the gap. A rectangular window¹⁵ was then applied and a fast Fourier transform was computed for the 24 hour interval. The spectral power in ms^2 was calculated in the following frequency bands: ultra low frequency (ULF, from 1.157×10^{-5} to 0.0033 Hz); very low frequency (VLF, from 0.0033 to 0.04 Hz).

The spectral density of shorter time windows (that is, daytime and night time) and of the 24 hour low frequency (LF, from 0.04 to 0.15 Hz) and high frequency (HF, from 0.15 to 0.40 Hz)¹⁶ was calculated, as described by Rottman *et al.*¹⁷ Briefly, the time windows were divided into consecutive, non-overlapping segments of five minutes' duration. At least 95% of RR in a five minute segment were required to be normal, otherwise the segment was excluded from further processing. After subtracting the mean RR, a Welch window¹⁵ was applied to the time series and a fast Fourier transform was computed. The spectra of all usable five minute segments were averaged to obtain the spectral power in the LF and HF range for the 24 hour and for the daytime and night time periods. Since the numbers of hours that each patient slept varied, a five hour period ending one hour before the patient's awakening was designated as "asleep." Likewise, an interval of five hours between 1200 and 2000 was taken as the "daytime activity" period. The power of the spectral components was calculated in absolute units (ms^2).

SHORT TERM RR INTERVAL VARIABILITY

Lead II of the ECG and a non-calibrated signal of respiration induced changes in chest impedance (Minimon 7136, Kontron Instruments, UK) were measured for 10 minutes during rest in the supine position, during 60° head up tilt, and during a mental stress test, in a quiet room at a controlled temperature of 22°C. ECG recordings from 12 patients had to be excluded from spectral analysis because they contained more than 5% of ectopic beats. The signals were digitised on-line by a 12 bit analogue to digital converter (AT-Codas, USA) at a sampling rate of 400 Hz and stored on an optical

disk (Panasonic LF-5010E, Slough, UK). The QRS complex was then identified by using a classic adaptive derivative/threshold algorithm.¹⁸ The mean RR and its variance were computed from series of 256 consecutive RR. Autoregressive spectral analysis was used to evaluate the power spectral density of the time series. This technique has been described in detail before.¹⁹ Spectral analysis of the chest impedance signal was performed on the signal sampled once every cardiac cycle. These spectra were used as a reference to identify the frequency of respiratory sinus arrhythmia (that is, of the HF component). The spectral power was computed in the LF and HF range and was expressed both in absolute (ms^2) and normalised units (nu) calculated as: [power of the component, ms^2]/[total power, ms^2 - very low frequency power (< 0.03 Hz), ms^2].

MENTAL STRESS TEST

Patients, in the semireclined position, were asked to click the right or left button of a computer mouse to identify the hand in which a red or green balloon was held by a figure appearing on a computer screen. The balloon had to be of the same colour as the figure's trousers. The figure could appear full frontal or from the rear and would normally hold a balloon in each hand. A correct answer was accompanied by an increase in score and in the speed by which different combinations appeared on the screen. A wrong answer was associated with a noise and a decrease in score. Patients were encouraged to aim for a high score.

BAROREFLEX SENSITIVITY AND PLASMA

CATECHOLAMINES

Baroreflex sensitivity was assessed by the phenylephrine method.¹² Three to six rapid intravenous injections of phenylephrine hydrochloride were given at approximately three minute intervals. The initial dose of 0.05 mg was adjusted to obtain an increase between 15 and 25 mm Hg in systolic blood pressure (Finapres BP Monitor, Ohmeda, Hatfield, Herts, UK). The baroreflex sensitivity, expressed in ms/mm Hg , was obtained from the average slope of at least three regression lines relating beat to beat change in RR to the change in the preceding systolic pressure. Plasma catecholamines in the venous blood were measured by high performance liquid chromatography.²⁰ The blood was collected in chilled heparinised tubes and immediately centrifuged. Plasma was stored at -70°C until assayed.

EXERCISE STRESS TEST

Symptom limited, incremental upright cycle ergometry (Tunturi-piora, Turku, Finland) was performed at the end of each visit. The starting work rate of 50 W was increased by 25 W every four minutes. $\dot{V}_i$ (litres/min) (Harvard Apparatus, Kent, UK), $\dot{V}_{\text{O}_2}$ (ml/min), and $\dot{V}_{\text{CO}_2}$ (ml/min) (Servomex 570A and Servomex PA404, Sussex, UK) were measured for five minutes at rest, sitting on the cycle ergometer, and during the exercise test. The gas analysers were calibrated with gases of known composition before each test and all volumes were cor-

rected to standard temperature and pressure. The peak $\dot{V}_{\text{O}_2}$ was taken from the mean over the last completed minute of exercise. A 12 lead ECG was recorded throughout the test and heart rate was calculated over the last minute of each work rate.

QUALITY OF LIFE ASSESSMENT

CNS related symptoms were assessed using the minor symptom evaluation (MSE) profile. This questionnaire is specifically designed to evaluate subtle changes in subjective symptoms, such as contentment, vitality, and sleep.¹³ The answers were recorded using a visual analogue scale; low values on the scale indicate positive feelings, and high values indicate negative ones.

STATISTICAL METHODS

Data were examined for balanced allocation and absence of carryover effects, according to the recommendation of Hills and Armitage²¹ for crossover trials. Since the frequency distribution of the spectral measures of RR interval variability were positively skewed, data were analysed after log transformation. Repeated measures analysis of variance (SuperANOVA, Abacus Concepts, Berkeley, California, USA) was used to test for differences within the trial stages. Data from the three treatment periods were compared (irrespective of the β blocker treatment) for assessing time effect after myocardial infarction. Finally, since the pharmacokinetic properties of atenolol and metoprolol CR differ,²² the interaction between time after drug intake and effect of treatment was also evaluated using analysis of variance. Values are presented as mean (SEM) and as 95% confidence intervals (CI) for the quality of life assessment. Significance was accepted at p values < 0.05 .

Results

PATIENTS

Of the 50 patients who entered the trial, 10 were withdrawn for the following reasons: development of congestive heart failure (3), reinfarction (1), unstable angina (1), claudication (1), impotence (1), and introduction of a new therapeutic agent (3). The occurrence of adverse events did not differ between treatments. The mean (SD) age of the 40 patients who completed the study was 57 (1) years (ranging from 40 to 75 years); 35 were male and 5 female. Twelve patients had an anterior myocardial infarct, five had an anterolateral myocardial infarct, and 23 had an inferior myocardial infarct. Eighty five per cent of the patients received thrombolytic treatment. Before randomisation 98% of the patients were on aspirin, 100% were on β blockers, 14% were on nitrates, and 9% were on angiotensin converting enzyme inhibitors. Eighty three per cent of the patients were smokers, 20% had a past history of high blood pressure, and 47% had a raised plasma cholesterol.

24 HOUR RR VARIABILITY

Data from seven patients had to be excluded because of the poor quality or failure of the

Table 1 Time and frequency domain measurements of the 24 h RR interval variability

	Atenolol	Metoprolol CR
RR means (ms)	1076 (32)*	1006 (26)
SDNN (ms)	155 (8)	159 (9)
ULF (ms ² /Hz)	23 006 (2625)	24 855 (3035)
ln ULF	9.85 (0.10)	9.89 (0.11)
VLF (ms ² /Hz)	2153 (313)	1858 (199)
ln VLF	7.35 (0.14)	7.29 (0.13)
LF (ms ² /Hz)	985 (131)	832 (116)
ln LF	6.60 (0.14)*	6.45 (0.14)
HF (ms ² /Hz)	639 (90)	471 (64)
ln HF	6.13 (0.14)*	5.83 (0.14)
LF/HF ratio	1.89 (0.17)	2.30 (0.28)
ln LF/HF	0.47 (0.11)	0.62 (0.12)

Values are means (SEM).

* $p < 0.05$ between treatments.

SDNN, standard deviation of all normal RR values; ULF, ultra low frequency power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; ln, natural logarithm.

ECG recordings (4) or because of a high incidence (more than 50% of the beats) of supraventricular and ventricular premature complexes (3). The mean and maximum heart rates in the 24 hours were significantly lower with atenolol than with metoprolol CR (56 (2) *v* 60 (2) beats/min, and 94 (2) *v* 102 (3) beats/min, respectively, $p < 0.05$), while the minimum heart rate was not different (41 (1) *v* 42 (1) beats/min). The total number of ventricular and supraventricular premature complexes in the 24 hours did not differ significantly between treatments (68 (19) *v* 138 (67), and 74 (20) *v* 163 (79) for atenolol *v* metoprolol, Mann-Whitney U test: $p = 0.55$ and $p = 0.60$, respectively). While there was no significant difference between treatments in the standard deviation of all normal RR intervals (SDNN), or in ULF and VLF, the spectral power in the LF and HF range was significantly higher during treatment with atenolol (table 1). This trend was more obvious during daytime activity (table 2), when treatment with atenolol was associated with a significantly lower LF/HF ratio. Conversely, there were no differences between treatments during sleep (table 2).

HEAD UP TILT AND MENTAL STRESS

During mental stress the LF/HF ratio was significantly lower with atenolol than with metoprolol CR (fig 2). This was due to a significantly greater HF power with atenolol, while the LF power did not differ between treatments (table 3). Furthermore, during treatment with atenolol there were no significant differences between rest and mental stress

in SDNN, HF power, and the LF/HF ratio; however, during metoprolol CR the stress test caused a significant reduction in SDNN and HF (both in normalised and absolute units) (fig 2, table 3) and an increase in LF/HF ratio (fig 3). Heart rate was not significantly increased by either test but it tended to be lower during treatment with atenolol than with metoprolol CR. The analysis of variance showed no significant interaction between the time after drug intake and effect of treatment (data not shown).

No difference between treatments was found in the baroreflex sensitivity (10.97 (7.04) ms/mm Hg with atenolol *v* 10.20 (6.41) ms/mm Hg with metoprolol CR, $p = 0.56$) or in the concentration of circulating catecholamines (adrenaline 39.8 (6.1) *v* 43.4 (5.8) pg/ml; noradrenaline 461.4 (41.6) *v* 505.7 (62.9) pg/ml, atenolol *v* metoprolol CR, $p = 0.88$ and 0.71, respectively).

EXERCISE STRESS TESTING

Neither $\dot{V}_i$, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ (table 4), nor exercise duration (10.0 (0.6) *v* 9.8 (0.5) minutes, $p = 0.65$) and peak work rate (93.7 (4.0) *v* 95.6 (3.9) W, $p = 0.32$) differed between treatments with atenolol or metoprolol CR. Heart rate at submaximal and peak exercise, however, was significantly lower during treatment with atenolol than with metoprolol CR, at 78 (2) *v* 86 (2) beats/min at 50 W, and 101 (2) *v* 111 (3) beats/min at peak exercise, $p < 0.0001$ for both. When the data were analysed taking into account the differences in time after drug intake, the results did not change—that is, atenolol achieved a comparably lower exercise heart rate than metoprolol CR four to six and 10 to 12 hours after dose intake ($p = 0.52$ for the interaction between exercise heart rate, time, and treatment).

CNS RELATED SYMPTOMS

There were no differences between metoprolol CR and atenolol in the dimensions of contentment, vitality, or sleeping. Likewise, the analysis of the single items of the MSE profile (for example, sexual interest, sociability, appetite, physical activity) did not show significant differences between treatments. The mean values and 95% CI for the three dimensions during atenolol and metoprolol CR were: 33.8 (28.8 to 38.8) and 33.2 (28.9 to 37.5) for contentment; 30.6 (26.6 to 34.6) and 31.8 (27.0 to 36.6) for vitality; and 31.8 (25.4 to 38.2) and 34.8 (26.4 to 43.2) for sleep.

TIME EFFECTS AFTER MYOCARDIAL INFARCTION

The mean data for each of the four periods are summarised in table 5. Twenty four hour RR variability and the power spectra at rest and during tilt and mental stress did not change significantly with time. Baroreflex sensitivity tended to increase throughout the study but the change was not statistically significant. Conversely, exercise duration, peak work rate, and peak $\dot{V}_{O_2}$ were significantly higher at the end of period III compared to period I.

Table 2 Daytime and night time RR interval variability

	Day		Night	
	Atenolol	Metoprolol CR	Atenolol	Metoprolol CR
RR mean (ms)	1033 (32)†	929 (24)	1194 (35)‡	1146 (32)‡
SDNN (ms)	109 (6)	104 (6)	97 (6)	97 (7)
LF (ms ² /Hz)	792 (163)	584 (94)	1287 (218)	1225 (240)
ln LF	6.16 (0.16)	6.02 (0.16)	6.70 (0.18)‡	6.58 (0.20)‡
HF (ms ² /Hz)	458 (67)	295 (45)	749 (127)	723 (159)
ln HF	5.77 (0.15)†	5.25 (0.17)	6.18 (0.16)‡	5.99 (0.19)‡
LF/HF ratio	1.78 (0.16)	2.96 (0.55)	2.25 (0.30)	2.31 (0.31)
ln LF/HF	0.45 (0.11)*	0.74 (0.13)	0.52 (0.13)	0.59 (0.11)

Values are means (SEM)

* $p < 0.05$, † $p < 0.005$ between treatments; ‡ $p < 0.005$ between day and night.

SDNN, standard deviation of all normal RR values; LF, low frequency power; HF, high frequency power; ln, natural logarithm.

Discussion

In a crossover trial of 50 patients four to six weeks after an acute myocardial infarct we found that treatment with atenolol (50 mg once daily) was associated with a significantly lower 24 hour mean heart rate and a higher spectral power in the LF and HF ranges when compared with metoprolol CR (100 mg once daily). The differences between β_1 blockers were more pronounced during daytime activity and during

orthostatic and mental stress, when both heart rate and LF/HF ratio were lower with atenolol than with metoprolol CR (figs 2 and 3). Conversely, baroreflex sensitivity, plasma catecholamines, and the spectral power of RR interval variability at rest in the supine position or during sleep did not differ between treatments. Although there was no difference in peak $\dot{V}O_2$ or in exercise duration between the two β_1 blockers, the heart rate during submaximal and

Figure 2 Power spectra of RR interval variability and of the non-calibrated respiration signal in a representative patient at rest in the supine position and during mental stress during treatment with atenolol (50 mg once daily) or metoprolol CR (100 mg once daily). Note that the low frequency to high frequency (LF/HF) ratio during mental stress is higher during treatment with metoprolol CR than with atenolol. This reflects a greater stress induced vagal withdrawal with metoprolol, as indicated by the more pronounced reduction in HF power (0.15 to 0.4 Hz) during mental stress with this agent. Conversely, the LF component (0.04 to 0.15 Hz) increased with mental stress but its power did not differ between treatments.

Table 3 Time and frequency domain measures at rest, during head up tilt, and during mental stress test

	Supine		Head up tilt		Mental stress	
	Atenolol	Metoprolol CR	Atenolol	Metoprolol CR	Atenolol	Metoprolol CR
RR mean (ms)	1126 (31)	1065 (28)	1107 (32)	1040 (30)	1115 (30)	1043 (27)
SDNN (ms)	37 (3)	36 (3)	36 (2)	34 (3)	34 (3)	30 (3)
ln SDNN	3.55 (0.07)	3.50 (0.08)	3.55 (0.06)	3.48 (0.07)	3.42 (0.09)	3.33 (0.08)†
LF (ms ² /Hz)	384 (144)	275 (72)	211 (35)	195 (42)	303 (76)	297 (91)
ln LF	5.03 (0.21)	5.07 (0.18)	5.13 (0.15)	5.16 (0.20)	5.16 (0.23)	5.14 (0.21)
LF nu	37 (4)	36 (4)	37 (4)	44 (5)	42 (5)	49 (4)
HF (ms ² /Hz)	456 (106)	365 (69)	322 (70)	262 (83)	331 (83)	166 (47)
ln HF	5.59 (0.21)	5.37 (0.22)	5.33 (0.19)	4.80 (0.24)*†	5.28 (0.22)	4.57 (0.21)*†
HF nu	49 (4)	46 (4)	46 (4)	41 (5)	45 (5)	29 (3)*†
HF c	0.23 (0.01)	0.23 (0.01)	0.24 (0.01)	0.22 (0.01)	0.27 (0.01)†	0.29 (0.02)‡

Values are means (SEM).

*p < 0.05 between treatments; †p < 0.05 v rest in supine position; ‡p < 0.05 v rest in supine position and head up tilt.

SDNN, standard deviation of all normal RR values; LF, low frequency power; HF, high frequency power; ln, natural logarithm; nu, normalised unit; HF c, centre frequency of the high frequency power.

Table 4 Ventilation and gas exchanges during exercise

	Rest		50 W		Peak exercise	
	Atenolol	Metoprolol CR	Atenolol	Metoprolol CR	Atenolol	Metoprolol CR
$\dot{V}_i$ (l/min)	10.4 (0.5)	9.9 (0.4)	24.7 (0.9)	25.4 (1.2)	41.3 (1.8)	43.2 (1.7)
$\dot{V}_{O_2}$ (ml/min)	260 (10)	257 (11)	933 (26)	942 (24)	1414 (60)	1436 (56)
$\dot{V}_{CO_2}$ (ml/min)	230 (10)	221 (10)	797 (26)	817 (26)	1356 (73)	1433 (60)

$\dot{V}_i$, ventilation; $\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{CO_2}$, carbon dioxide production.

peak exercise was significantly lower with atenolol. Consistent with the results of others,²³ we did not find a significant difference in the CNS related symptoms between the two treatments, indicating that a higher degree of β_1 blockade in the CNS is not associated with a worsening of the quality of life. Our data indicate that atenolol 50 mg once daily prevents stress induced sympathetic activation and vagal withdrawal more effectively than metoprolol CR 100 mg once daily in patients shortly after an acute myocardial infarct. Since the concentration of atenolol in the CNS is lower than that of metoprolol,²⁴ the differences between treatments must be due to a greater peripheral β_1 adrenergic blockade with atenolol. This finding was unexpected as previous studies in healthy subjects²² and in patients with mild to moderate essential hypertension²³ have shown that metoprolol CR 100 mg once daily and atenolol 50 mg once daily attain the same degree of β_1

adrenergic blockade (as assessed by the percentage reduction in exercise induced tachycardia achieved with either agent at these doses). It should be noted, however, that the two agents have different pharmacokinetic properties: atenolol (50 mg once daily) achieves higher plasma concentrations and a more pronounced β_1 adrenergic blockade than metoprolol CR (100 mg once daily) two to four hours after dose intake, while between eight and 24 hours after intake the effects of the two drugs are equivalent.²² Since our patients were studied either at noon or late in the afternoon, we evaluated whether time after drug intake was a significant factor in determining the difference between treatments. We found that atenolol was more effective than metoprolol CR in blunting the autonomic response to stress and in reducing exercise heart rate both at the time of its peak concentration and 10 to 12 hours after dose intake.

Figure 3 Ratios between the low frequency (LF) and high frequency (HF) power of the RR interval variability at rest in the supine position, head up tilt, and mental stress during treatment with atenolol (50 mg once daily) or metoprolol CR (100 mg once daily). *p < 0.05 between treatments, p < 0.05 from rest.

HYDROPHILIC v LIPOPHILIC β BLOCKERS IN ISCHAEMIC HEART DISEASE

The majority of long term trials of the use of β blockers in postmyocardial infarction patients have involved lipophilic agents.¹ The analysis of pooled data, however, indicates that hydrophilic β blockers might be equally effective in improving prognosis, although the small size of the trials in which they have been involved makes it difficult to evaluate their beneficial effect accurately.¹ Furthermore, the largest long term trial of hydrophilic β blockers in postmyocardial infarction patients employed sotalol, an agent that combines β blocking properties with a class III antiarrhythmic effect.²⁵ Although this trial showed a significant reduction in reinfarction rate and an 18% decrease in mortality, the latter might have been adversely affected by the potential proarrhythmic effect of this agent.²⁶

Crossover studies comparing treatment with atenolol and metoprolol have shown that both

Table 5 Time effects after myocardial infarction

	Period I	Period II	Period III
24 Hour RR interval variability			
RR means (ms)	1047 (33)	1015 (28)	1063 (39)
SDNN (ms)	158 (9)	185 (31)	154 (9)
ln ULF	9.88 (0.12)	9.84 (0.13)	9.83 (0.13)
ln VLF	7.27 (0.18)	7.34 (0.14)	7.27 (0.16)
ln LF	6.49 (0.18)	6.49 (0.16)	6.38 (0.19)
ln HF	6.06 (0.15)	5.86 (0.18)	5.75 (0.19)
Short term RR interval variability			
<i>Supine rest</i>			
RR mean (ms)	1108 (26)	1100 (32)	1078 (29)
SDNN (ms)	34 (2)	40 (3)	33 (2)
LF/HF ratio	1.01 (0.21)	1.32 (0.22)	1.63 (0.39)
<i>Head up tilt</i>			
RR mean (ms)	1071 (29)	1073 (32)	1053 (30)
SDNN (ms)	36 (2)	35 (3)	34 (2)
LF/HF ratio	2.12 (0.49)	1.86 (0.46)	2.08 (0.59)
<i>Mental stress</i>			
RR means (ms)	1060 (23)	1084 (31)	1092 (31)
SDNN (ms)	30 (2)	31 (3)	33 (2)
LF/HF ratio	1.66 (0.36)	2.14 (0.49)	2.06 (0.54)
<i>Exercise test</i>			
Exercise duration (min)	9.60 (0.54)	10.40 (0.57)	10.60 (0.62)*
Maximum work load (W)	93 (3.5)	98 (3.8)	99 (4.1)*
Peak $\dot{V}O_2$ (ml/min)	1396 (58)	1462 (61)	1505 (63)*
BRS (ms/mm Hg)	9.8 (0.86)	11.5 (1.24)	12.2 (1.84)
Noradrenaline (pg/ml)	499 (66.2)	478 (39.3)	483 (48.4)
Adrenaline (pg/ml)	0.424 (0.063)	0.429 (0.058)	0.603 (0.097)

Values are means (SEM).

* $p < 0.05$ between periods I and III.

SDNN, standard deviation of all normal RR values; ULF, ultra low frequency power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; ln, natural logarithm; BRS, baroreflex sensitivity; $\dot{V}O_2$, oxygen uptake.

β_1 blockers are equally effective in increasing 24 hour RR variability in patients with ischaemic heart disease.^{9, 27} In patients with severe angina ($n = 18$), however, indices of cardiac vagal activity during the daytime tended to be higher during treatment with atenolol (100 mg once daily) than with metoprolol CR (200 mg once daily).²⁷ Likewise, consistent with our results, Tuininga *et al*⁹ reported a significantly lower 24 hour mean heart rate during treatment with atenolol (100 mg once daily) as compared to metoprolol CR (200 mg once daily) in patients three to 12 months after myocardial infarction. Unlike us, however, they did not find significant differences in peak exercise heart rate and in the LF/HF ratio during mental performance tasks (although there was a tendency for these variables to be lower during treatment with atenolol). This might be due to the different time after myocardial infarction in which the patients were studied, or to differences in the exercise and mental task protocols. In particular, while the mental performance task used by Tuininga *et al*⁹ was essentially a mental work test, the one used by us, by including an element of competition, was also an emotional stressor. Consistent with this, while they reported an increase in HF power during the mental performance task, we observed a reduction in HF (both in absolute and in normalised units) with our mental stress that was statistically significant only during treatment with metoprolol CR (fig 2, table 3). Furthermore, in our study β_1 adrenergic blockade with atenolol was associated with a significantly higher HF power during daytime activity (table 2), mental stress, and head up tilt (table 3, fig 2) when compared with metoprolol CR.

While both metoprolol CR and atenolol have been shown to increase RR variability in patients with ischaemic heart disease,^{9, 27} they appear to have no effect on baroreflex sensitivity.²⁸ As with all measurements taken at rest in the supine position, we found no difference in baroreflex sensitivity with the two β_1 blockers (table 1). However, it would have been interesting to ascertain whether this would have held true during mental stress.

TIME COURSE OF RECOVERY OF RR INTERVAL VARIABILITY AND BAROREFLEX SENSITIVITY AFTER MYOCARDIAL INFARCTION

Bigger *et al*¹¹ have shown that four weeks after myocardial infarction, frequency domain measures of 24 hour RR variability are one third to one half those found in age matched healthy subjects. They also found that these measures increase significantly with time (though they never reach normal values), and the recovery is generally complete three months after myocardial infarction.¹¹ Although our patients were studied on average one to four months after myocardial infarction, we saw no significant changes in frequency domain measures of 24 hour RR variability with time. Treatment with β blockers or the exclusion of patients with congestive heart failure, or both, might be responsible for this discrepancy since a study of uncomplicated post-myocardial infarction patients treated with atenolol similarly found that the pNN50 (a time domain measure of 24 hour RR variability that is strongly correlated with HF power) did not change significantly 42 to 140 days after myocardial infarction.²⁹ Conversely, in our patients baroreflex sensitivity tended to increase during the study (table 5). This is consistent with the findings of Schwartz *et al*¹⁰ who found that baroreflex sensitivity recovers towards normal values two to five months after an uncomplicated myocardial infarct. Likewise, exercise duration and peak $\dot{V}O_2$ increased with time. Since patients were exercised only once before randomisation, this could reflect an habituation to the test rather than a real improvement in exercise performance.³⁰

SUMMARY

Our study showed that in patients four to six weeks after myocardial infarction, atenolol 50 mg once daily achieved a greater β_1 adrenergic blockade than metoprolol CR 100 mg once daily. This was associated with a higher HF power and a lower LF/HF ratio during day time activity, head up tilt, and mental stress. When taken together with the results by Tuininga *et al*,⁹ our findings indicate that peripheral rather than central β adrenergic blockade plays an important part in preventing stress induced cardiac vagal withdrawal. In addition we have shown that the results of dose-response studies with β adrenergic blockers in healthy or hypertensive subjects may not apply to patients early after an acute myocardial infarction. This may be due to the effect of concomitant treatment with nitrates and aspirin on the hepatic metabolism of metoprolol. Indeed, unlike atenolol, metoprolol is

extensively metabolised in the liver by enzymes belonging to the cytochrome P-450 system.³¹ This metabolic pathway is also involved in the bioactivation of organic nitrates and can be induced by acetylsalicylic acid.^{32,33}

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