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Evaluation of antiarrhythmic effect of metoprolol treatment after acute myocardial infarction: relationship between treatment responses and survival during a 3-year follow-up

G. OLSSON AND N. REHNQVIST

Department of Medicine, Karolinska Institutet, Danderyd Hospital, S-182 88 Danderyd, Sweden

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Three hundred and one patients were randomized to 3 years double-blind postinfarction treatment with metoprolol ($N=154$) 100 mg b.i.d. or matching placebo ($N=147$). Repeated 6 h electrocardiograms were performed pretreatment and after 3 days, 1 month, 6, 12, 24 and 36 months treatment. There were no significant differences in pretreatment ventricular arrhythmia in the two groups. In the placebo group there was an increase both in complexity of the arrhythmia ($P<0.001$) and frequency of premature ventricular complexes (PVCs) ($P<0.001$) by time. These increases were blunted by metoprolol treatment.

Treatment effect on mortality was similar in patients both with and without complex PVCs before treatment. In a retrospective analysis, the outcome of patients with an initial PVC frequency of >1 PVC h^{-1} was evaluated. In metoprolol treated patients in whom the arrhythmia frequency was reduced by $>75\%$ after three days of treatment, mortality was lower as compared to those metoprolol treated patients who did not show this treatment response (3% vs 28%, $P=0.013$). Mortality in placebo treated patients with frequent PVCs was 24%.

In conclusion, chronic metoprolol treatment after acute myocardial infarction blunts the naturally occurring increase of PVC frequency and PVC complexity by time. Patients with frequent PVCs in the early postinfarction phase who respond to metoprolol with $>75\%$ reduction of the arrhythmias may have an excellent prognosis. However, this latter hypothesis has to be further tested in a prospective study.

Introduction

Most deaths in ischaemic heart disease are sudden and due to ventricular fibrillation[1]. Following the institution of coronary care units[2] and out-of-hospital resuscitation[3] it has become evident that ventricular fibrillation is treatable and not always the result of an inexorable culmination of advanced coronary atherosclerosis. As a consequence, mortality in acute myocardial infarction in hospitalized patients has been reduced by treatment in coronary care units[4]. However, mortality remains high after discharge from hospital. Several factors such as the age of the patient[5,6], left ventricular failure[7–9], indices of residual myocardial ischaemia[8,10] and electrical instability of the heart[11–16] have been shown to carry prognostic information on mortality after a myocardial infarction. Accordingly, considerable efforts have been made to reduce postinfarction mortality by various interventions[17,18]. Since most deaths after myocardial infarction are sudden[1], intervention with antiarrhythmic drugs has appeared logical. However, as reviewed by May *et al.*[17], postinfarction trials using phenytoin, procainamide, disopyramide, mexiletine, aprindine and tocainide have failed to show beneficial effects on mortality. These negative results may in part be explained by the small numbers of patients included in these trials[19]. Untoward effects of treatment may, however, also have influenced the prognosis negatively[20–23].

During the mid 1970s three studies using the beta-blockers alprenolol[24,25] and practolol[26], showed significant reductions of sudden deaths during 1–2 years after myocardial infarction.

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Address for correspondence: Gunnar Olsson, M.D., Department of Medicine, Karolinska Institutet, Danderyd Hospital, S-182 88 Danderyd, Sweden.

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These positive results inspired us to plan the present study. While the study was under progress, three large well performed beta-blocker studies[27–29] have convincingly shown that cardiac mortality can be reduced by some beta-blocking agents. Additional support for this view has been reported from other beta-blocker studies[30–33], including our own in which we have shown a beneficial effect on sudden death and cardiac mortality among high risk patients[34]. The primary aims of the study were to prospectively evaluate the influence of chronic metoprolol treatment on ventricular arrhythmias and performance on exercise tests. Secondly, therapeutic effects on mortality and morbidity in relation to predefined risk groups were studied.

In previous papers we reported the effects of metoprolol on exercise capacity[35] and on chronic ventricular arrhythmias during the first year after myocardial infarction[36]. This presentation deals with the results concerning ventricular arrhythmias from the entire three year treatment period as well as therapeutic considerations concerning treatment response in relation to survival.

Material and methods

Between May 1976 and December 1980, 301 consecutive patients who had suffered an acute myocardial infarction were entered in a study of double-blind treatment with 100 mg b.i.d. metoprolol (120 men, 34 women) and placebo (122 men, 25 women). The first 221 patients were treated in the coronary care unit at the Seraphimer Hospital in Stockholm from May 1976 until the hospital closed in December 1979. From February 1980, 80 consecutive patients were included from the coronary care unit at Danderyd Hospital.

The inclusion criteria for the study were:
(1) age below 70 years and domicile in the catchment areas;
(2) admission within 48 hours of onset of symptoms and development of an acute myocardial infarction, i.e. fulfilling two of the following: severe chest pain, typical electrocardiographic changes, typical enzyme pattern;
(3) sinus rhythm without bundle branch block.

Exclusion criteria were: systolic blood pressure less than 100 mmHg, severe cardiac failure not responding to conventional treatment with digitalis and diuretics, severe intermittent claudication, bronchial asthma, apparent need for beta-adrenoceptor blockade (i.e. severe angina pectoris or symptomatic ventricular arrhythmias responding to beta-blockade), other major illness, unwillingness to participate.

Four days before discharge, i.e. 7 to 14 days after admission, a 6 hour electrocardiogram[37] with telemetry was recorded on paper (from 2.00 to 5.00 am and 9.30 am to 12.30 pm). After this investigation the patients were stratified according to type of ventricular arrhythmia [6 groups: no PVCs, uniform PVCs, multiform PVCs (i.e. initial and mean axis of QRS-complex and the T-wave differed), paired PVCs, R-on-T PVCs or $\geqslant 3$ consecutive PVCs of rate >100 beats min^{-1}], estimated size of infarction (maximum thermostable lactate dehydrogenase <20 or $\geqslant 20\,\mu kat\,l^{-1}$) and age (less than 65 years or 65–69 years).

The patients in each stratification group were immediately thereafter randomly assigned to double-blind treatment with metoprolol (100 mg b.i.d.) or placebo for three years. During the initial three days while the patients were still in hospital they received half a tablet t.i.d. thereafter 1 tablet b.i.d. After three days of therapy (i.e. the first day on 100 mg b.i.d.) another identical 6 hour electrocardiogram was recorded on paper. 6 hour follow-up electrocardiograms from the same 6 hour periods as mentioned above were repeated after 1, 6, 12, 24 and 36 months of therapy. In the first 170 patients the 6 and 12 months recordings were performed by telemetry on paper while the patients were in hospital. According to changes in the routines due to the closing of the Seraphimer Hospital, the remaining 6 and 12 months electrocardiograms as well as all 1 month, 24 and 36 months recordings were obtained from ambulatory patients using an Oxford Medilog 1 tape recorder (two channel). The patients were recorded during 24 hours, but only the 6 hours mentioned above were analysed. In patients with uninterpretable recordings, a new recording was performed or the recording was classified as missing data. The tapes were manually evaluated by specially trained nurses who used the Oxford Medilog semi-automatized analysing system or Oxford fibreoptic prints-outs. Both total number of PVCs per registration and the complexity of PVCs were evaluated. Multiform, R-on-T and repetitive PVCs have been denoted complex PVCs.

In the evaluation of anti-arrhythmic response to metoprolol treatment we evaluated patients with more than 1 PVC per hour. Reduction of the PVC frequency by more than 75% in these patients was registered as a positive response[36].

Clinical investigations were performed and blood samples taken for determination of standard biochemistry at 1, 3, 6, 12, 18, 24, 30 and 36 months after the myocardial infarction. These results have been given elsewhere[38].

All patients gave their informed consent to participate in the study, which was approved by the local ethical committee. After completion of the three year treatment periods, the study treatment was withdrawn according to a special protocol[39].

In the statistical analysis the chi-square test or Fisher's exact t-test was used for comparisons of proportions. Due to the lack of complete ECG recordings in surviving patients at each intended registration, analysis of variance was not applied in the comparisons of arrhythmias in order to minimize the loss of obtainable information (i.e. those patients with missing ECG data on one occasion). PVC numbers/registration were compared within each treatment group by Wilcoxon matched pairs test. Furthermore, the mean ranks of the difference in PVC frequency (PVC_t–PVC_0, t = time, 0 = pretreatment) in the two treatment groups have been compared by the Mann–Whitney test. All statistical analyses were performed in a two-tailed fashion. All data presented are according to the intention to treat principle if not otherwise stated.

Results

A complete report on the clinical characteristics of the patients have been reported elsewhere[34]. Table 1 gives a summary of the most important features. Antiarrhythmic drugs were used in a few cases and only to prevent symptomatic arrhythmias (Table 2). During the three year period there were 31 deaths (29 cardiac) and 25 deaths (20 cardiac) in the placebo and metoprolol groups, respectively (NS). Twenty-one and 9 of the cardiac deaths in the placebo and metoprolol groups ($P<0.05$) were classified as sudden (i.e. death within 2 hours from onset of symptoms). Thirty-one and 18 patients in the placebo and metoprolol groups ($P<0.05$), respectively, suffered a non-fatal reinfarction during the follow-up. 35 and 38 patients in the placebo and metoprolol groups, respectively, were withdrawn due to side effects. Reasons for withdrawal of the study treatment are shown in Table 3. Of those patients still alive after 36 months, 88 and 98 surviving patients in the placebo and metoprolol groups, respectively, were

Table 1 Patient characteristics

Variables	P ($N=147$)	M ($N=154$)
Age (years)	59·2 ± 7·2	60·1 ± 6·7
LD_t max (μkat l^{-1})	19·6 ± 13·7	19·8 ± 14·0
Heart volume (ml m^{-2})	470 ± 88	471 ± 89
Site of infarction (%)		
anterior	51	44
inferior	31	38
unknown	18	18
VF in the CCU (%)	2·7	3·2
VT in the CCU (%)	45·9	36·4
Pulmonary congestion in CCU (%)	66·7	64·7
Complex PVCs at randomization (%)	33	38
Treatment at discharge (%)		
digitalis	24·0	23·4
diuretics	47·9	41·6
antiarrhythmic agents	6·2	5·8
Previous infarction (%)	19·7	20·8
Non-transmural infarction (%)	27·8	25·3
Smokers (%)	60·3%	53·2%

LD_t max — maximum thermostable lactate dehydrogenase; VF — ventricular fibrillation; VT — ventricular tachycardia; CCU — coronary care unit; M — metoprolol group; P — placebo group.

Table 2 Antiarrhythmic treatment during follow-up

	P ($N=147$)	M ($N=154$)
1 month		
Beta-blockade (open)	2	1
Verapamil	4	—
Disopyramide	—	2
Quinidine	—	1
3 months		
Beta-blockade	4	1
Verapamil	5	1
Disopyramide	—	1
Quinidine	—	1
Procainamide	1	—
6 months		
Beta-blockade	2	1
Verapamil	3	1
Quinidine	1	1
12 months		
Beta-blockade	4	2
Verapamil	6	—
Disopyramide	—	1
Quinidine	1	2
18 months		
Beta-blockade	11	4
Verapamil	8	2
Disopyramide	—	1
Quinidine	—	1
24 months		
Beta-blockade	10	6
Verapamil	7	4
30 months		
Beta-blockade	11	7
Verapamil	7	3
36 months		
Beta-blockade	11	7
Verapamil	9	4
Disopyramide	—	1

P — placebo, M — metoprolol.

Table 3 Withdrawals during the follow-up

Attributed cause	Withdrawals		
	P		M
Uncontrolled angina	16	*	6
Heart failure	1	*	7
Symptomatic bradycardia	1		1
Symptomatic arrhythmia	4		2
Hypotension	—		2
Intermittent claudication	1		5
Asthma	1		2
Nightmares	1		2
Suspected allergic reactions	3		2
Impotence	—		2
Fatigue	1		1
Unwillingness to participate	6		6
Total	35		38

P — placebo, M — metoprolol, $*P \leqslant 0{\cdot}05$.

Table 4 Treatment with digitalis and diuretics (%)

	P ($N=147$)	M ($N=154$)
Digitalis		
1 month	33	32
3 months	37	33
6 months	39	35
12 months	44	34
18 months	45	34
24 months	43	34
30 months	37	32
36 months	35	31
Diuretics		
1 month	59	49
3 months	62	52
6 months	57	53
12 months	57	51
18 months	55	48
24 months	50	49
30 months	46	44
36 months	46	44

P — placebo, M — metoprolol.

still on the study treatment. The percentages of patients treated with digitalis and diuretic are shown in Table 4.

Mean PVC number pretreatment was 75 ± 278 (standard deviation) and 238 ± 1066 in the placebo and metoprolol groups (NS), respectively. In the placebo group there was a progressive increase in PVCs with time (184 ± 490 at 36 months, $P < 0{\cdot}001$). This increase was not found in the metoprolol group (83 ± 251, NS, Fig. 1). In a comparison of the PVC frequency between the two groups, the mean rank of $PVC_t - PVC_0$) was always significantly lower in the metoprolol group (Table 5). The pretreatment proportions of patients with complex PVCs were 33% and 38% in the placebo and metoprolol groups (NS), respectively. During the follow-up there was a continuous and significant increase in the proportion of patients with complex PVCs in the placebo group with time

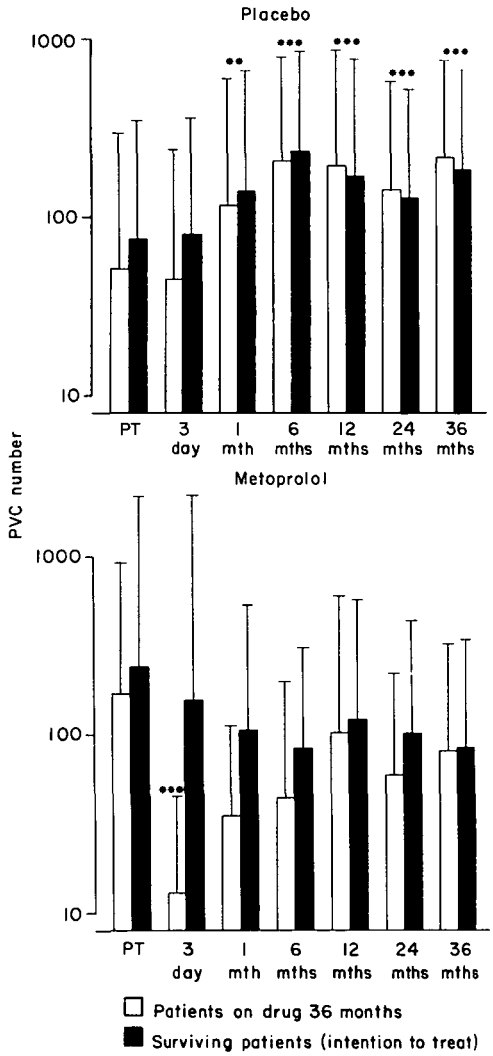

Figure 1 Mean number of PVCs during the follow-up. *** = $P<0{\cdot}001$. Patient numbers and abbreviations as in Table 5.

(54% at 36 months, $P<0{\cdot}001$). The increase in the placebo group was significant already after 6 months treatment. In the metoprolol group no significant change in the proportion of patients with complex PVCs was seen during the follow-up (42% at 36 months). In patients who continued on study treatment a significantly larger proportion of the placebo treated patients showed complex PVCs at three years as compared to metoprolol treated patients (55% *vs* 38%, $P<0{\cdot}05$). The proportion of patients with complex PVCs during follow-up according to presence or absence of complex PVCs pretreatment is shown in Fig. 2.

Table 5 Mean rank of PVC_t–PVC_0 in the two treatment groups during the follow-up

Time		*N*	Mean rank	*P*
3 d	P	145	171	
	M	151	127	<0·001
1 m	P	124	138	
	M	132	119	=0·04
6 m	P	127	146	
	M	132	115	<0·001
12 m	P	124	140	
	M	134	120	=0·03
24 m	P	105	120	
	M	113	100	=0.019
36 m	P	107	127	
	M	120	103	=0·006

d — days, m — months, P — placebo, M — metoprolol.

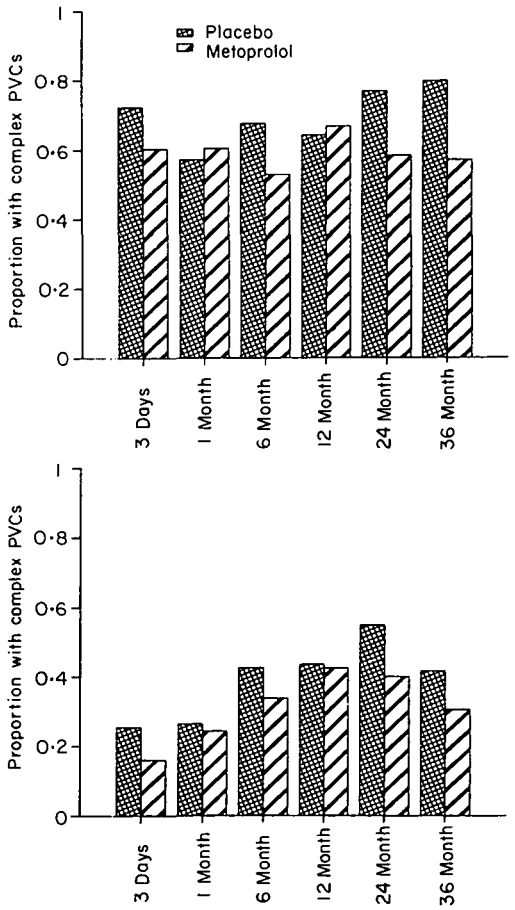

Figure 2 Proportion of patients with complex PVCs during the follow-up according to presence (upper panel) or absence (lower panel) of complex PVCs at randomization.

Table 6 Cardiac mortality according to arrhythmia pattern

Placebo		Metoprolol		
≤ 1 PVC h^{-1} ($N=96$)	>1 PVC h^{-1} ($N=51$)	≤ 1 PVC/h ($N=91$)	>1 PVC/h, R ($N=34$)	>1 PVC/h, NR ($N=29$)
17 (18%)	12 (24%)	11 (12%)	1 (3%)	8 (28%)

R — responder (i.e. $\geq 75\%$ reduction of PVC frequency after 3 days therapy), NR — non responders.

Cardiac mortality was 22·9% and 15·5% in the placebo and metoprolol groups, respectively, in patients with complex PVCs pretreatment (NS). The corresponding figures for patients without complex PVCs were 18·2% and 11·5% (NS). An extended report on mortality according to complexity of PVCs has been presented elsewhere[34].

On the initial 6 hour electrocardiogram before start of therapy, 51 and 63 patients in the placebo and metoprolol groups, respectively, showed more than 1 PVC per hour. Sixteen patients in the placebo group as compared to 34 in the metoprolol group ($P=0·026$) showed more than 75% reduction of PVC frequency after 3 days of treatment. Mortality data in patients with initial PVC frequency >1 PVC h^{-1} and therapy response are given in Table 6. In metoprolol treated patients with a PVC frequency >1 PVC h^{-1} the mortality was 3% *vs* 28% in responders and non-responders, respectively ($P=0·013$).

Discussion

Complex ventricular arrhythmias detected in the post-coronary care unit period have been shown to carry an independent prognostic weight for subsequent mortality and morbidity[11–16]. Similar to our findings, previous reports have shown that 36%–42% of predischarge long-term electrocardiographic recordings contain complex PVCs[13,16,37]. The lack of influence on mortality of true antiarrhythmic agents is in contrary to the beneficial effects of beta-adrenoceptor antagonists[17]. The most prominent antiarrhythmic effect of metoprolol shown in this study was the blunting of the naturally occurring increase in PVC complexity and PVC frequency by time, which is in accordance with a previous study using propranolol[40]. In a previous study chronic postinfarction mexiletine therapy was shown to blunt this increase during the initial 4 months[41]. However, no concomitant effect on mortality was observed. These results may indicate that reduction in postinfarction mortality by beta-blockers is not due to a pure and classical anti-arrhythmic effect.

With regard to the change in arrhythmias by time and mortality and morbidity outcome of our patients, it is tempting to speculate that the arrhythmias serve as markers of the severity of the underlying disease. This would be in accordance with previous studies[42,43] which showed crude correlations between ventricular arrhythmias and the severity of the ischaemic heart disease.

When evaluating repeated long-term electrocardiographic recordings, the spontaneous variability of ventricular arrhythmias must be considered. Our method has been evaluated and has shown a good reproducibility regarding group evaluations of PVC frequency and PVC complexity[38]. This is in accordance with findings by Winkle[44]. We therefore consider the method used for group comparisons as relevant. However, in the evaluation of antiarrhythmic efficacy of a specific treatment in the individual patient, the influence of spontaneous variability of the arrhythmia is greater. According to previous studies a 65%–83% reduction in PVC frequency during a 24 hour monitoring period in the individual patient is required in 'stable patients' with frequent PVCs to establish a significant effect of treatment[45,46]. For shorter monitoring periods this figure is higher[46]. In this study the monitoring periods and patient characteristics differ from those in these earlier studies on PVC frequencies[45–47].

Probably the 16 patients in the placebo group showing more than 75% reduction of PVC frequency after 3 days placebo treatment is an expression of large intra-individual spontaneous

variability. However, the proportion of patients in the metoprolol group with this kind of reduction of PVC frequency was larger than that in the placebo group, indicating that the initial arrhythmia reduction can be ascribed to the active treatment with metoprolol. The different mortality outcome in metoprolol treated patients with frequent PVCs with and without PVC reductions after 3 days therapy, suggests that the acute treatment response concerning ventricular arrhythmias is of clinical relevance. Thus, even if our method for detection of arrhythmias and treatment response may be insufficient for a careful evaluation of pure anti-arrhythmic effects, the method seems to have the ability to identify a population with a high probability for survival (i.e. those with a positive anti-arrhythmic response to metoprolol treatment) after myocardial infarction. The finding concerning treatment response to metoprolol and survival was obtained in a subgroup analysis and the findings must be interpreted with caution.

The different mortality in the three different subgroups of metoprolol treated patients (patients with a PVC frequence of $\leqslant 1$ PVC/hour, non-responders and responders with >1 PVC h^{-1}), may indicate that several different mechanisms are involved in cardiac death after myocardial infarction and that metoprolol treatment may influence mortality differently in the various subpopulations of post-infarction patients. In patients with a high PVC frequency who are responders, an anti-arrhythmic effect of metoprolol may be important. Whether the observed anti-arrhythmic effect is primarily due to pure anti-arrhythmic actions or secondary due to diminished myocardial ischemia is unclear. However, it seems most likely that an anti-ischemic action is involved as true anti-arrhythmic drugs do not influence mortality despite reduction of arrhythmia[41].

Metoprolol and propranolol have been shown to decrease the incidence of ventricular fibrillation during acute myocardial infarction in previous studies[48,49]. As the underlying mechanism of ventricular fibrillation is not entirely understood, it is difficult to relate these findings to the present results.

In conclusion, during a 3 year period after acute myocardial infarction there is an increase of both PVC frequency and PVC complexity. These increases are blunted by chronic metoprolol treatment. Patients with more than 1 PVC h^{-1} in the post coronary care unit phase, in whom metoprolol treatment results in more than a 75% reduction of PVC frequency seem to have an excellent prognosis during a subsequent 3 year treatment period. However, the latter finding has to be confirmed in further prospective studies.

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