therapeutic role in the management of oedema and hypertension in chronic renal disease.

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Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction

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Abstract

The effect of intravenous atenolol on ventricular arrhythmias in acute myocardial infarction was assessed in 182 patients admitted within 12 hours of the onset of chest pain. Ninety-five patients were randomised to receive 5 mg intravenous atenolol followed immediately by 50 mg by mouth and 50 mg 12 hours later, then 100 mg daily for 10 days; 87 patients served as controls. The treated patients had significantly fewer ventricular extrasystoles; 58 control patients (67%) had R-on-T

extrasystoles compared with only 25 treated patients (26%) ($2p < 0.0001$); repetitive ventricular arrhythmias were detected in 64 control patients (74%) and 55 treated patients (58%) ($2p < 0.05$). Heart rate was significantly reduced from 77 ± 1 beats/min at entry to 65 ± 1 beats/min ($2p < 0.001$) in the first hour after intravenous atenolol, and in addition the rate was significantly different from that in the control group. There was no difference in the incidence of heart failure, but fewer patients in the treated group received other antiarrhythmic agents or digoxin.

These results show that early intravenous atenolol prevents ventricular arrhythmias in suspected acute myocardial infarction.

Introduction

Beta-adrenergic-blocking drugs reduce the incidence, frequency, and severity of ventricular arrhythmias after experimental coronary artery occlusion,¹⁻³ and an increase in the ventricular fibrillation threshold associated with myocardial ischaemia has

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also been shown in dogs pretreated with atenolol.³ The increase in circulating catecholamine values in patients with acute myocardial infarction is associated with an increase in the severity of cardiac arrhythmias,⁴⁻⁶ and in several non-randomised clinical studies intravenous beta-blocking agents were effective in the treatment of some of these arrhythmias.⁷⁻¹¹ Randomised controlled trials, however, have shown no benefit in reducing ventricular arrhythmias in the first 24 hours after acute myocardial infarction.^{12,13} These disappointing results may be due to (a) the use of an initial oral dose of the trial drug leading to delay in achieving effective beta-blockade; (b) the inclusion of patients late after the onset of chest pain, at a time when ventricular arrhythmias have considerably decreased; and (c) the small numbers of patients actually included in the arrhythmia studies.

The main aim of this study was to assess the antiarrhythmic effect of an initial intravenous dose of atenolol followed by oral treatment, when administered early in the course of acute myocardial infarction when ventricular arrhythmias are prevalent. Other end points were morbidity and infarct size, of which a preliminary report has been published.¹⁴

Patients and methods

All patients admitted to the coronary care units of the John Radcliffe Hospital, Oxford, and to the Regional Cardiac Centre, Wythenshawe Hospital, Manchester, presenting with chest pain suggestive of acute myocardial infarction within the previous 12 hours were considered eligible for the trial whether or not electrocardiographic abnormalities were already present. Patients were considered unsuitable for beta-blockade if the heart rate was less than 40 beats/min, if the systolic blood pressure was below 90 mm Hg, if second-degree or third-degree heart block was present, or if heart failure requiring digoxin or more than 80 mg of frusemide was present. Patients already taking a beta-blocker on admission or requiring immediate beta-blockade were not eligible for study. From October 1978 to August 1981, 479 patients were randomised, and 24-hour electrocardiographic recordings were made on 224 of these, the patients being selected at random according to availability of tape recorders. Thirty-eight of these tapes were blank due to faulty cable, and four others had less than three hours of recording, leaving 182 tapes for the final analysis. At entry an electrocardiogram was taken and patients allocated at random to a treatment or control group according to instructions kept in sealed envelopes. Patients randomised to treatment received 5 mg atenolol intravenously (slowly over five minutes) followed by an oral dose of 50 mg immediately and 12 hours later, and 100 mg daily from the second to 10th days. Control patients did not receive placebo.

Data are presented as follows: all patients randomised (n=182); patients who had electrocardiographic signs of acute myocardial infarction at entry¹⁴ (n=121); and patients who were admitted with characteristic chest pain but without definite electrocardiographic changes (threatened infarction, n=61).¹⁴ In the results section we present data from all patients randomised; figures 1 to 4 give further detailed analysis of subgroups.

Recording and analysis of ventricular arrhythmias—Twenty-four-hour electrocardiographic recordings were obtained in 182 patients by means of the Oxford Medilog Recorder I or II and analysed by the Oxford DA-II ECG Analyser¹⁵ or the Reynolds High Speed Analyser¹⁶ at 60 times real time. The QRS triggering and detection of ventricular extrasystoles were continuously checked visually by one of us (PR). This was supplemented by careful counts from printouts of periods during which extrasystoles were very frequent. Hourly counts of isolated extrasystoles and episodes of repetitive ventricular arrhythmias were made. The following definitions were used: couplets, two consecutive ventricular extrasystoles with an R-R interval ≤ 500 ms; triplets, three consecutive ventricular extrasystoles with the two cycles measuring ≤ 1000 ms and a rate ≥ 120 beats/min; ventricular tachycardia, four or more consecutive ventricular extrasystoles with a rate ≥ 120 beats/min; and primary ventricular fibrillation, ventricular fibrillation occurring in the absence of shock or cardiac failure.

Electrocardiographic measurements—The following electrocardiographic measurements were made for both isolated ventricular extrasystoles and repetitive ventricular arrhythmias: (a) coupling interval (R-R) of ventricular extrasystoles, the interval from the preceding sinus beat to the extrasystole; (b) Q-T interval, interval from the beginning of the QRS to the end of the T wave and according

to published criteria¹⁷; and (c) prematurity index of ventricular extrasystoles, relation between the coupling interval and the Q-T interval (R-R'/Q-T). R-on-T extrasystoles were defined as ventricular extrasystoles having a prematurity index ≤ 0.85 . The frequency of R-on-T ventricular extrasystoles per patient was assessed by counting the number of hours in which they were detected. The patients were matched for serum potassium concentrations on entry (mean $4.05 \pm \text{SEM } 0.07$ mmol(mEq)/l in controls, 4.02 ± 0.07 mmol/l in atenolol group; $2p > 0.50$) and at the end of the first 24 hours (4.27 ± 0.08 mmol/l in controls, 4.27 ± 0.05 mmol/l in atenolol group; $2p > 0.50$).

Statistical analysis—Standard *t* test for unpaired and paired data, χ^2 test, and Wilcoxon's rank sum test were used. All *p* values are two-tailed. All values are expressed as mean $\pm$ standard error of mean (SEM).

Results

Entry characteristics—Of 182 patients randomised, 95 received atenolol and 87 were allocated to the control group. The patients were matched for age, sex, systolic and diastolic blood pressures, heart rate, presence of heart failure on admission and previous medical history of myocardial infarct or diabetes mellitus, primary ventricular fibrillation before randomisation, prior antiarrhythmic treatment, and site of infarct based on the initial electrocardiogram. The mean time after the onset of chest pain to randomisation was similar in both groups—5.5 hours in the atenolol group and 5.1 hours in the control group (table 1).

TABLE 1—Entry characteristics. Mean values expressed $\pm$ SEM. (Percentages in parentheses)

	Atenolol (n=95)	Control (n=87)
Average age (range)	55.6 (32-73)	55.1 (26-75)
Sex:		
Male	85 (89)	69 (79)
Female	10 (11)	18 (21)
Systolic blood pressure (mm Hg)	140 ± 2	141 ± 2
Diastolic blood pressure	89 ± 1	89 ± 1
Heart rate (beats/min)	77 ± 1	75 ± 1
Heart failure	13 (14)	13 (15)
Previous myocardial infarction	15 (16)	10 (11)
Diabetes mellitus	4 (4)	3 (3)
Ventricular fibrillation	1 (1)	2 (2)
Antiarrhythmic drugs	5 (5)	2 (2)
Site of infarct*:		
Anterior	39 (41)	38 (44)
Inferior	43 (45)	38 (44)
Indefinite	12 (13)	10 (11)
Time from onset of chest pain (hours):		
<2	3 (3.2)	5 (5.8)
2-4	35 (36.8)	30 (34.5)
4-6	27 (28.4)	25 (28.7)
6-8	19 (20.0)	12 (13.8)
8-10	7 (7.4)	10 (11.5)
>10	4 (4.2)	5 (5.7)

*Notes lost for one patient in each group.

Heart rate was significantly reduced from 77 ± 1 beats/min at entry to 65 ± 1 beats/min in the first hour ($2p < 0.0001$) after atenolol, and this reduction was maintained throughout the 24-hour period; heart rate in the control group did not change significantly from the initial value (75 ± 1 v 74 ± 2 beats/min).

Ventricular extrasystoles and R-on-T ventricular extrasystoles—Since ventricular extrasystoles are not normally distributed in patients with acute myocardial infarction, the individual total values were transformed into logarithms to the base 10 and standard *t* tests for statistical analysis of the differences then applied.¹⁸ The total number of ventricular extrasystoles was reduced from a mean $\log_{10}$ of 2.12 ± 0.10 in the control group to 1.67 ± 0.09 in the atenolol group ($2p < 0.001$). A similar reduction was observed whether the patients had electrocardiographic evidence of acute myocardial infarction or "threatened infarction" at entry (fig 1). R-on-T ventricular extrasystoles were seen in 58 (67%) of the control patients compared with only 25 (26%) of the treated patients ($\chi^2 = 29.81$; $2p < 0.0001$) (fig 2). The frequency of R-on-T extrasystoles was reduced from 2.9 hours per patient in the control group to 0.8 hour per patient in the atenolol group ($z = -5.28$; $2p < 0.0001$) (fig 2).

Incidence of repetitive ventricular arrhythmias—There was a significant reduction in the incidence of couplets from 72% (63 patients) in the control group to 48% (46 patients) in the atenolol

group ($\chi^2 = 10.88$; $2p < 0.001$), and of triplets from 41% (36 patients) to 20% (19), respectively ($\chi^2 = 9.84$; $2p < 0.005$). The incidence of ventricular tachycardia was reduced from 44% (38 patients) in the control group to 33% (31) in the atenolol group ($\chi^2 = 2.35$; $2p < 0.20$).

FIG 1—Total number of isolated ventricular extrasystoles in first 24 hours after acute myocardial infarction. Treated patients had significantly fewer ventricular extrasystoles overall or whether subdivided into definite myocardial infarction or threatened infarction at entry. Values expressed as $\log_{10}$ mean $\pm$ SEM. All p values two-tailed (2p).

FIG 2—Top: Incidences of R-on-T ventricular extrasystoles in beta-blocker and control groups (prematurity index < 0.85). Bottom: Effect of treatment on frequency of R-on-T extrasystoles (No of hours/patient) in first 24 hours after acute myocardial infarction. All p values two-tailed (2p).

There was, however, a significant reduction in the incidence of ventricular tachycardia in patients admitted with threatened infarction from 34% (11 patients) in the control group to 7% (2 patients) in the treated group ($\chi^2 = 6.85$; $2p < 0.01$). There was a significant reduction in the incidence of repetitive ventricular arrhythmias as a whole from 74% (64 patients) in the control group to 58% (55) in the treated patients ($\chi^2 = 4.92$; $2p < 0.05$) (fig 3).

Frequency of repetitive ventricular arrhythmias—The total numbers of episodes of repetitive ventricular arrhythmias per patient were transformed to $\log_{10}$ in the two groups. There was a significant reduction in the mean $\log_{10}$ of couplets from 0.479 ± 0.05 in the control group to 0.241 ± 0.04 in the atenolol group ($2p < 0.001$), and the mean $\log_{10}$ for triplets from 0.117 ± 0.03 to 0.030 ± 0.01 , respectively ($2p < 0.02$). There was a reduction in the mean $\log_{10}$ for episodes of ventricular tachycardia from 0.127 ± 0.03 in the control group to 0.078 ± 0.02 in the atenolol group ($2p < 0.20$). There was a highly significant reduction in the total number of repetitive ventricular arrhythmias as a whole, from a mean $\log_{10}$ of 0.601 ± 0.06 in the control group to 0.327 ± 0.04 in the treated patients ($2p < 0.001$) (fig 4).

Ventricular fibrillation was observed in five control patients and in one patient in the atenolol group after randomisation ($2p < 0.10$).

FIG 3—Incidence (No of patients developing arrhythmia) of couplets, triplets, and ventricular tachycardia in first 24 hours after acute myocardial infarction. Treatment consistently reduced incidence of arrhythmias either isolated or as group (repetitive ventricular arrhythmias). All p values two-tailed (2p).

TABLE II—Ancillary treatment in coronary care unit after randomisation (Percentages in parentheses)

	Atenolol	Control	χ^2	2p
Antiarrhythmic drugs	13 (14)	24 (27)	5.42	< 0.025
Diuretics	30 (31)	32 (37)	0.55	> 0.50
Digoxin	2 (2)	9 (10)	5.43	> 0.025
Atropine	9 (9)	7 (8)	0.11	> 0.50
Temporary pacemaker	5 (5)	1 (1)	1.44	> 0.30

TABLE III—Cardiac events in hospital. (Percentages in parentheses)

	Atenolol	Control	χ^2	2p
Hospital mortality	5 (5.3)	11 (12.6)	3.08	< 0.10
Ventricular fibrillation	1 (1.0)	5 (5.7)	3.14	< 0.10
Hospital mortality and ventricular fibrillation*	6 (6.3)	15 (17.2)	5.31	< 0.025

*Patients who developed ventricular fibrillation but were discharged alive.

FIG 4—Frequency of repetitive ventricular arrhythmias in first 24 hours after acute myocardial infarction. Patients randomised to beta-blocker group had fewer episodes of repetitive arrhythmias irrespective of subgroup analysis. Note that the greatest effect is shown when these arrhythmias are analysed as groups (couplets, triplets, and ventricular tachycardia). Values expressed as $\log_{10}$ mean $\pm$ SEM. All p values two-tailed (2p).

Ancillary treatment after randomisation—There was a significant reduction in the use of other antiarrhythmic drug treatment in the atenolol-treated patients (such as lignocaine, disopyramide, mexiletine, or a combination of these—13 patients in the atenolol group, 24 in the control group). Fewer atenolol-treated patients required digoxin (2 v 9). No difference was found in the use of diuretics, atropine, or inotropic agents. One control patient and five treated patients had a temporary pacemaker inserted (table II).

Hospital mortality—Five patients in the treated group (5.3%) and 11 in the control group (12.6%) died in hospital. Six patients in the atenolol group and 15 in the control group either died or had ventricular fibrillation and were discharged alive ($\chi^2 = 5.31$; $2p < 0.025$) (table III).

Discussion

Our results show that intravenous atenolol followed by oral treatment significantly reduced the number of ventricular extrasystoles, the incidence and frequency of R-on-T extrasystoles, and the incidence and frequency of repetitive ventricular arrhythmias in the first 24 hours after acute myocardial infarction. The reduction in incidence (fig 3) and frequency (fig 4) of repetitive ventricular arrhythmias was consistent in all subgroups analysed. Patients admitted with threatened infarction and receiving atenolol had a significantly reduced incidence of ventricular tachycardia, and this may be attributed, in addition to the antiarrhythmic effect, to prevention of myocardial infarction in a proportion of these patients by beta-blockade.¹⁴

The reduction in early ventricular arrhythmias was supported by a significant decrease in the requirements for further antiarrhythmic drug treatment during the first 24 hours, and also by a trend in the reduction of ventricular fibrillation. Our data show that ventricular arrhythmias regarded as serious (R-on-T, couplets, and ventricular tachycardia) were very frequent in patients with acute myocardial infarction. Of the 55 patients in

the control group who showed electrocardiographic evidence of acute myocardial infarction at entry, 45 (82%) had at least one episode of repetitive ventricular arrhythmia, though most had two or more episodes. R-on-T extrasystoles were detected in 44 (80%) of these patients. These results show a slightly higher but comparable incidence of serious ventricular arrhythmias in previous clinical trials: 64% to 76%^{12 19 20} for serious ventricular arrhythmias, and 53%²⁰ and 59%¹⁹ for R-on-T extrasystoles alone. We found a significant reduction of R-on-T extrasystoles in the treated group, and the clinical importance of this merits consideration. Though undoubtedly ventricular fibrillation can be initiated by a late coupled ventricular extrasystole, it will more frequently do so by an early coupled extrasystole,²¹⁻²⁴ and an increased prevalence of R-on-T extrasystoles before the onset of primary ventricular fibrillation has recently been described.²³

Previous randomised beta-blocker trials using oral²⁵⁻²⁷ or intravenous propranolol²⁸ have failed to show a reduction in ventricular arrhythmias. These studies adopted conventional monitoring in the coronary care unit to record ventricular arrhythmias, and the unreliability of this method is well recognised.^{29 30} Our findings also contrast with the two disappointing reports from Nottingham^{12 13} in which continuous recordings of the electrocardiogram were used. This may have been due to (a) the administration of an initial oral dose resulting in inadequate beta-blockade in the early hours of infarction, when ventricular arrhythmias are common^{31 32}; (b) the inclusion of patients late after the onset of chest pain (mean times from pain to electrocardiographic recordings 17 hours¹² and 19 hours,¹³ compared with five hours in our study); and (c) electrocardiographic recordings in only a small number of patients, an average of 18 patients¹² and 30 patients¹³ with definite and probable myocardial infarction in each treatment group.

Our results are in accordance with a previous report utilising intravenous acebutolol in a non-randomised but controlled trial¹⁸ and support the concept that an initial intravenous dose is essential to achieve a reduction in ventricular arrhythmias by producing rapid and adequate beta-adrenergic blockade.

In addition there was a significant reduction in enzyme activities in patients with electrocardiographic signs of myocardial infarction at entry, confirming earlier reports from our study¹⁴ and from other workers.³³ The antiarrhythmic action of atenolol in acute myocardial infarction is in part probably due to competitive antagonism of circulating catecholamines. Catecholamine concentrations are abnormally high in acute myocardial infarction, which may cause an increase in the severity of cardiac arrhythmias⁴⁻⁶ and is also associated with an increase in complications.^{4 34} The arrhythmogenic actions of catecholamines in acute myocardial infarction may be attributed to a direct effect on the myocardial cell membrane increasing automaticity³⁵ or indirectly by its metabolic effects. Catecholamine-mediated lipolysis increases circulating free fatty acids^{36 37} and, although the arrhythmogenic properties of free fatty acids in myocardial ischaemia are disputed,³⁸⁻⁴⁰ these increase myocardial oxygen consumption in the presence of catecholamine stimulation in man.⁴¹ Low plasma potassium concentrations have been associated with serious cardiac arrhythmias in patients with acute myocardial infarction,⁴² an alteration which may be induced by adrenaline and has been shown to be inhibited by beta-blocking drugs.⁴³ Intravenous beta-blockade produces an immediate decrease in the high concentrations of circulating catecholamines and a concomitant decrease in plasma free fatty acids⁴⁴ in patients with acute myocardial infarction.

Although this trial was not designed to study mortality, an encouraging trend was observed in favour of atenolol; and when we combined hospital mortality with patients resuscitated from ventricular fibrillation and discharged alive we found a significant result (table III). Such a retrospectively identified subgroup benefit, however, must await confirmation from prospective studies.

In conclusion, the results of this randomised clinical trial using early intravenous atenolol followed by oral treatment for 10 days

showed a reduction in the incidence and frequency of severe ventricular arrhythmias (some of which have been shown to precede ventricular fibrillation^{23 24}) in the initial 24 hours of acute myocardial infarction in man. This antiarrhythmic effect, in addition to our preliminary report of a reduction in enzyme activities in patients with definite myocardial infarction and prevention of myocardial infarction in patients with threatened infarction,¹⁴ and reduction in chest pain⁴⁵ after early intravenous atenolol confirm that beta-adrenoceptor blockade is beneficial in the early hours of acute myocardial infarction and that a worthwhile reduction in mortality is possible. Unfortunately, reliable information on the effects of intravenous beta-blockade on mortality may not be obtained unless a large trial in which several thousands of patients have been randomised is completed.

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ONE HUNDRED YEARS AGO Professor Filippi of Florence, writing in the journal he edits, *Lo Sperimentale*, has some hard words for Harvey. Dr. George Johnson has charged the Italians with systematic attempts to snatch from Harvey the honour of the discovery and of the demonstration of the general circulation of the blood. But, says Professor Filippi, it is not the history of Italian science that is so stained; in other pages and in a foreign tongue is that crime to be found. Not all the water that bathes the shores of England would suffice to cleanse Harvey of the sin of ingratitude towards Cesalpini, in that he does not name him even once in his *Exercitatio de Motu Cordis et Sanguinis*, published in 1628; but on the contrary, with veiled allusions and with a show of magnanimity, he slights him, and criticises or depreciates and forgets. The professor, indeed, accords to Harvey the credit of being the first to demonstrate the circulation and to show the exact manner in which it was performed; but he claims for Cesalpini the recognition not merely of the circulation through the lungs, but throughout the whole body. (*British Medical Journal* 1883;ii:168.)