EARLY INTRAVENOUS β -BLOCKADE IN MYOCARDIAL INFARCTION

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Introduction

Yusuf (1980) showed that there was a reasonable correlation between 'infarct size', measured by praecordial ECG mapping, and by cumulative creatine kinase enzyme (CKMB). Praecordial mapping showed that after six hours only about half of the total R wave loss had occurred, and we speculated whether up to this time the size of the infarct could be modified by treatment, (Figure 1 in Yusuf *et al.*, 1981). The natural history of untreated infarction was not consistent: some (type A) produced a rapid CKMB release, but in an equal number (type B), the total release was slower and peaked at times up to 32 hours. We speculated that β -blockade might have several roles in myocardial infarction—firstly, acute, in reducing infarct size preventing serious arrhythmias and perhaps reducing cardiac rupture, and, secondly chronic, preventing arrhythmias and reinfarction. Having abandoned a preliminary placebo-controlled study of early oral atenolol because of a significant delay in reducing the heart rate (Figure 2 in Yusuf, 1980), we then began a trial of the drug given intravenously. A preliminary report on the first 200 patients has been published (Yusuf *et al.*, 1980). The final data on all 479 patients is in preparation. An analysis of the effect of early β -blockade on arrhythmias has been submitted for publication (Rossi *et al.*, 1982).

Methods

Preliminary calculations suggested that there was a good probability of a reduction of infarct size by 25–33% with a population of 400 patients. We finally studied a total of 479 patients.

To be included in the trial, patients had to be randomized within 12 hours of the onset of pain, and to be thought clinically to be having an infarction. Treated patients received 5 mg atenolol intravenously, slowly over five minutes, followed by oral therapy with 50 mg half an hour later, 50 mg at 12 hours, and 100 mg a day for 10 days or

Figure 1 Evolution of ECG changes in 41 patients during acute myocardial infarction; R wave loss at each period is calculated as the percentage of the final R wave loss to the loss seen at each period. Note the rather slow evolution suggesting that there may be possibilities for active intervention in the last 12 hours. (Yusuf *et al.*, *Br. Heart J.*, with permission).

Figure 2 Change in mean heart rate during the first few hours of acute myocardial infarction; placebo compared with oral and intravenous β -blockade. Therapeutic bradycardia was more rapid and more consistently sustained with the intravenous route. ● controls ■ oval AT ▲ IV and oval AT (Yusuf, 1980).

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thereafter for the rest of their hospital stay. Control patients received routine coronary care unit treatment, but were not given an intravenous placebo. Patients were excluded from the trial on the usual contraindications to β -blockade, or if their physicians wished to use β -blockade, or if they were already receiving a β -blocker.

We measured CKMB activities four hourly for 72 hours, as well as 12-lead and 35-lead ECG's on days 1, 3 and 10. Our preliminary analysis of ECG R-wave measurements is only on the 12 lead data. Our end points were total cumulative CKMB release, ECG criteria of R wave loss, arrhythmia, and morbidity.

Results and comment

The time to randomization was relatively short: the majority were entered in the first six hours of the 12 hour period from the onset of pain, with a mean of 4 hours. Hence we studied a group of patients with relatively early infarction. Table 1 shows an analysis of the entry time for the first 200 patients.

On the basis of the ECG we divided the first 400 patients into two groups (Sleight *et al.*, 1981): 143 had no ECG changes of infarction or 'threatened infarction' (that is, a change in the ST segment of less than 1 mm in the limb leads and 2 mm in the chest leads); 257 had ECG changes greater than this and were labelled 'infarction' (although of course many had only early changes, which would not meet conventional criteria for an ECG diagnosis of definite infarction).

Of the control patients with 'threatened infarction', 59% went on to develop infarction (as defined by a doubling of the normal value of CKMB or a 20% reduction in the R wave score ($p < 0.01$)). Of the atenolol-treated patients, only 37% developed infarction. In the patients with 'definite infarction' there was a highly significant diminution in the cumulative rise in CKMB activity in the atenolol-treated group (114 ± 8 i.u. vs 179 ± 15 i.u. [$p < 0.0001$]). This reduction of 35% had confidence limits of 17–55%. There was a less dramatic effect on the size of the remaining R

Figure 3 Patients with 'definite' ECG changes at entry showing less release of myocardial CKMB and greater presentation of the R wave in the atenolol treated group. ■ atenolol □ control (Sleight *et al.*, *Acta Med. Scand.*, with permission).

wave (34.5 vs 43.4% ($2p < 0.003$)). (Figure 3 from Sleight *et al.*, 1981).

Analysis of 24-hour tapes in 182 of these patients showed that 26% of the 95 atenolol-treated patients compared with 67% of the 87 controls showed R on T ectopic beats ($p < 0.0001$), defined as those with a prematurity index < 0.85 . As might have been expected from the bradycardia in patients given atenolol, there was a high preponderance of later ectopics ('escape beats') in treated patients.

Adverse effects of atenolol included hypotension and bradycardia (44 vs 18 and 23 vs 8 respectively) in the total group of 400 patients. It was rarely severe, and the use of inotropic agents was little different between the two groups; most patients in both groups with bradycardia were treated with atropine. Fewer patients in the atenolol group developed heart failure ($2p < 0.05$).

The mortality rate was higher in the control group; 5 vs 13 at one week ($2p < 0.05$), 3 vs 10 ($2p < 0.05$) had non-fatal cardiac arrests. These values are on small numbers and no comparable reduction in mortality has been seen in other early trials; we are therefore conducting a large multi-centre study of mortality, aiming at 8–10,000 patients.

Discussion

Campbell *et al.*, (1981) showed in the Newcastle C.C.U. that an increasing incidence of R on T ectopic beats may herald the development of dangerous arrhythmias. Such R on T ectopics occur particularly frequently in the first few hours after myocardial infarction, the time when ventricular

Table 1 Time to randomization from chest pain

	Atenolol	Control
≤ 2 hrs	4	10
> 2 ≤ 4 hrs	45	39
> 4 ≤ 6 hrs	24	22
> 6 ≤ 8 hrs	14	12
> 8 ≤ 12 hrs	13	12
	100	95

Figure 4 Double blind randomized study of iv atenolol versus iv saline. Effects on blood pressure, heart rate, rate pressure product and estimates of pain relief by patient (subjective) and attending home staff (objective) ● atenolol ■ saline * $p < 0.05$ ▲ $p < 0.01$ (Ramsdale *et al.*, *Am. Heart J.*, with permission).

fibrillation is also most common as a complication. For this reason it is especially important to study the effect of drugs in the very early period after infarction rather than in the later stages. To avoid the problem of skewness of distribution (e.g. some patients may have very many ectopic beats), Rossi (1982) used the logarithm of the number of ventricular ectopic beats and showed that there was a highly significant decrease in the atenolol-treated patients; the proportion of patients with couplets and triplets of ventricular ectopic beats was also significantly different in the two groups. Fewer antiarrhythmic drugs were used in atenolol treated patients compared with controls.

In a double-blind study of intravenous atenolol, using both subjective and objective pain scores, Ramsdale *et al.* (1982) (Figure 4) found that systolic pressure tended to go up slightly in controls but fell in treated patients by about 20 mm Hg; both the heart rate and the heart rate/pressure product fell, and there was a striking parallelism between these haemodynamic changes and relief of pain.

Table 2 Heart failure during hospital stay

	Atenolol <i>n</i> = 100	Control <i>n</i> = 95
1. No. of pts with failure at entry	11	9
2. Late failure (no. of pts given diuretics)	36 $\chi^2 = 3.61$	47 $p < 0.10$
3. No. of pts given digoxin	3	9
4. Mean frusemide dose	145 ± 33	247 ± 54
5. No. of pts on thiazides only	8	9
6. No. of pts on frusemide + thiazide	4	11
7. No. of pts on spironolactone	0	2

Two conclusions may be drawn from these findings. Firstly, it is difficult to conduct a truly controlled, double-blind study of intravenous β -blockers in myocardial infarction, and hence we did not use an intravenous placebo in our trial. Secondly, they confirmed a Swedish study (Waggstein *et al.*, 1975) which showed that β -blockade is an extremely effective analgesic in myocardial infarction.

About 10% of our patients had some degree of heart failure at entry, and more controls than treated patients developed this during their hospital stay (needing diuretics and/or digoxin). Certainly, therefore, treatment was not precipitating heart failure, and might have been reducing its occurrence, perhaps as a result of reducing the amount of cell death. (Table 2 from Yusef *et al.*, 1980).

We conclude that intravenous β -blockade, given early in infarction, appears to reduce 'infarct size', does not precipitate heart failure, and is not associated with a higher death rate. We must recognize however, that enzyme and ECG measurements of infarct size are only semi-quantitative estimates and we therefore need to be somewhat cautious. We are now carrying out a much larger multicentre trial in Europe and Australia. This is designed as a mortality study of intravenous β -blockade aimed at including several thousand patients, which we hope should give us answers fairly quickly.

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