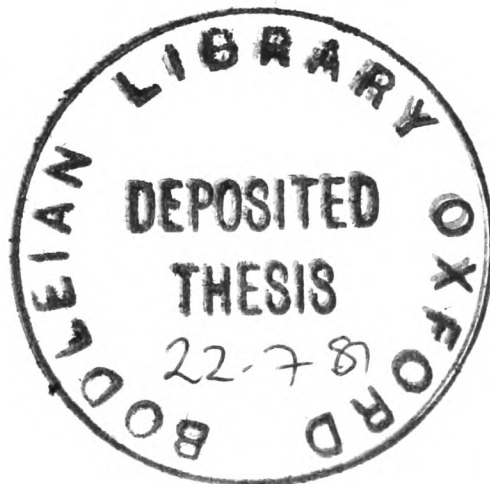


BETA ADRENERGIC BLOCKADE IN
MYOCARDIAL INFARCTION

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To my father

PUBLICATIONS FROM THIS THESIS

- (i) Value of electrocardiogram in predicting and estimating infarct size in man.
Yusuf S., Lopez R., Maddison A., Maw P., Ray N., McMillan S. and Sleight P.
British Heart Journal, 1979, 42:286-293.
- (ii) Effect of Atenolol on recovery of the electrocardiographic signs of myocardial infarction.
Yusuf S., Lopez R. and Sleight P.
The Lancet, 1979, II:868-869.
- (iii) Early Intravenous Atenolol in suspected acute myocardial infarction.
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ABSTRACT

This thesis is concerned with the influence of acute and long-term beta-adrenergic blockade on myocardial infarction in man. An original statistical evaluation of all published and some available unpublished clinical trials is presented in Chapter I.

Chapter III and IV concern the measurement and evolution of infarct size in man. In Chapter III, praecordial ECG mapping and the standard 12 lead ECG have been correlated with cumulative release of the MB isomer of creatine kinase. Using these techniques, I have found that approximately 50% of eventual infarction is complete in 6 hours; implying that interventions designed to salvage ischaemic myocardium may be feasible (Chapter IV).

In Chapter V, I have demonstrated delayed beta-**adrenergic** blockade after oral administration of atenolol and that an initial intravenous dose is essential to achieve early and effective beta-blockade.

In a randomised control trial of 215 patients, atenolol administered intravenously within 12 hours of pain, prevented infarction in treated patients with initial threatened infarcts and reduced infarct size and morbidity in those with initial definite infarcts (Chapter VI).

Patients with anterior myocardial infarction, randomised to receive atenolol for a year, showed significantly greater R wave recovery and Q wave disappearance on serial praecordial maps compared to placebo patients. In a further study, this was demonstrated to be due to lowering the heart rate. This phenomenon of improved ECG recovery with atenolol was reproduced in experimental infarction and was shown to be due to improved scar shrinkage (Chapter VII).

The implications of these studies are discussed. It is likely that both early and long-term beta-blockade will be beneficial to patients with myocardial infarction.

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CHAPTER 1

REVIEW OF LITERATURE

Introduction

This thesis concerns first with the measurement and evolution of myocardial damage in patients with myocardial infarction, second with a study aimed at reducing the amount of damage by early beta-adrenergic blockade and third with the effect of long-term beta blockade on the recovery of the electrocardiographic signs of infarction.

Coronary heart disease (CHD) is without doubt the major cause of death in the Western World. Our present knowledge of this disease is derived from the accumulated results of clinical and pathological observations (Herrick, 1912; Leibowitz, 1970), laboratory experiments and epidemiologic investigations (Epstein, 1965; Borhani, 1966; Report of the Inter Society commission for Heart disease resources, 1970). Although mortality due to CHD has decreased recently in several countries (Gordon & Thom, 1975; Stern, 1979); we still need a greater reduction in mortality than any hitherto achieved before a major impact on CHD will be felt in the community as a whole.

Is prevention at any stage in the natural history of CHD feasible? Ideally, the most desirable aim would be to prevent the disease altogether i.e. the development of atherosclerosis and its clinical manifesta-

tions like myocardial infarction, sudden death and angina pectoris. Attempts so far have been unimpressive both for primary prevention by modifying risk factors (before the clinical manifestations of the disease) or secondary prevention (modification of risk after overt disease). Although lowering blood cholesterol levels by diet or drugs has been possible, little change in overall mortality due to this has been demonstrated (Rose et al., 1965; Report of the Medical Research Council 1968; Leren, 1966; Miettinen et al., 1972; U.S. Coronary Drug Project, 1975; Report of a co-operative trial in primary prevention of ischaemic heart disease using clofibrate, 1978). Similarly, although control of hypertension would be expected to decrease mortality due to CHD, no convincing evidence exists showing a lowering of blood pressure has led to a decrease in coronary heart disease (V.A. Co-operative Studies, 1967, 1970). In contrast, it has been demonstrated that cigarette smoking is associated with an increased risk of coronary heart disease (Doll & Hill, 1964; 1966), that the habit can be altered and that abandoning the habit will reduce the risk even though there have been no large formal controlled trials (Wilhelmsson et al., 1975; Doll & Peto, 1976; Hickey et al., 1978).

As the case for alteration of risk factors other than cigarette smoking is far from proved, attempts at reducing mortality have therefore been directed at preventing or treating complications of the disease once myocardial infarction has occurred. It is, therefore, of importance to review briefly the prognosis and natural history of myocardial infarction, and the effect of present day treatment in altering this. I shall then outline the scope for improvements in management.

Natural History and Prognosis after Acute Myocardial Infarction

Data obtained from three British community studies into "acute coronary attacks" have clearly demonstrated that mortality is maximal in the early hours (Table I). Between 45% and 64% of all deaths in the first 30 days occur in the first hour after the onset of symptoms; and by 24 hours 70 to 80% of these deaths have occurred (Armstrong et al., 1972; Kinlen, 1973; Tunstall Pedoe, 1975). Clearly, therefore, attempts at reducing community mortality will have their greatest impact within this high risk period. As the majority of deaths are due to dangerous arrhythmias (ventricular fibrillation or

TABLE I SUMMARY OF THREE BRITISH COMMUNITY STUDIES ON CORONARY HEART ATTACKS

| | <u>Edinburgh</u> | | | <u>Oxford</u> | | <u>Tower Hamlet</u> | | |
|--|---------------------------|----------|------------|------------------|----------|--------------------------------|--------------|------------------------------|
| Reference | Armstrong et al (1972) | | | Kinlen (1973) | | Tunstall-Pedoe et al (1975) | | |
| Population characteristics | ∠ 70 years | | | ∠ 70 years | | ∠ 65 years | | |
| Annual Attack rate | <u>M</u> | <u>W</u> | overall | <u>M</u> | <u>W</u> | <u>M</u> | <u>W</u> | overall |
| Incidence (per thousand) | 15.5 | 5.1 | (9.8) | 4.5 | 1.1 | 6.08 | 1.5 | (3.35) |
| Mortality Rates: | | | | | | | | |
| ∠ at 28 day | | 33% | | 59% | | | 40% | |
| ∠ at 1 year | | | | | | | 50% (approx) | |
| ∠ of 1 mth mortality occurring | | | | | | | | |
| ∠ 15 mins | | | | | | | 50% | |
| ∠ 1 hour | | 45.5% | | 64% | | | 60% | |
| ∠ 4 hours | | | | | | | 70% | |
| ∠ 24 hours | | 73.5% | | | | | 73% | |
| Proportion of medically unattended patients | <u>M</u> | <u>F</u> | | | | | | |
| | 20% | 19% | | 38% | | | | |
| Proportion of medically unattended deaths | | | 61% | 65% | | <u>M</u> | <u>F</u> | |
| | | | | | | 25% | 33% | |
| Proportion of deaths: | | | | | | | | |
| outside hospital | | | 72.6% | 63% | | | | 68% |
| in hospital | | | 27.4% | 37% | | | | 32% |
| Median time of death | | | 1hr 54min | | | | | |
| Median times: | | | | | | | | |
| onset of symptoms to summoning for help (G.P.) | | | 1hr 30min | | | | | |
| arrival of G.P. | | | 2hrs 14min | | | | | |
| arrival of patient to hospital | | | 3hrs 40min | | | | | 45% reach hospital ∠ 4hrs |
| arrival of patient to CCU/ward | | | 4hrs 9min | | | | | 31% reach ward/CCU ∠ 4hrs |

standstill), the first advances in therapy have been the establishment of coronary-care units for the detection and treatment of ventricular arrhythmias. However, the delay in admission of patients to hospitals has meant that approximately 70% of deaths occurred before admission to hospital (Armstrong, 1972) (Median time to admission of over 4 hours in the Edinburgh study; 45% of patients in the Tower Hamlet study arrived in hospital by 4 hours).

It is difficult to conceive that under any system much can be done about patients dying soon after symptoms unattended by medical staff or relatives. (In the Tower Hamlet study about a third of pre-hospital deaths were unwitnessed). Attention has recently been directed to the application of coronary care at an earlier stage for those who die later than this and before they reach hospital. Two complementary approaches have been tried; by-stander resuscitation combined with mobile coronary care by paramedical or medical staff (Cobb et al., 1975; Pantridge & Geddes, 1967; Briggs et al., 1976). These workers have shown that the correction of ventricular fibrillation outside hospital was possible using a portable defibrillator. The ambulance must, therefore, reach the patient very soon after the onset

of symptoms, but we know that the single biggest cause of delay was the time taken in calling for medical help (a median time of 1 hour 30 minutes in the Edinburgh study, Armstrong et al., 1972). Although education of the public may not be successful in some instances or lead to the proliferation of 'false calls' (Hill et al., 1978), these problems have been overcome by several workers. Remarkable success has been achieved by the Seattle, Belfast and Brighton workers (Cobb et al., 1975; Pantridge & Geddes, 1967; Briggs et al., 1976). Education of the public has led to more bystander resuscitations (increase from 5% to 20% over 4 years), very short response times of under 5 minutes, an increase in successful resuscitations from 34% in the first two years to 43% in the last two years and better long-term survival rates (11% in the first two years to 23% in the second two years) after out of hospital resuscitations (Cobb et al., 1975). This indicates that a certain degree of success in decreasing pre-hospital mortality due to a "coronary heart attack" can be achieved. However, coronary ambulances reduced long-term community mortality in Belfast by only 3% (W.H.O. report, 1970).

Another alternative is to identify patients at high risk of myocardial infarction (MI) and to treat them with antiarrhythmic, antiplatelet or anticoagulant drugs. In Kinlen's study (1973), over half the patients had prodromal symptoms of increasing chest, epigastric pain or recent onset of angina pectoris. Norlander and Nyquist (1979) have reported a high incidence of subsequent myocardial infarction or sudden death in patients with chest pain admitted to a coronary care unit without MI. Whether high risk patients can be prospectively identified and their eventual outcome favourably altered by drug therapy remains to be seen.

The hospital phase of myocardial infarction has received considerable attention. Coronary care units were established with an aim to decrease deaths due to dangerous arrhythmias. Two arguments have been raised against coronary care units: first that they do not, in fact, lower hospital fatality rates compared to ordinary hospital care (Hill et al., 1977); and second that even if they are effective in this regard, their overall impact is inherently limited by the high coronary mortality occurring outside hospital.

Most of the evidence usually cited to "prove" that coronary care units lower hospital fatality due to myocardial infarction is based on "historical" rather than "concurrent" controls (Lawrie et al., 1967;

Day, 1965). Two important considerations must be taken into account when interpreting claims for a lowering of hospital mortality using "historical" controls. Firstly, with better awareness of the disease both among the public and physicians, more milder cases (unrecognized earlier) may be admitted to hospital. This would cause an apparent decrease in hospital mortality. On the other hand, with earlier hospitalisation patients who would formerly have died outside may now be reaching hospital. Such a change may result due to improved public education and with the advent of mobile coronary ambulances or their equivalents (Pantridge et al., 1967). In Belfast, the number of patients admitted within 1 hour of chest pain increased from 13.4% in 1966 to 27.5% in 1969 (cited by Armstrong et al., 1972).

Two randomized controlled trials (Mather et al., 1971; Hill et al., 1978) comparing home versus hospital treatment failed to show any significant difference. Both these studies excluded patients who were "poor risk" (these patients were electively hospitalised) and only randomised what appears to be uncomplicated good risk patients (these patients had a low mortality). It is likely that the relatively small number of good risk patients studied, late hospitalisation and exclusion of poor risk patients may have contributed to

TABLE II Chapman (1979)

| | General Ward July 1966- June 1968 | General Ward Aug 1968- Feb 1970 | CCU Aug 1968- Feb 1970 |
|---------------------------------------|--|--|------------------------------|
| n = | 476 | 193 | 432 |
| Hospital days | 22.4 \pm 13.8 | 20.5 \pm 13.5 | 21.7 \pm 12.0 |
| Admission delay (hrs) | 16.3 \pm 19.6 | 17.2 \pm 20.8 | 13.6 \pm 15.9 |
| Modified coronary prognostic index | 13.0 \pm 15.1 | 12.3 \pm 16.5 | 16.3 \pm 17.7 |
| Mortality rates | 30.0% | 28% | 16.3% |

the negative results of the above studies. The value of the hospital CCU may never be really resolved by randomised controlled trials as it may be considered unethical to deny "poor risk" patients and those with frequent ventricular arrhythmias, management in a CCU when this is available. In a recent study, Chapman (1979) has shown that, for groups of patients with myocardial infarcts of similar severity the hospital mortality was significantly less in patients treated initially in a coronary care unit than those treated throughout in general wards, either before (i.e. historical controls) or after the introduction of coronary care (concurrent controls)(Table II).

Even if coronary care decreased hospital mortality, their overall impact in terms of reducing community mortality from the disease is limited because the bulk of the deaths occur outside hospital (Armstrong et al., 1972; Kinlen, 1973; Tunstall Pedoe, 1975). Estimates of hospital mortality may have changed due to increased public awareness, utilisation of prehospital coronary care and earlier hospitalisation of such patients (Pantridge, 1967; Cobb, 1975). Stern (1979) in an analysis of factors which may have contributed to the lowering of deaths due to CHD in the U.S.A., presents persuasive arguments that coronary care units, in addition

TABLE III

Mode of dying of hospitalized patients treated before the introduction of a coronary-care unit (1 year, 1966-67). compared with those treated recently in a coronary-care unit (2 years, 1977-79)

(data from Auckland, New Zealand, with permission R.M. Norris)

| Mode of dying | Number of patients* | |
|------------------------------------|---------------------|-------------|
| | (1966-67) | (1977-79) |
| Arrhythmia | 105 (52) | 10 (12) |
| Cardiogenic shock | 54 (27) | 34 (41) |
| Cardiac failure | 29 (14) | 17 (21) |
| Arrhythmia causing cardiac failure | 3 (1.5) | 0 (0) |
| Cardiac rupture | 3 (1.5) | 8+6? (10+7) |
| Pulmonary embolus | 2 (1) | 1 (1) |
| Other causes | 6 (3) | 7 (8) |
| Total deaths | 202 (100) | 83 (100) |
| Total patients | 757 | 574 |
| % Mortality | 26 | 14 |

* percentages of total deaths are given in parentheses

to various other factors, have also played a role. Rose calculates from U.K. data that coronary care units could improve overall CHD mortality by at most 4 or 5% (1975).

The next question of importance is whether coronary care units have been successful in all aspects of management of hospital patients. Although few statistics are available it is generally believed that deaths due to primary ventricular fibrillation and dangerous arrhythmias have fallen since the advent of coronary care units. Data from Auckland (Norris & Sammel, 1979 - personal communication) comparing mortality in patients before coronary care and after coronary care is shown in Table III. These results show a striking decline in the proportion of deaths attributed to arrhythmias, and a steady state (resulting in a proportional increase) in deaths due to shock and cardiogenic failure. In addition the overall drop in mortality from 26% to 14% is largely accounted for by the decrease in "arrhythmic" deaths (from 52% to 12% of total mortality).

The leading causes of mortality now are cardiac failure and cardiogenic shock, both of which are associated with large infarcts (Page et al., 1971).

In addition, late hospital and long-term prognosis has been clearly shown to be related to the size of infarction (Sobel et al., 1972; Norris, 1975; Chapman, 1972; Thompson et al., 1979; Page et al., 1971; Alonso, 1973; Bleifield, 1977). Thus infarct size is the main determinant of prognosis for the late hospital phase, a large infarct being manifest in the acute phase by severe left heart failure and cardiogenic shock. Left ventricular failure and cardiac enlargement are, together with age, very sensitive clinical predictors of prognosis for the years after discharge from hospital (Norris et al., 1969; Norris et al., 1970; Norris et al., 1974). It follows that limitation of infarct size is likely to prove an effective means for the reduction of late hospital mortality due to myocardial infarction.

Preventive measures have been advocated in the late stage of myocardial infarction, since about 15% of those who leave hospital die in the first year, and thereafter the annual death rate is about 5%. This represents a 30 times greater risk of death compared to a healthy man of the same age, but this excess risk disappears after about 10 years (Zukel et al., 1968; Norris et al., 1974; Pohjola et al., 1978).

As mentioned earlier, extensive myocardial damage at the time of infarction, is the main prognostic

determinant in such patients and that a large infarct is a permanent liability and a long-term threat to life. It is noteworthy that presence or absence of antecedent primary risk factors - hypertension, a history of cigarette smoking and hyperlipidaemia - do not affect prognosis in the acute phase of infarction, and (with the probable exception of continued cigarette smoking) have a lesser effect on long-term survival than do age, loss of functioning myocardium and already extensive coronary atheroma (Editorial Lancet, 1977).

Other measures to improve long-term mortality have been tried. Anticoagulants, antiplatelet drugs and fibrinolytic therapy are of value and appear to reduce long-term mortality by approximately 20% (Chalmers et al., 1977; Peto, personal communication; Anturane reinfarction study, 1978; Doll & Peto, 1980; Peto and Yusuf, in preparation). In general there is little to suggest that coronary artery bypass after myocardial infarction, long-term therapy with procainamide or diphenylhydantoin are of value (Norris et al., 1977; Kosowsky et al., 1972; Collaborative study, 1971). Trials using beta-adrenergic blocking drugs have yielded conflicting results. These trials will be reviewed in detail and a statistical synthesis has been presented on page 23.

In summary, although most deaths occur before medical or paramedical help is available, a substantial proportion of these lives may be saved if emergency resuscitation is started within minutes of the onset of symptoms. A reduction in mortality in the prehospital phase may be achieved by identification of high risk patients, public health education and awareness, bystander resuscitation and quick delivery of coronary care. Monitoring and intensive care have reduced arrhythmic deaths. However, coronary care units, advances in drug therapy and devices like the intra-aortic balloon counterpulsation have done little to alter early and late mortality which is chiefly determined by a large infarct. It is therefore evident that the greatest improvement in the prognosis of hospital patients may be achieved by controlling infarct size.

I shall now review the metabolic consequences of myocardial ischaemia, factors modifying the extent and severity of ischaemia and then present evidence suggesting that beta adrenergic blocking drugs may reduce myocardial infarct size. I shall then review and present a synthesis of all betablocker trials. In the final part of this chapter, I shall discuss how we can quantify infarct size in man.

The Metabolic Consequences of Anoxia and Ischaemia

Anoxia

During anoxia, the myocardial concentration of high energy phosphates (Adenosine triphosphate:ATP; Adenosine diphosphate: ADP; and creatine phosphate: CP) fall quickly. In response, glycolysis is augmented through the following mechanisms:

- (1) The rate of glucose uptake is increased by greater activity of the enzyme hexokinase leading to increased conversion of glucose to glucose-6-phosphate (Sobel, 1974).
- (2) Glycogenolysis is accelerated by increased activity of phosphorylase kinase leading to increased conversion of inactive to active phosphorylase (Hillis & Braunwald, 1977).
- (3) Increased activity of phosphofructokinase resulting in increased conversion of fructose-1-6-diphosphate from fructose 6 phosphate (Sobel, 1974; Rovetto et al., 1975).

Reactions 2 and 3 are stimulated by the declining levels of ATP and CP and the increased levels of AMP, ADP and inorganic phosphate.

Ischaemia

During ischaemia, there is also an initial burst of increased glycolysis but in contrast to anoxia, it is brief. The rate of glycolysis falls rapidly reaching a level well below control values (Sobel, 1974; Rovetto, 1975) since the concentrations of lactic acid and hydrogen ions also increases within the ischaemic cells (Liedtke et al., 1976) suppressing the activity of several key enzymes in the glycolytic pathway even though substrates may be present in high concentrations (Neely et al., 1975):

- (1) Phosphofructokinase is suppressed resulting in the accumulation of glucose-6-phosphate, which in turn inhibits hexokinase.
- (2) Phosphorylase kinase is suppressed inhibiting glycolysis (Dobson et al., 1973).
- (3) Inhibition of glyceraldehyde-3-phosphate dehydrogenase (Sobel, 1974).

Fatty Acids

Unlike the normal myocardium which derives most of the energy requirements from the oxidation of fatty acids (Neely et al., 1972), in the presence of ischaemia,

this process declines because of the reduction in the activity of carnitine palmitoyl coenzyme A (Wood et al., 1973). This results in increased intracellular concentration of long chain fatty acyl CoA esters (Shrago et al., 1976) which suppresses adenine nucleotide translocase, the enzyme which catalyses the exchange of ATP and ADP between the mitochondria and cytoplasm and leads to a reduction of cytoplasmic ATP concentration (McLean et al., 1971).

The mechanism of the toxic effects of the intracellular accumulation of fatty acids is debatable (Oliver, 1972). It is possible that any deleterious effect is not due to the fatty acid per se but may be due to any of its intermediates after impaired oxidation (Shug et al., 1973). Regardless of which compounds (i.e. FFA or its metabolites) are directly involved, this leads to increased oxygen demand (Mjøs et al., 1974) which in the presence of limited oxygen supply intensifies ischaemia, depresses myocardial contractility and precipitates arrhythmias (Kjekhus & Mjøs, 1972). As fatty acid oxidation is impaired by ischaemia, glucose becomes the principal source of energy (Opie, 1975). Metabolic interventions like glucose-insulin-potassium are aimed at supplying glucose as an alternative substrate (Calva et al., 1965). Beta-adrenergic blockers also decrease the concentration of FFA.

Myocardial Infarction and Ischaemia in Terms of the Ratio between Oxygen Supply and Demand

The extent of myocardial infarction after coronary occlusion depends on the balance between oxygen supply and demand. Certain interventions known to increase myocardial oxygen consumption also increase the severity and extent of myocardial injury. In the laboratory animal, digitalis (in the absence of heart failure), glucagon and bretylium tosylate, pacing induced tachycardia increased the extent of myocardial ischaemia in dogs (Maroko et al., 1971) and in man (Richmans, 1974). Similarly hyperthermia leads to an increase in heart rate and a direct stimulation of oxygen consumption (Liedtke et al., 1976). Isoprenaline leads to increased ischaemia in the centre of ischaemic zones and a reduction in ischaemia in the border zones of conscious dogs. However, in the anaesthetised open chest dog an increase in infarct size is observed (Maroko et al., 1971). When isoprenaline is given to patients with acute MI, there is a rise in myocardial lactate, lactate extraction diminishes or reverses to lactate production (Mueller et al., 1970).

Hypoxaemia (Radvany et al., 1975) and anaemia (Yoshikawa et al., 1973) increase myocardial ischaemia

after coronary occlusion due to the reduction of available oxygen to the ischaemic zone. Similarly, hypoglycaemia also augments ischaemia (Libby et al., 1975).

Catecholamines and Myocardial Infarction

Catecholamine levels are known to be elevated during acute myocardial infarction (Richardson, 1963; Videabak et al., 1972) and high levels occur with large infarcts (Jewitt et al., 1969) or with cardiogenic shock (Benedict & Grahame-Smith, 1979). Increases in both adrenaline and noradrenaline have been observed, suggesting a role not only of the sympathetic nerve terminals but also of the adrenal medulla. Indeed, large increases in adrenaline release from the adrenal gland have been reported in dogs (Staszewska-Barczak et al., 1968) and cats (Kelliher et al., 1975) after coronary occlusion. Noradrenaline is released from the heart (Lammerant et al., 1966) and depletes myocardial noradrenaline stores in ischaemic regions (Richardson et al., 1960). Part of the release of catecholamines from the ischaemic heart muscle may be due to increased efferent sympathetic nerve activity rather than impaired neurotransmitter re-uptake (Mathes & Gudbjarnson, 1970). The depletion is far more pronounced from the ischaemic regions so that other

factors may be involved (Mathes & Gudbjarnson, 1971). Anoxia releases about one-fourth of the total cardiac catecholamine content in 3 minutes from the isolated heart (Wollenberger & Shahab, 1965). Potassium is known to be released within minutes after myocardial ischaemia (Harris, 1954) and this ion has been shown to release noradrenaline, presumably due to a presynaptic site of action (Borda et al., 1977).

Catecholamines increase myocardial infarct size by increasing myocardial oxygen demand by increasing cardiac work (Raab et al., 1962). They also increase platelet aggregation and thrombus formation (Haft et al., 1972). Isoprenaline has been shown to cause a selective decrease in subendocardial blood flow in the ischaemic dog heart (Winear et al., 1975). It decreases collateral flow to ischaemic areas by dilatation of normal vessels causing a "coronary steal" (Baker et al., 1969; Downey et al., 1973). Infusion of isoprenaline causes an infarct like lesion in rats (Rona, 1959) and focal fibrosis of the myocardium occur in patients with phaeochromocytoma (Kline, 1961; Baker et al., 1972; Garcia & Jennings, 1972). Myocardial lesions have also been described in patients treated with adrenaline and related substances (Szakacs & Cannon 1958; Szakacs et al., 1959).

Recently Waldenström et al. (1975) have shown enzyme release from isolated rat hearts perfused by noradrenaline. Electron microscopy of the myocardial cells revealed fibres with hypercontracted myofibrils and swollen mitochondria which correspond to "coagulative myocytolysis" seen in human infarcts (Baroldi, 1975). Myocardial cells with myofibrils in a stage of lysis corresponding to Baroldi's description of "colliquative myocytolysis" were also observed.

In conclusion, there is strong evidence to believe that:

- (i) abnormally high levels of catecholamines observed in myocardial infarction are released from the heart and adrenals.
- (ii) This causes an increase in infarct size by indirectly increasing oxygen demand.
- (iii) Catecholamines are also directly cardiotoxic.

Beta Adrenergic Blockers in Myocardial Infarction

Black, in one of his earliest papers, speculated on the possible beneficial effect of beta-adrenergic blocking drugs in myocardial ischaemia (Black, 1962). In recent years considerable experimental work has been

done on limitation of infarct size and betablockers have been extensively used.

A. Experimental Evidence for the Cardioprotective Effect of Betablockers.

Betablockade has been shown to decrease the epicardial ST segment elevation after MI (Libby et al., 1973) and reduce the development of Q waves (Miura et al., 1979). It has been shown to decrease the extent of enzyme release (Shell et al., 1973; Nayler et al., 1978). Although betablockers reduce blood flow to the normal heart, during ischaemia a selective redistribution of coronary flow occurs with maintenance or increase to the ischaemic zone and a greater amount being diverted to subendocardial regions (Becker et al., 1971; Pitt & Craven, 1970; Vatner et al., 1977). In addition, propranolol protects the microvasculature and the mitochondria during ischaemia (Kloner et al., 1977).

In isolated perfused hearts, propranolol prevents enzyme leakage and decreases lactate production during anoxia (Nayler et al., 1978) and during high levels of catecholamines (Waldenstrom, 1976). Opie et al. (1976) have demonstrated a significant decrease in the uptake of FFA and an improvement in the utilisation of glucose in the ischaemic myocardium after propranolol.

Although global cardiac function is depressed, propranolol causes improvement in the function of the 'marginal' zone (Theroux et al., 1976). Reimer et al. (1973) and Miura et al. (1979) have demonstrated a reduction in anatomical infarct size.

The protective effect of propranolol is mainly due to its beta blocking effects (Reimer et al., 1976) and is not seen when l-propranolol is used. However, Nayler et al. (1978) have demonstrated cardioprotection 72 hours after the last dose of betablockers (when beta blockade was absent) in isolated perfused hearts. They propose that the synthesis and release of noradrenaline may be limited similar to that shown by Raine and Chubb (1977) with chronic beta blockade.

Betablockers reduce oxygen consumption by reduction of systolic intraventricular pressure (Lucchessi & Whitsitt, 1969) and heart rate (Reimer et al., 1973; Furnival et al., 1970). They also counteract the positive inotropic effect of catecholamines on the heart and reduce ventricular wall tension (Bodenheimer et al., 1976). There has been controversy over the left ventricular end-diastolic pressure after beta blockade. Weiner et al. (1969) have shown little increase in end diastolic pressure in angina patients after propranolol. Mueller et al. (1977) have shown little change in pulmonary capillary wedge pressure in patients

with normal initial values and a decrease in patients with high initial values after intravenous propranolol within 12 hours of infarction.

B. Recent Clinical Studies of Betablockers in Acute Myocardial Infarction

With better understanding of the process of myocardial ischaemia and the influence of O_2 demand and supply during acute myocardial infarction, there has been renewed interest that betablockers may favourably influence infarct size in man. The stress in recent times has been towards earlier administration of the drug intravenously (IV) and towards measurement of infarct size or "metabolic" end points. Reports by Mueller et al. (1977) have shown a decrease in myocardial O_2 requirements, and a shift from lactate production to lactate extraction during acute myocardial infarction after IV propranolol. The above workers also demonstrated a fall in pulmonary capillary wedge pressure in 6 patients with values above 16 mmHg. This would suggest that ischaemia causes loss of compliance in these ventricles and propranolol (probably by reducing ischaemia) is more effective in decreasing stiffness than increasing the size of the ventricle. Cairns and Klassen (1975) have demonstrated a decrease in the

release of creatine kinase in a small group of patients. More recently Peter et al. (1978) and Norris et al. (1978) demonstrated a decrease in creatine kinase levels in patients with MI and the prevention of ECG signs and enzyme release in patients with threatened infarction treated with intravenous propranolol within 4 hours after onset of chest pain. Reid et al. (1976) and Waagstein et al. (1976) have demonstrated a reduction in ST segment elevation in patients with anterior infarction following the administration of practolol. The latter workers also demonstrated relief of pain after the injection of betablocker.

C. Clinical Trials with beta adrenergic blocking agents in Myocardial Infarction.

Since Snow's initial report beta adrenergic blocking agents (BB = betablocker) have been used in several clinical trials (either in the hours or in the months) after acute myocardial infarction in an attempt to decrease mortality. To date at least 22 randomised trials (published or unpublished) have been completed, but no consensus has yet emerged as to the real value of these agents. No detailed review of the entire topic has been published.

In this section, I shall review the methodology, results and conclusions of these 22 trials and present a statistical synthesis.

Methods:

A Medline computer search was made of the English language periodical literature from 1964 onwards, and combined with a manual bibliographic search of all references found in review articles and reports of clinical trials. Where detailed results of the trials were not available, more information was obtained by direct correspondence with the authors. Twenty-two randomised trials were unearthed. Only the most recent information published or provided by the authors is used here.

Many different betablockers were used and there was considerable variation in dose, time of onset and duration of therapy between different trials (Table IV). Mortality is the only end point reported by all the trials. This information about mortality in each separate trial has been combined using the statistical techniques of "retrospective stratification" (Peto et al., 1977). The principle underlying retrospectively stratified analysis of many trials is as follows. First, within each single trial we compare all patients randomly allocated to betablockers (irrespective of whether they actually completed their allocated treatment - most will, but some will not)-with all patients allocated to control,

and we calculate the quantity observed minus expected or $O-E$, for the number of deaths in the betablocker group. If treatment is without material effect on mortality, then in one trial ($O-E$) will differ only randomly from zero (being positive if they happened by chance to have allocated more of the moribund patients to treatment than to control and negative otherwise). If, however, treatment really does reduce the risk of death then ($O-E$) will tend to be negative, although of course, the effect of chance in small trials may swamp this tendency. In a retrospectively stratified analysis we therefore calculated one ($O-E$) for each of the 22 separate trials, (comparing only the patients in that trial with each other) and then sum all these 22 ($O-E$)'s. If beta blockers are without effect then each ($O-E$) differs only randomly from zero and so will their sum; while if beta blockers do materially reduce mortality the negative tendencies in the separate ($O-E$) values should reinforce each other, yielding a total which is much more negative than chance alone could plausibly permit.

Difficulties arise only when authors have excluded some of their randomised patients from their published report (e.g. Balcon et al., 1966; Ahlmark et al., 1974; The Multicentre Practolol trial, 1977) because as a general rule the patients excluded from the betablocker group might be those with a particularly bad prognosis and thus result in a bias in favour of the remaining

TABLE IV. CLINICAL DETAILS OF 22 RANDOMISED BETA BLOCKER TRIALS (mortality figures are given in Table V)

| Reference | Selection of patients | Beta-blocker and dose | Time started | Duration of therapy | Side Effects | | Patient Withdrawals | Author's Conclusions | | |
|--|---|--|--|---------------------|--|-----------------------------------|---------------------|----------------------|--|--------------------------------------|
| | | | | | Heart failure B-block control | Complete ht.block B-Block control | | | | |
| <u>EARLY ENTRY:-</u> Hospital follow-up only: | | | | | | | | | | |
| (i) Norris, Caughey Scott 1968 | Excl. Pulm oedema systolic BP ≥ 80 mm HR ≥ 50 /min | Propranolol 20mgm qid | ≥ 3 days of onset of symptoms | 3 weeks | 17 | 19 | 3 | 3 | All with- drawals reported 11 with- drawal deaths in propranolol 7 in the control group | No benefit from beta- blockers |
| (ii) Multicentre Trial Stephen et al. 1966 | Excl. Broncho- spasm HR ≥ 60 /min, syst. BP ≥ 80 mm | Propranolol 20mgm qid | ≥ 48 hrs of pain Mean propr- anolol = 16.2 hrs. Mean control = 13.4hrs | 28 days | 14 (Twice as many pts had heart failure in the BB group on entry) | 7 | not available | not available | 14 pts. with- drawn in the BB group and 16 in the placebo. No details available | No benefit |
| (iii) Balcon et al. 1966 | Excl. uncon- scious pt. and complete heart block. | Propranolol 20mgm qid | On admission to the CCU Mean for BB = 9hrs. Mean t for control = 10hrs | 28 days | 30 cardiogenic shock 14 | 33 14 | 0(?) | 0(?) | Only 114/155 pts reported 5pts later withdrawn. 6pts not admitted to trial.. 2 of whom died be- fore admini- stration of tabs. | No benefit |
| (iv) Clausen et al. 1966 | Excl. bronchial asthma | Propranolol 10mgm qid | ≥ 24 hrs of symptoms | 14 days | 22 | 27 | not available | not available | No with- drawals | No benefit |
| (v) Sloman and Stannard 1967 | Excl. cardio- genic shock, complete ht. block, asthma | Propranolol 0.1mgm/kg IV+10mgm qid P.O. | On admission | 3 weeks | 1(?) | 0(?) | 0(?) | 0(?) | No with- drawals | No benefit |
| (vi) Barber 1967 | Excl. HR ≥ 60 /min Complete heart block, BP ≥ 90 syst Bronchial asthma | Propranolol 40mgm qid | ≥ 24 hrs of symptoms | 4 weeks | 20 | 18 | not available | not available | 8 with- drawals as they did not meet diag- nostic criteria No details provided | No benefit |

| vii) Kahler 1968 | Excl. (vert 60% shock, complete ht. block, abstr. pulmonary disease) | Propranolol 200mgm qid | No time limit Mean t in Prop = 6.2hrs Placebo=6hrs | Hospital stay Mean time Prop = 15days Placebo=16.5d | 3 | 4 | 0 | 0 | All patients reported | No benefit |
|------------------------------|---|---|--|---|---------------|---------------|---------------|---------------|--|---|
| viii) Briant and Morris 1970 | Excl. complete heart block syst. BP/90mmHg Frank pulm. oedema. HR /50/min. Bronchial asthma | Alprenolol 100mgm qid | On admission | Hospital stay | 1 | 0 | 7 | 7 | All patients reported | No benefit |
| ix) Puccella 1968 | not available | Oxprenolol | On admission | 21 days | not available | not available | not available | not available | 37 withdrawals 10 had no infarct 27 for a "variety of nondrug reasons" Details not available | No benefit |
| x) Lombardo et al | not available | Oxprenolol 120mg/day | /24hrs after pain | 21 days | 40 | 36 | not available | not available | 24 withdrawn as diagnosis not confirmed | No benefit |
| xi) Peter et al. 1978 | Excl: 2°/3° heart block HR /60/min. Pulm. oedema | Propranolol 0.1 mgm/kg IV followed by | Within 12hrs of pain | 24 hrs | 5 | 5 | 0 | 0 | Nil | Propranolol given / 4hrs reduces CPK release |
| xii) Yusuf et al. 1980 | Excl: 2°/3° heart block HR /40/min syst BP /90 mm Pulm. oedema | Atenolol 5 mgm IV followed by 50 mgm 12 hrly orally | Within 12hrs of pain | 10 days | 36 | 47 | 6 | 6 | Nil | Atenolol reduces ECG and enzyme estimates of infarct size |

EARLY EMIRY:

Long-term studies

| Reference | Selection of patients | Beta-blocker and dose | Time started | Duration of therapy | Side Effects | | | Patient Withdrawals | Author's Conclusions |
|-------------------------------|--|--|--|---------------------|--|--------------------|--|--|----------------------|
| | | | | | Heart failure | Complete ht. block | | | |
| | | | | | B-block / control | B-block / control | | | |
| (xiii) Barber et al. 1976 | No exclusions (186 pts. with prolonged chest pain were included in addition to the 298 pts. with MI after discharge) | Practolol 300mgm bd | on admission Median time = 3hrs 15mins approx. | 2 years | In the first 8hrs 49 29 No difference in the rest of the first 24 hrs. Post discharge: 85 99 | Equal incidence | | A benefit in pts. with an initial HR > 100/min. treated with practolol | |
| (xiv) Anderson et al. 1979 | Excl: cardiogenic shock, pulm. oedema 2nd or 3rd degree AV block, bradycardia < 40/min. Previous treatment with beta-blockers. Obstr. airways disease. | Alprenolol 5mgm IV + 200 mgm b.d. | On admission Median = 6hrs | 1 year | 4 3 | 4 0 | All patients reported | Benefit in pts. under 65 yrs. but increased deaths in patients over 65 yrs treated with beta-blocker | |
| (xv) Reynolds & Whitlock 1972 | Excl: heart block BP < 90 mm syst. Pulm. oedema HR < 50/min. asthma | Alprenolol 100 mgm qid | On admission No time criteria | 1 year | 4 3 | 0 0 | 32 pts. withdrawn. 13 not infarcts, 3 deaths and 10 due to complications". No details as to which groups they belonged | No benefit | |
| (xvi) Wilcox et al. 1980 | Excl. Syst BP < 90, HR < 40/min. moderate or severe heart failure, ht. block, asthma diabetes | Propranolol 40 mgm tid Atenolol 50mgm b.d. | On admission Mean = 9hrs | 1 year | 10 8 | 5 2 | All patients reported | No benefit | |
| (xvii) Burley et al. 1979 | Excl: ht. failure ht. rate < 60, asthma, diabetes or serious current illness | Oxprenolol 40mg b.d. | Mean entry 2.1 days | 56 days | 5 3 | 0 0 | 21 BB and 17 controls All deaths available | No benefit | |
| (xviii) Evemy et al. 1978 | Excl: syst BP < 95mmHg. HR < 60/min overt LVF, 2/3 ht. block. Age > 70yrs. Previous infarct | Practolol 15 mgm IV followed by 200 mgm orally 12 hrly X 48hrs | Median delay of 3.5hrs in the treated and 3hrs in the controls | 48 hours | 13 13 | 3 1 | MI | No benefit | |

| <u>LATE ENTRY</u> | | <u>Long-term Studies:</u> | | | | | | | | | | | |
|--------------------------------------|--|----------------------------|---|--------------|----|----|---------------|--------------------------|---|---|--|--|--|
| (xix) Ahlmark* et al. 1974 | 231 pts. / 66 yrs 231 pts. with- drawn after randomisation | Alprenolol 100mgm qid | 2 weeks after onset | 2 years | 2 | 1 | 0 | 0 | 393 patients randomised on admission - 158 withdrawn as no infarct - 35 deaths in hospital - 17 lived outside catchment area - 21 had contra- indications for BB at discharge .. 231 pts. withdrawn | Reduction in sudden deaths in alprenolol treated group | | | |
| (xx) Wilhelmsson* 1974 | Excl: cardiac failure after treatment with | Alprenolol 400mgm daily | Around 6 weeks after infarct- ion | 2 years | 1 | 1 | 1 | 1 | 8 patients with- drawn in each group 4 deaths in the alprenolol with- drawals and 3 in the control | Reduction in sudden death | | | |
| (xxi) Multicentre* Practolol 1977 | Excl: >70yrs, CCF, 1° AV block bradycardia H/O bronchial asthma | Practolol 200mgm b.d. | 7-28 days after infarct- ion | about 1 year | 57 | 49 | not available | See table for details | Practolol reduces mortality especially in anterior infarcts | | | | |
| (xxii) Baber et al. | Only anterior infarcts | Propranolol 40 mgm tds | 2-14 days after infarct- ion | 9 months | | | | All patients reported | No benefit | | | | |

* These are trials which reported a beneficial effect from treatment. A further analysis and up-to-date information on these trials is presented in Tables V and VI, and in the text.

patients or the treated group (excluded patients may be those who died too early to receive active treatment or those who developed side effects like heart failure Wilcox et al., 1980). In some cases, I was able to obtain the full data from the authors (Practolol trial) but in others, I have included the study, drawing attention to the risk of bias. The study of Ahlmark et al. (1974) in which after withdrawal of 21 patients with contraindications to beta blockers there remained only 69 treated patients as against 93 controls, shows how severe such bias maybe.

In several trials, a proportion of patients are later found not to have an infarct. These patients have generally been withdrawn by the authors and no information about these patients has been provided.

Route of administration:

Except for the recent report by Andersen et al. (1979), which used intravenous alprenolol, and the study of Evemy et al. (1978) all trials have used oral beta blockers which is acceptable for long-term trials but may be suboptimal for trials of early beta-blockade because of poor absorption (Rutherford et al., 1977).

TABLE V COMBINED INFORMATION FROM RANDOMISED TRIALS OF BETA BLOCKERS AMONG MI PATIENTS

NOTE: Patients in one trial are only compared with each other in this table, never with patients in any other trial

| BASIC DATA FROM TRIAL | | | | STATISTICAL CALCULATIONS | | |
|---|--------------------------|--------------------|----------------------|-------------------------------|-------------------------|-------------------|
| Year and Reference | Beta-blocker deaths/pts. | Control deaths/pts | Ratio of percentages | Observed minus expected (O-E) | Standard error of (O-E) | Variance of (O-E) |
| <u>Group I: Treated in hospital only</u> | | | | | | |
| Norris 1968 | 31/226 (14%) | 24/228 (11%) | 1.3 | 3.62 | 3.48 | 12.11 |
| Multi Prop 1966 | 15/100 (15%) | 12/95 (13%) | 1.2 | 1.15 | 2.42 | 5.84 |
| Balcon 1966 | 13/56 (23%) | 14/58 (24%) | 1.0 | -0.26 | 2.28 | 5.20 |
| Clausen 1966 | 18/66 (27%) | 19/64 (30%) | 0.9 | -0.78 | 2.58 | 6.67 |
| Sloman 1967 | 3/26 (12%) | 4/23 (17%) | 0.7 | -0.71 | 1.24 | 1.53 |
| Barber 1967 | 10/52 (19%) | 12/47 (26%) | 0.8 | -1.56 | 2.08 | 4.31 |
| Kahler | 3/38 (8%) | 6/31 (19%) | 0.4 | -1.96 | 1.40 | 1.96 |
| Briant 1970 | 5/62 (8%) | 4/57 (7%) | 1.1 | 0.31 | 1.45 | 2.09 |
| Fuccella per.comm. | 15/106 (14%) | 9/44 (6%) | 2.3 | 4.82 | 2.31 | 5.32 |
| Lombardo per comm. | 8/130 (6%) | 11/130 (8%) | 0.7 | -1.50 | 2.10 | 4.42 |
| Peter 1978 | 1/47 (2%) | 2/48 (4%) | 0.5 | -0.48 | 0.86 | 0.73 |
| Yusuf 1980 | 4/100 (4%) | 9/95 (9%) | 0.4 | -2.67 | 1.75 | 3.05 |
| Evemy 1978 | 3/46 (7%) | 6/48 (13%) | 0.5 | -1.40 | 1.43 | 2.06 |
| Totals for Group I: | 129/1055 (12.2%) | 132/1068 (12.4%) | 0.98 | -1.42 | $\sqrt{55.29}$ | 55.29 |
| <u>Group II: Randomised in hospital, long-term treatment</u> | | | | | | |
| Barber 1976 | 41/151 (27%) | 46/147 (31%) | 0.9 | -3.08 | 3.93 | 15.45 |
| Anderson 1979 | 61/238 (26%) | 64/242 (26%) | 1.0 | -0.98 | 4.81 | 23.16 |
| Reynolds 1972 | 3/38 (8%) | 3/39 (8%) | 1.0 | 0.04 | 1.18 | 1.40 |
| Wilcox 1980 | 36/259 (14%) | 19/129 (15%) | 0.9 | -0.71 | 3.24 | 10.50 |
| Burley per.comm. | 9/177 (5%) | 5/136 (4%) | 1.25 | 1.08 | 1.82 | 3.30 |
| Totals for Group II: | 150/863 (17.4%) | 137/693 (19.8%) | 0.88 | -3.65 | $\sqrt{53.81}$ | 53.81 |
| <u>Group III: Randomised after discharge, long-term treatment</u> | | | | | | |
| Ahlmark 1974 | 5/69 (7%) | 11/93 (12%) | 0.6 | -1.81 | 1.88 | 3.55 |
| Wilhelmsson 1974 | 7/114 (6%) | 14/116 (12%) | 0.5 | -3.41 | 2.19 | 4.79 |
| Multi Pract 1977 | 102/1533 (7%) | 127/1520 (8%) | 0.8 | -12.99 | 7.28 | 52.97 |
| Multi Prop 1980 | 28/355 (8%) | 27/365 (7%) | 1.1 | 0.88 | 3.57 | 12.71 |
| Totals for Group III: | 142/2071 (6.9%) | 179/2094 (8.5%) | 0.81 | -17.33 | $\sqrt{74.03}$ | 74.03 |
| TOTALS FOR ALL TRIALS: | 421/3989 (10.6%) | 448/3855 (11.6%) | 0.91 | -22.40 | $\sqrt{183.12}$ | 183.12 |

Time from pain to first administration of drug:

Most early betablockade studies admitted patients within the first 24 hours after chest pain; one however included patients up to 3 days after pain onset (Norris, 1968), and one other specified no time limit. In only six studies is it likely that most patients began treatment within 6 hours of pain (Andersen, 1979; Barber, 1976; Kahler, 1969; Evemy et al., 1978; Peter et al., 1978; present study, 1980).

Trial size:

Only the practolol study was of reasonable size (>3000 patients); the remaining 16 were small (mean = 250 patients) and most would therefore have been unlikely to detect even a halving of the risk of death (e.g. from 12% to about 6%). The negative results reported by 14 of the trials are therefore untrustworthy.

Reanalysis of 4 'positive' trials:

Four trials reported a significant reduction in mortality from treatment. Ahlmark's (1974), Wilhelmsson's (1974) and the Multi-centre Practolol trial (1977) all reported a decrease in sudden death in the treated groups ($p < 0.05$ to $p < 0.02$ in their analysis). However, none of these above trials included the mortality of the patients withdrawn from the study after randomisation.

TABLE VI. UP TO DATE RESULTS OF THE PRACTOLOL TRIAL (personal communication from John Lewis)

| Principal cause of withdrawal | Placebo | | | Practolol | | | | |
|-------------------------------|--------------------|------|---------------------------------|----------------|--------------------|------|---------------------------------|----------------|
| | Number of patients | Died | Died / 1 month after withdrawal | Cardiac deaths | Number of patients | Died | Died / 1 month after withdrawal | Cardiac deaths |
| Arrhythmia | 49 | 4 | 1 | 4 | 25 | 4 | 2 | 4 |
| Angina | 74 | 6 | 3 | 6 | 35 | 1 | 0 | 1 |
| Myocardial Infarction | 43 | 9 | 5 | 9 | 36 | 11 | 8 | 11 |
| Cardiac Failure | 49 | 8 | 2 | 8 | 57 | 11 | 6 | 11 |
| Adverse Reaction | 70 | 1 | 0 | 1 | 134 | 5 | 0 | 5 |
| Non-collaboration | 55 | 2 | 2 | 2 | 49 | 3 | 1 | 3 |
| Other reason † | 81 | 15 | 9 | 11 | 101 | 14 | 8 | 9 |
| Not withdrawn | 1099 | 82 | 0 | 78*** | 1096 | 53 | 0 | 48*** |
| Total | 1520 | 127* | 22 | 119** | 1533 | 102* | 25 | 90** |

* Difference statistically significant, P = 0.09

** Difference statistically significant, P = 0.04

*** Difference statistically significant, P = 0.01

† Mainly for other medical condition or change of abode

On further analysis of Ahlmark's and Wilhelmsson's reports to see if total mortality had been reduced, no significant difference between treated and untreated groups is seen.

In a recent personal communication from the organisers of the practolol trial (Table VI) the outcome of all patients are reported. Again, if all deaths are included the significance of the study falls to 0.09. The recent report of Andersen et al. (1979) is of particular interest as this study has used an initial IV dose of the betablocker in patients soon after chest pain (< 6 hrs in more than 50% of patients). These authors stratified their patients at entry into two groups based on age (< 65 years and 65 and more) for reasons that are not readily apparent. They reported a significant decrease in mortality in the treated patients in the younger age group but a trend towards increased mortality in the treated patients > 65 years. When their entire data is pooled together (61 deaths among 238 treated patients and 64 deaths among 242 controls), no evidence of benefit is seen. It is implausible for betablockers to be so strongly beneficial in younger patients and to be so strongly harmful in older ones; and therefore a pooled analysis of all their data is to be preferred. Further analysis

of this study shows an equal incidence of withdrawals due to suspected side effects in both younger and older patients, which certainly does not suggest that older people could not tolerate the treatment. It is therefore likely that the results of Andersen's trial are due to 'statistical interaction' (Peto et al., 1977).

Initial determination of trial size:

Only in two studies (Multicentre Practolol study and Baber et al., 1978) does the initial trial size seem to have been calculated to detect or exclude a particular degree of benefit (and Baber et al.'s calculations assumed a rather high degree of benefit i.e. a 50% reduction in mortality). In the other trials, the studies were stopped for reasons which are not now obvious when they were still too small to detect reliably even a big benefit (i.e. 50%) from treatment. One study was stopped because of apparent benefit (Ahlmarm, 1974).

This can cause difficulties unless sequential methods of analysis are then used (McPherson, 1974; Peto, 1977). The practolol study was stopped because of the detection of side effects leading to its withdrawal.

As a "reasonable" probability of detecting a "reasonable-sized" effect of treatment on mortality (although not, of course, on physiological end points

like infarct size or arrhythmias) probably requires admission of some thousands of patients, most studies have been hopelessly small. Two small trials (Peter et al., 1978, present study 1980) were designed primarily to study the effect of beta blockers on infarct size.

Pooled data from 22 trials (Table V)

A total of 421 deaths occurred in 3989 patients (10.6%) randomised to receive a betablocker as compared to 448 deaths in 3855 patients (11.6%). Crudely, this suggests a prevention of 9% deaths by betablockers which is not significant ($2p < 0.10$) but before even this small benefit is accepted as real it must be remembered that in some trials a few of the more seriously ill patients were improperly removed from the betablocker group.

The mortality in early entry studies with or without long-term treatment was identical (14.5% v 15.3% in the betablocker and control groups respectively). Studies randomising patients after discharge to long-term treatment or placebo demonstrate a 19% reduction in mortality (6.9% in the betablocker group v 8.5% in the controls; $2p < 0.05$). Pooling of all trials with long-term therapy demonstrates reduction in mortality by a mean of about 16% ($2p = 0.05$).

However, 7 of the 12 hospital entry trials may not have achieved betablockade early enough to influence infarct size or dangerous ventricular arrhythmias. An initial dose of intravenous betablocker was used in only 3 of these 12 trials. Pooling data from these 3 trials suggest an 18% reduction in early mortality (not significant). It is therefore obvious that the hypothesis that early betablockade may be of benefit has not been adequately tested.

Heart failure and Heart block:

No trial reported a statistically significant increase in the incidence of heart failure or heart block after the use of betablockers. Pooling the data from trials which reported these conditions (Table IV) gives a 10.4% incidence of heart failure in the treated group compared to 10.57% in the controls.

Most trials excluded patients presenting with severe heart failure or who were already in complete heart block. Even in those which did not (Snow et al., 1965; not randomised; Balcon et al., 1966; Clausen et al., 1966) no significant difference in the incidence of heart failure was observed (50% in the treated v 55% in the controls).

Discussion

It is obvious that to date there is no strong objective evidence from any single trial that the administration of betablockers to patients after myocardial infarction reduces mortality.

Several reasons for these inconclusive results exists. Suppose the total benefit is in the order of preventing 20% of deaths, then a randomised study of a total of over 8000 patients would be required to detect this reliably (if mortality is reduces from 12% to 10%, with 4500 patients randomised, there is an even chance of detecting a difference at $p \leq 0.05$; with 7,500 patients an even chance of $p \leq 0.01$ and about a 70% chance of $p \leq 0.05$; with 15,000 patients there would be an 80% chance of detecting $p \leq 0.01$ and a virtual certainty of being in the right direction).

However, if a drug is of benefit, it is important to use the drug optimally and in the right dose to have a reasonable chance of demonstrating any benefit. The two separate areas where a betablocker may be of potential benefit are the **early** phase in an attempt to decrease infarct size and in the late phase to decrease the incidence of sudden death.

To test the first hypothesis, the drug should be given intravenously and within the first 6-12 hours, as the bulk of myocardial necrosis is complete by this time (Selwyn et al., 1977; Yusuf et al., 1978). It is important to administer the first dose of the beta blocker intravenously as there may be a delay in achieving betablockade after oral administration in some patients with acute myocardial infarction (Rutherford et al., 1977). Only three of the trials test the early effects of beta-blockers adequately as all other studies either started late or used oral treatment only.

To test the second hypothesis adequately, (i.e. reduction of sudden deaths after myocardial infarction) the study should continue for at least a year or more after discharge when a greater number of events are likely to occur. (This gives a better chance of detecting any benefit from the drug). Only 10 of the above studies have followed the patients for at least a year. In 12 other instances, the trials were stopped within 4 weeks or less of infarction. In addition, many of these studies started too late to have any real possibility of affecting initial infarct size or serious ventricular arrhythmias.

Strictly, the sensitivity of a study depends on the number of end points (i.e. deaths, or physiological parameters), not on the total number of patients. The percentage mortality in the trials reported are on average about 12%. The number of deaths occurring in the study is likely to increase if the trial enrolled very early patients, continued for a year or more, and by the inclusion of patients with more severe infarcts (as these are the patients more likely to die). In general, it is believed that heart failure is a contraindication to the administration of betablockers. Although this may be true of patients suffering from "chronic" myocardial disease, this does not seem true of "acute" infarction. None of the above trials (or the pooled data) suggests that patients given a betablocker are more prone to develop heart failure. This may in part be due to the exclusion of patients with heart failure in some trials; but most trials included patients with "mild" to "moderate" heart failure. The studies of Balcon et al. (1966), Clausen et al. (1966) and the non-randomised study of Snow, included all patients irrespective of the presence of any degree of heart failure, pulmonary oedema or cardiogenic shock; none of these studies reported a greater incidence of heart failure in the betablocker treated patients. Recent studies by Mueller et al. (1977)

showed that after the administration of propranolol to patients soon after AMI, IV propranolol, pulmonary artery and diastolic pressure (PAEDP) was unchanged. Moreover, PAEDP fell in patients with high initial pressures. Further, Waagstein et al. (1976) have actually used betablockers successfully in the treatment of congestive cardiomyopathy, when digoxin and diuretics had failed. It is therefore likely that betablockers may even be of benefit (and not dangerous as thought generally) in patients presenting soon after their first infarct (within 6 to 12 hours) even if they are in heart failure (Barber et al., 1975; Mueller et al., 1977). This may be due to the preservation of threatened ischaemic myocardium as a result of reduction in work by decreasing tachycardia and improving compliance of the ventricle.

Another approach would be to study physiological end points like infarct size or ventricular arrhythmias which may be related to prognosis. Although this would mean replacing a definite and clear end point (like death) with a less clear one, it is to be recommended for studies of infarction which are unlikely to enroll at least a thousand patients. In all these studies mortality can in addition be monitored at little cost (e.g. through the NHS central computer in the U.K.) and should be reported irrespective of withdrawals. This will enable a synthesis of trials and detection of benefit

TABLE VII. BETA BLOCKER TRIALS IN PROGRESS

| Study | Selection of patients | Total estimated intake | Number of participating centres | Drug Dose duration of therapy | End points | Duration of follow-up | Coordinating Officer |
|---|--|--|---------------------------------|---|---|--|---|
| <u>Acute Intervention Studies</u> | | | | | | | |
| (1) Goteborg | 40-69yrs chest pain /48hrs | 1200 patients at least | 1 | Metoprolol initial dose IV rest orally Therapy for 3 months | Infarct size Arrhythmias Mortality | 3 months | A. Hjalmarson |
| (2) MILIS Myocardial Infarct Limitation Study | 76yrs suspicious ECG evidence of infarct chest pain /18hrs | 1500 patients randomised to hyaluronidase, beta-blocker or placebo or if beta-blocker contra-indicated only randomised to hyaluronidase or placebo | 5 | Propranolol IV dose initially | Infarct size Arrhythmias Ventricular function Mortality | 3 years | E. Braunwald |
| (3) Oxford-Wythenshawe Study | No age bar chest pain /12hrs | 500 patients | 2 | Atenolol IV initial dose oral for 10 days | Infarct size Arrhythmias Morbidity Mortality | at least 3 years Longer follow-up possible on MHS computer | S. Yusuf |
| <u>Long-term Intervention Studies</u> | | | | | | | |
| (1) BHAT Beta-blocker Heart Attack Trial | 30-69yrs Definite infarcts. within 21 days of infarct | 4200 | 32 | Propranolol 20mgm QID | Mortality Arrhythmias Infarction | 3 years | National Heart Lung and Blood Institute, Bethesda |
| (2) Newcastle | | 1600 | 22 | Sotalol | Mortality | 1 year | D. Julian |
| (3) Norway | Long-term study with Propranolol (details not known) | | | | | | Hans Leen |

when individual trials are inconclusive. (e.g. Chalmer's et al. (1978) for anticoagulants; Peto and I have done this for aspirin and streptokinase).

More definite answers regarding the use of beta blockers in myocardial infarction must await the results of several larger studies in progress. Table VII gives a summary of the studies that are known to me at the time of writing this thesis. In conclusion, there is little evidence that betablockers reduce mortality in patients after acute myocardial infarction. Small trial sizes in several studies, short follow-up, too late administration of the drug and probably also the exclusion of "high risk" patients may all prevent a firm conclusion regarding the real value of betablockade in myocardial infarction.

The Border Zone in Myocardial Infarction and Ischaemia

Essential to the concept that ischaemic myocardium can be salvaged has been the hypothesis of a "border zone" of intermediate and reversible ischaemia wedged between the completely normal and totally necrotic myocardium. If this zone of reversibly damaged tissue is large, it is intuitively apparent that its fate should ultimately relate to individual patient survival (Braunwald & Maroko, 1974). Therefore, great interest has focussed on

defining the existence, the extent and nature of the border zone in experimental infarction. Although there is increasing awareness that the endocardial layers are more ischaemic than the epicardial layers (Kjekshus & Sobel, 1970), lateral "border zones" of intermediate tissue damage are implicit in the description by many authors (Becker et al., 1971; Vokonas et al., 1972; Kloner, 1973; Hood, 1975). This picture corresponds to the similar concept of the acutely ischaemic regions, where the flow has been found to decrease gradually from the surrounding normal myocardium through zones of intermediate flow levels to the severely ischaemic central region (Becker et al., 1971; Vokonas et al., 1973; Kloner et al., 1973). This concept of the "border zone" (Hood, 1975) has been supported by observations of differences in the mechanical (Theroux, 1973; Ross et al., 1976) and the electrophysiological (Maroko et al., 1971; Ross et al., 1976; Janse et al., 1979) behaviour of the centre and the border regions of ischaemic myocardium. Measurements of intramyocardial pressures of O_2 (Sayen et al., 1958) and the depletion of myocardial CPK (Maroko et al., 1971; Kjekshus et al., 1976) support this view. In addition pathological and histochemical studies have also provided evidence for the existence of a border zone (Cox et al., 1968).

However, several workers have questioned the above view. Linder et al. (1966) and Herzel et al. (1977) showed a sharp demarcation in myocardial blood flow within a narrow lateral border zone between normal and ischaemic cells. In addition, Fischl et al. (1974) and Marcus et al. (1975) demonstrated that the blood flow in the acutely ischaemic tissue was similar in the centre and lateral borders. Herzel et al. (1977) have also shown that the CPK depletion was uniform throughout the ischaemic zone and no gradient of CPK depletion was observed from the centre of the infarct, to the edges through to the normal myocardium.

The discrepancies in results between the two groups are probably, at least in part, due to the techniques used and methodology employed. The latter studies showing a sharp demarcation between ischaemic and normal zones had a resolution of 1mm or less (Hirzel, 1977; Marcus et al., 1975; Fischl et al., 1974). The earlier reports used techniques which had a resolution of about 4-5mm and contamination of "border zone" samples by normal tissue could have occurred. Hirzel et al. (1977) have clearly demonstrated that throughout the ischaemic myocardium, normal cells are seen, although these are less frequent in the centre and increase towards the periphery of the infarct. Lack of correction for the percentage of normal tissue in each sample leads to an apparent gradient in CPK from centre to periphery. However, correction for this 'contaminant' factor,

demonstrated a sharp demarcation of the boundary between normal and ischaemic cells. Additional evidence is provided by Harken et al. (1978) using NADH fluorescence, who demonstrated a border of less than 1mm. However, the distance between homogeneously NADH-fluorescent ischaemic tissue and homogeneously NADH-nonfluorescent tissue was 6-8mm due to interdigitating normal and ischaemic cells.

It is therefore apparent that:

- (i) The 'border' between ischaemic and normal myocardium is narrow
- (ii) However a zone in which normal and uniformly ischaemic cells interdigitate surrounds an infarct
- (iii) all ischaemic cells are uniformly ischaemic whether situated centrally or laterally

Although the existence of a lateral 'border zone' has been questioned, there is general consensus that ischaemia is more severe in the endocardial regions compared to the epicardial regions (Hirzel et al., 1977; Kjekhsus et al., 1971). Further, a transmural gradient in myocardial blood flow has been shown to exist (Becker et al., 1973; Wüsten et al., 1974). Finally, Riemer et al. (1978) have demonstrated an endo to epicardial progression of the ischaemic wave front in the posterior papillary muscle in dogs.

It is therefore likely that the border zone of intermediately ischaemic cells may be in the transmural plane and that the lateral borders comprise of varying proportion of homogeneously ischaemic and non-ischaemic cells. Or it may be even less well defined than this - "the patchy" histological evidence of infarction may be due to the patchy reduction in myocardial blood flow 5 minutes after coronary ligation (Marcus, 1975).

Measurement of Myocardial Infarct Size

In order to study the effect of drug treatment we need to measure reliably myocardial infarct size in man. The techniques should ideally be:

- (1) nonhazardous
- (2) noninvasive
- (3) capable of assessing and expressing quantitatively, the size of the infarct
- (4) rapidly applicable immediately after the patient's admission as delay in treatment reduces the population of injured cells that are salvageable.
- (5) relatively simple, inexpensive and easy to apply so that its usefulness will not be limited to few specialized centres.

- (6) applicable to all patients with myocardial infarction.

Although several techniques to measure infarct size have been proposed, few actually meet the above criteria. Serum enzymes and ECG methods probably come close to meeting the above criteria. It is, therefore, pertinent to review the principles, background work, advantages and limitations of these techniques.

Infarct Size Quantification from Serum Enzymes

Serum enzyme tests have been used for over twenty years in the diagnosis of myocardial infarction and even the early workers (Nydic et al., 1955) noted a relationship between enzyme activity and infarct size. More recently Chapman et al. (1972) and Thomson et al. (1979) reported a relationship between high enzyme levels and poor prognosis in patients after myocardial infarction. An approach towards more accurate use of serum enzymes in measuring infarct size was stimulated by the pioneering experimental work of Shell, Kjekhus and Sobel (1971). Since then this technique has been applied to human infarction (Sobel et al., 1972) and Bleifeld et al. (1976) have demonstrated a good correlation between enzyme estimates using CPK, left ventricular function and post-mortem infarct size.

Development and Principles of Enzyme Estimates of
Infarct Size

In general infarct size can be estimated using enzymes in the serum if the following conditions can be met:

- (1) Depletion of the enzyme is quantitatively related to the extent of damaged tissue.
- (2) The amount of the marker appearing in the circulation is a constant fraction of the amount lost from the myocardium.
- (3) The volume into which the enzyme is diluted after release from heart muscle remains constant and can be estimated accurately.
- (4) Haemodynamic changes do not alter the rate of disappearance of the enzyme from the circulation and can be accurately determined.
- (5) The enzyme is specific for damaged cardiac tissue.

Sobel and his co-workers (1971,1972) undertook experiments to explore these assumptions. Initially these workers demonstrated that CPK depletion from the infarcted rabbit myocardium correlated linearly with morphological measurements (Kjekshus et al., 1970).

This observation was extended more recently by Heng et al. (1976) to show a relationship between CPK depletion and reduction in myocardial blood flow. Shell et al. (1971) demonstrated a correlation between myocardial depletion of CPK and the total amount released into the serum. The total amount of CPK released was calculated on the assumption that the rate of change of CPK activity after acute myocardial infarction reflects two competing phenomena; release of enzyme from the heart as a function of time ($f(t)$) and the disappearance of enzyme activity from blood according to first order kinetics. (K_d)

Thus,

$$dE/dt = f(t) - K_d E$$

where E = serum CPK activity (Iu/e)

t = time after infarct

$f(t)$ = appearance function of CPK in serum u/ml/min

or

$$f(t) = \frac{dE}{dt} + K_d E$$

The estimation of CPK released from the myocardium between time₀ and time_t can be calculated by integrating the appearance function as follows:

$$\int_0^t f(t) dt = E(t) + \int_0^t K_d E(t)$$

The enzyme appearance function, $\int_0^t f(t)dt$ can be used to estimate grams of infarcted myocardium when knowledge of the distribution space, the fraction of cellular CPK which appears in the blood, and the total amount of CPK contained in a gram of tissue is available. Sobel's group initially used a mean k_d value but as considerable variations were observed in individual k_d values between different patients, Norris et al. (1975) proposed individualization of k_d calculated from the terminal part of the CPK curve.

The above assumptions are based on a one-compartment theory: i.e. that CPK diffuses out of necrotic myocardial cells, travels probably via cardiac lymphatic vessels (Malmberg, 1972) to the blood stream and is removed by the reticulo endothelial system (Roberts et al., 1975) removal occurring exponentially as a first order reaction. CPK metabolism may not be as simple as is suggested by this model. It has been pointed out by Witteveen et al. (1975) and Sobel et al. (1977) that a second or extra-vascular space for CPK distribution exists. The existence of such an extravascular compartment in addition to the plasma distribution space would imply a rate constant for diffusion of enzyme between these two spaces, and in turn the probability that the measured k_d in the plasma is an underestimate and is not representative of total k_d activity in the body (Slutsky, 1977).

These considerations are further complicated by the fact that k_d for exogenous and endogenous CPK may vary in the same animal (Sobel, 1977) and may be caused by differences in donor and endogenous CPK. However, the theoretical possibility that the measured k_d may not be wholly accurate must be borne in mind if movement of enzymes between vascular and extravascular compartments occur or if continuing enzyme is released from the infarct during the period when serum CPK activity appears to be falling exponentially. From the clinician's viewpoint, it is perhaps of more practical importance that the validity of the one-compartmental calculations be correlated with other independent indices of infarct size or severity in man. If such comparisons show good correlations, the method can be of practical use.

Practical Considerations and Limitations of the One-Compartmental Model

The following factors affecting the validity of the one-compartmental model must be considered before it can be used as a basis for infarct size estimations:

- (i) It must be reasonably certain that the enzyme appearing has all come from necrotic myocardial cells. CPK is known to be released from skeletal

muscle after IM injections (Meltzer et al., 1970) in cardiogenic shock and during cardioversion (Eshani et al., 1976). This certainly invalidates the use of CPK in such situations. However, the MB isomer of CPK could be used without error in such circumstances as IM injections, cardiogenic shock or cardioversion do not cause spurious elevations (Eshani et al., 1976).

- (ii) Inaccuracies in the calculation of the total CPK (or MB-CPK) appearance needs careful consideration. Total CPK appearance is calculated equal to $E(t) + kd \int_0^t E dt$ so that three variables must be considered:

(a) First the levels of enzyme (E) can be determined if a standard method is used and careful attention is paid to both the reaction temperature and the degree of dilution (Rosalki, 1967; Sobel, 1972).

(b) Second, the frequency of sampling is of importance as very frequent sampling is distressing to the patient, inconvenient to the research staff and expensive. It has been shown that with 4 hourly sampling, little accuracy is lost when compared to hourly sampling (Norris et al., 1975).

(c) Third, accurate estimations of k_d are essential. Individualised k_d is calculated from the terminal portion of the enzyme curve plotted on a log scale. The slope of the regression is used as the value for k_d (Norris et al., 1975). Whether individualised k_d offers any advantage over use of a mean value for k_d is unclear and depends on the true kinetics of CPK. Cairns and Klassen (1977) have shown that although a bi-exponential model fits k_d , a simpler mono-exponential model was adequate and little accuracy was lost using this simple approximation. Further, as the k_d of different isoenzymes is different (Rapaport, 1975), use of individual isoenzymes and their k_d may be more accurate. It may therefore be of practical importance to individualize k_d ; however, this only holds good if the one compartmental model is correct, and if CPK appearance has ceased during the monoexponential decline phase. If CPK diffuses to more than one compartment in the body or if enzyme release from the heart continues until values are near normal, neither mean or an individualized k_d is valid. Until more detailed information of duration of CPK released from the infarct and its movement between body spaces is available it has been recommended that k_d be measured individually and used in the calculation of total CPK appearance (Norris, 1979).

- (iii) It is necessary to assume that the total CPK appearance is a constant proportion of that lost from the myocardium. Shell et al. (1971) have shown that about 15% of the CPK depleted from the myocardium appears in the serum. Experimental studies have shown that the serum entry ratio (proportion of CPK lost from the myocardium appearing in the blood) may be inversely related to infarct size (Cairns et al., 1977) and that with progressively increasing infarct size, smaller proportions appeared in serum. Further Vatner et al. (1977) and Roe et al. (1975) have shown that the serum entry ratio increases after reperfusion. It must be emphasized that the above phenomena were described in experimental infarction and may not necessarily be applicable to man. Indeed, many clinical studies have demonstrated greater enzyme release associated with cardiogenic shock (Gutowitz et al., 1977).
- (iv) Calculation of the appearance function assumes that the distribution space for enzyme activity (assumed to be plasma volume (Roberts et al., 1975)) remains unchanged. Changes in plasma volume may occur during diuretic therapy and this could lead to an overestimation of infarct size in patients with heart failure (Smith et al., 1976).

Correlation of CPK with other Metabolic Markers or
Clinical Indices of Severity of Infarction

Norris et al. (1976) and Witteveen et al. (1975) have shown a close correlation between other enzymes released from the heart (HBDH, AST) and CPK. Total CPK released correlates well with prognosis (Sobel et al., 1972). Total CPK release is greater in patients with left ventricular failure (Norris et al., 1975; 1976) than in those without failure and is greater in transmural than in subendocardial infarction (Norris et al., 1976); and greater in patients developing right bundle branch block in association with anterior infarction - a known marker of massive anteroseptal infarction.

Good correlations between CPK estimates of infarct size and indices of LV function have been reported (Rogers et al., 1977; Bleifeld et al., 1977).

Quantitative estimates of noncontracting segments on biplane cine angiograms bear reasonable relation with infarct size estimates from CPK (Norris, et al., 1978).

Experimental studies in dogs (Sobel, 1972; Jarmakani et al., 1976) and one clinical study (Bleifeld et al., 1976) have shown good correlations between anatomical infarct size and total CPK release. However, Roe et al. (1976) have shown no correlation to exist

between histological infarct size and total CPK release. Analysis of their data reveals that this was mainly due to relatively small enzyme release in 5 dogs with large infarcts; exclusion of these dogs combined with subtraction of background non-cardiac CPK activity improved the correlation for the remaining 9 animals to $r = 0.84$ (Norris, 1979). This may be either ^{due} to poor flow or greater degradation of the enzymes in the centre of the infarct.

The Electrocardiogram in the Measurement of Infarct Size

Praecordial electrocardiographic mapping is now being used in studies on patients with myocardial infarction. In this review, data will be presented outlining its use, limitations and possible application to assess the effect of interventions on infarct size.

Historical background:

The first electrocardiogram in man was recorded by Augustus Waller in 1887 (Waller, 1887). Since then Smith (1918) demonstrated ST segment elevation in dogs after coronary artery ligation; followed by Pardee (1920) reporting ST segment elevation from praecordial leads

in a patient with acute myocardial infarction. It was Wilson and his colleagues (1933, 1944) followed by Prinzmetal (1954) who described the Q wave and QS changes in acute myocardial infarction and propounded that this resulted either from transmission of a negative cavity potential through necrotic myocardium or due to a resultant vector directed away from the injured area. The relationship between praecordial ST and Q changes were related to the changes in the myocardium at autopsy by Myers et al. (1948).

In recent times the shift in emphasis has been to use the ECG not only as a diagnostic tool in acute myocardial infarction but to use the various waves in trying to assess infarct size. The initial experiments in this field were to use changes from the epicardial ECG and relate it to the underlying myocardial damage (Maroko, 1971). As this obviously cannot be used in clinical infarction, praecordial mapping was proposed (Muller et al., 1975). Praecordial mapping may be of use if the following criteria can be fulfilled:

- (a) Is the praecordial ECG closely related to the epicardial ECG?
- (b) Is the epicardial ECG related to the underlying myocardial damage?

- (c) Is there any evidence that praecordial mapping is quantitatively related to myocardial damage ?
- (d) What are the conditions in which the ECG may be applicable and what are its limitations ?

Is the Epicardial ECG Related to the Underlying Myocardial Damage ?

- (i) Does the epicardial ST elevation, R wave change or Q wave relate to regional myocardial blood flow ?

The reports pertaining to the relationship of ST segment elevation to myocardial blood flow (MBF) are conflicting. Wegria et al. (1949) was the first to report a correlation between ST elevation and MBF. Kjekhsus et al. (1972) noted a relationship between ST elevation at 5 minutes after occlusion and subendocardial and subepicardial flow at 24 hours although the correlation between subendocardial flow and epicardial ST segment elevation was not linear. In contrast reports by Smith et al. (1975) and Heng et al. (1976) showed no correlation or at best a weak correlation between early ST segment elevation and MBF at 24 hours. This was largely due to areas with MBF less

than 10% of control demonstrating little ST segment elevation. Similar experience was reported by Irvin and Cobb (1977) although they noticed that whenever ST segment elevation occurred, this was associated with a $> 50\%$ reduction in regional MBF. Becker (1973) noted a great variability in the relation between ST segment elevation following occlusion and coronary blood flow but found a correlation between areas of high, medium and low flow and ST segment elevation.

Several factors probably are responsible for the poor correlation demonstrated by various workers. Firstly, sites with severe ischaemia often demonstrate intraventricular conduction defect which invalidates the ECG as a measure of ischaemic injury (Muller, 1975). Secondly, geometrical factors may be of importance as demonstrated by the solid angle theory in pigs by Holland et al. (1975, 1977). However, the validity of the solid angle theory to myocardial infarction has not been established and the appropriateness of the pig infarction to human infarction is uncertain. Thirdly, at constant MBF, O_2 demand can vary thereby varying ischaemia and this factor has not been taken into account. However, one can conclude that in the presence of ST segment elevation, without conduction defects and probably for small infarcts, a good relationship with MBF may exist.

Few data exist regarding the relationship of Q waves to regional MBF. However, in one study (Heng et al., 1976) a good relationship between the presence of epicardial Q wave sites and MBF reduction has been reported.

(ii) Relationship between epicardial ECG changes and myocardial enzyme depletion

The initial work of Maroko et al. (1971) demonstrated a good correlation between myocardial CPK depletion and the epicardial ST elevation. However, those observations have been challenged by Heng et al. (1976) who showed a poor relationship between epicardial ST elevation and underlying CPK depletion. The discrepancies between the above reports are probably due to the differences in size of infarct produced. With larger infarcts, spatial factors come into play (Holland, 1977) and may reduce the degree of ST elevation. However, it must be emphasized that in the study of Heng et al. (1976) no correlation between the total ST segment elevation in each dog and the total CPK depletion was attempted. By contrast, there is general agreement that Q wave changes correlate closely with CPK depletion (Heng et al., 1976; Muller et al., 1978;

Mickelborough et al., 1978) and with histologic evidence of cellular damage (Ergin et al., 1976).

Relationship of the Praecordial ECG to the Epicardial ECG

Work relating epicardial and praecordial mapping is surprisingly little. Maroko et al. (1972) and Muller et al. (1975) demonstrated similar directional changes in ST segment elevations using multiple lead simultaneous praecordial and epicardial ECG. Holland et al. (1977) have proposed theoretical models to assess this relationship and have shown that similar directional changes may not occur in pigs. However, these workers used only a single recording electrode and demonstrated that with increasing infarct size, epicardial ST segment elevation may fall whereas praecordial ST segment increases. Further, the intraventricular conduction delay seen on the epicardial surface has not been reported from praecordial ECG.

Another factor affecting the relationship between epicardial and praecordial ECG is the conductivity of the intervening tissue (Holland, 1977). It has been theoretically proposed and also shown in experimental infarction, that changes in conductivity of the intervening tissue completely alters the ECG recorded from the surface of the chest (Akiyama et al., 1978). This

may be of importance in patients with pulmonary oedema, pneumothorax etc.

Relationship between Praecordial Mapping and Other Indices of Myocardial Damage

Norris et al. (1974) showed that ST segment elevation 48 hours after the onset of pain correlated with maximum AST (SGOT) in patients with anterior and inferior infarction. Blomqvist et al. (1975) showed a significant correlation between the sum of the ST segment elevation and the area of pyrophosphate scan. By contrast, Norris et al. (1976), Thompson et al. (1976) and Selwyn et al. (1977) showed no correlation or at best a weak correlation between ST segment elevation and peak or total plasma enzyme. Similarly, Willerson et al. (1977) demonstrated a weak correlation between the ST segment elevation and the area of pyrophosphate scan in man.

However, data relating the Q waves to other indices of myocardial damage have consistently shown a good relationship. Myers et al. (1948a & b; 1949) described an excellent correlation between the development of Q waves in specific praecordial leads and pathological evidence of infarction in the corresponding areas of the heart. Similarly in patients undergoing cardiac surgery, it has been shown that praecordial Q waves generally overlie epicardial Q waves and that these indicate the

presence of myocardial fibrosis (Bodenheimer et al., 1976). In addition a close correlation between praecordial Q waves and ventricular performance in patients with coronary artery disease has been reported (Miller et al., 1972; Williams et al., 1973; Miller et al., 1974; Awan et al., 1977).

Limitations of the ECG in Assessing Myocardial Infarct Size

- (i) Firstly, the entire experimental work using ECG mapping has been confined to anterior infarcts. In the clinical situation, praecordial mapping may only be valid in patients with anterior or lateral infarction. Therefore care must be taken that patients' studied do not have inferior wall or posterior wall extensions.
- (ii) ST segment elevation may vary considerably in the same patient (Norris et al., 1976; Selwyn et al., 1977) and is known to decrease with increasing time. Therefore this may further limit the use of ST segment mapping.
- (iii) Factors other than ischaemia may cause ST segment changes and patients with these conditions should be excluded (e.g. pericarditis, conduction defects etc.).

(iv) Finally, it is possible that some drugs may reduce the ST segment elevation by altering local K^+ concentration even without reducing ischaemia (Holland & Arnsdorf, 1977).

However, the latter three problems are unlikely to occur with analysis of the Q waves and R waves.

CHAPTER II

METHODS

METHODS

This chapter describes the techniques used in this thesis and outlines the design and organisation of the atenolol (AT) trial. Details about patients in individual studies are provided later in the respective chapters.

Praecordial Electrocardiographic Mapping

Praecordial electrocardiographic mapping was done in patients with anterior myocardial infarction. Thirty-five praecordial sites were selected by focusing an ordinary projector beam through a 35mm slide with 35 holes arranged in 5 horizontal rows and 7 vertical rows. The horizontal rows were designated from top to bottom A to E and the vertical rows from right to left 1 to 7. The distance between the first and second vertical rows was twice the distance between the others to avoid electrode placement on the sternum. With the patient sitting up at 45 degrees, A1 was focused on a point 2.5cm to the right of the sternal edge in the second intercostal space. E1 was focused 2cm below the level of the xiphisternum in the same line as A1. The position of the projector was adjusted so that A7 fell on a spot high in the left mid-axillary line in such a way that rows A to E were horizontally placed. All spots were

then marked using indelible ink to allow accurate repositioning of the electrodes each time a recording was obtained.

The electrocardiograms were recorded using a four-channel ink-jet Elema-Schonander Mingograf 34 recorder. Suction cup electrodes with a contact diameter of 15 mm were used. The electrocardiogram was recorded from each praecordial site at two different gains simultaneously (1mv = 10mm and 1mV = 40mm) so that an accuracy of 0.025 mV could be obtained. Paper speed was 25 mm/s.

Each recording was made during quiet breathing and great care was taken to reposition the patient at the same angle on each occasion. The first recording was obtained at a mean time of 6 hours after the onset of pain. Subsequently, recordings were obtained at 8-hourly intervals during the first 24 hours, at 12-hourly intervals on the second day, and thereafter daily.

Initial studies showed that praecordial electrocardiographic mapping was of limited value in inferior infarction. Therefore, in order to record changes from the inferior surface of the heart, the standard 12 lead electrocardiogram was recorded serially, the V lead positions being marked on the chest wall to obtain reproducible recordings.

Electrocardiographic Measurements

Anterior infarct patients

The amplitude of the Q, R, and S waves, and of ST segment elevation (at 60 ms after the J point) was measured in 5 beats from each site, using the TP segment as a baseline. Measurements were made on both the magnified (1 mV = 40 mm) and regular recordings (1 mV = 10 mm). These were then summed from 35 leads to obtain ΣR , ΣQ , ΣS , and ΣST . In addition, $\Sigma(Q+S)$ and $\Sigma R / \Sigma(Q+S)$ were calculated for each map.

Inferior infarct patients

In patients with inferior infarction, $R_{II} + III + aVF$, $Q_{II} + III + aVF$ and ST segment elevations in $II + III + aVF$ were calculated.

Serial CK and CK MB Analyses

Blood samples were obtained from a peripheral vein through an indwelling cannula at 4-hourly intervals for 72 hours after the onset of pain. Samples were immediately centrifuged for 15 minutes. Plasma was pipetted into plain sterile glass tubes and stored at -20°C .

Creatine kinase isoenzyme separation

Several methods exist for the determination of CK isoenzymes including various immunological (Jockers-Wreton & Pfleiders, 1975; Nicholson & O'Sullivan, 1973), electrophoretic (Roberts et al., 1974; Anido et al., 1974; Smithies, 1959; Smith, 1972), and kinetic (Wong & Smith, 1976; Witteveen et al., 1974) techniques. Recently, a procedure has been reported that measures CK activity after inhibition of the M subunit using a specific antiserum (Neumeier et al., 1976).

Criticisms of electrophoretic methods have been made because of the asymmetrical distribution of the isoenzymes in the support media and the inability of the chemical reactants to diffuse completely into the media. Mercer (1974), and Mercer and Varat (1975) developed a method which separates the CK isoenzymes by anion exchange chromatography using small columns of DEAE Sephadex A-50. Yasmineh and Hanson (1975) compared this method with the electrophoretic technique and concluded that the method correlated well in their separation patterns for CK isoenzymes but that the anion exchange method of Mercer was superior in both precision and sensitivity.

This study included the measurement of CK isoenzymes in subjects suspected of having acute myocardial infarction who may have normal values and

for this reason the method of Mercer and Murray (1975) was the one of choice.

Materials

1. 50 mM Tris-HCl buffer, pH 8.0 containing 100 mM sodium chloride (Buffer 1).
2. 50 mM Tris-HC- buffer, pH 8.0 containing 200 mM sodium chloride (Buffer 2).
3. 50 mM Tris-HCl buffer, pH 7.0 containing 300 mM sodium chloride (Buffer 3).
4. DEAE Sephadex A-50 equilibrated with Buffer 1.

Apparatus

A series (approximately 20) of disposable 15 Pasteur pipettes were positioned vertically on a wooden frame such that collection tubes could be placed on the bench beneath the tip of the pipette for the purpose of fraction collection. The pipettes were packed with a bed support of glass wool followed by about 50mg of DEAE Sephadex A-50 (Reagent 4, above) to form a column approximately 0.5 x 5 cms.

Procedure

Each of the mini columns (described above) was equilibrated with Buffer 1. A 1 ml plasma sample was applied to the column followed by 5 x 1 ml volumes of Buffer 1. The 1 ml fractions of eluate (Nos. 1 to 5) were pooled and contained the MM isoenzyme of CK.

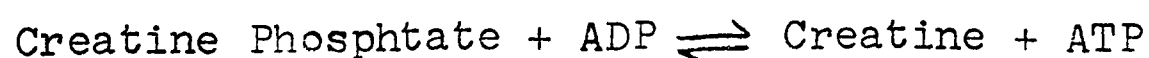
3 x 1 ml volumes of Buffer 2 were added and 1 ml eluate fractions (Nos. 7 to 9) were collected and pooled. These contained the MB isoenzyme of CK.

Finally, 3 x 1 ml volumes of Buffer 3 were added to elute the BB isoenzyme of CK in the pooled fractions (Nos. 10 to 12).

Measurement of creatine kinase activity

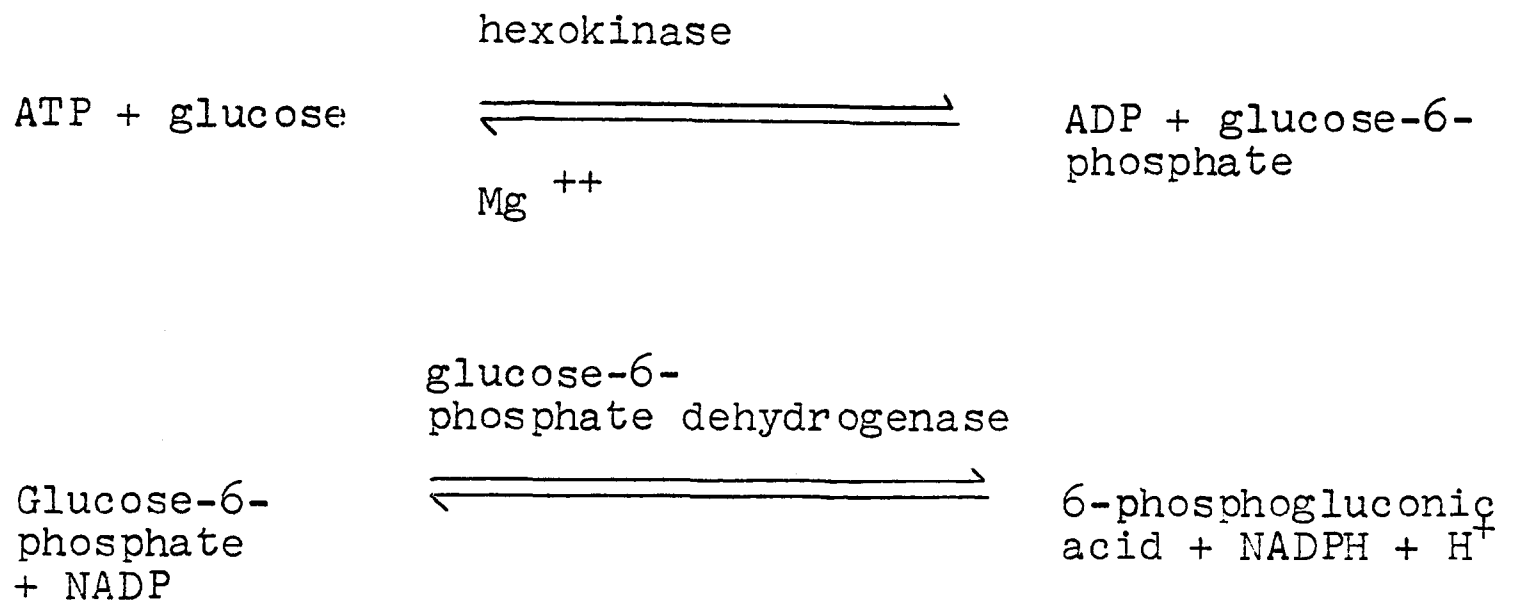
Creatine kinase activity in plasma and the column eluate pools was assessed using the method of Oliver (1955) with dithiothreitol as activator. Rather than reproduce this well established method, a kit package was purchased from Searle Diagnostic (Searle CPK-UV11 Kit).

Creatine Kinase catalyses the reversible reaction -



The reaction rate is monitored in the assay by a multi-enzyme system linking ATP formation to the reduction of

NADP which can be followed by the increases in absorbance of the reaction mixture at a wavelength of 340 nm, e.g:



For the plasma assay, the kit was used as instructed by the manufacturers, but for the column eluates which required larger sample volumes, the substrate reagent was made up in less water so that the final concentration of reactants in the test mixture remained constant.

Final Test Concentrations

| | |
|--------------------|--------------|
| Creatine phosphate | 35 mM |
| ADP | 1 mM |
| NADP | 0.6 mM |
| Glucose | 20.0 mM |
| AMP | 10.0 mM |
| Magnesium Acetate | 10.0 mM |
| Dithiothreitol | 5.0 mM |
| Hexokinase | 1.2 Units/ml |

| | |
|-----------------------------------|---|
| Glucose-6-Phosphate dehydrogenase | 1.2 Units/ml |
| Sodium Chloride | 126 mM in 35 mM Pipes buffer pH 6.9 |

The enzyme activity measurements were performed using an LKB 8600 Reaction Rate Analyser.

Volumes Used in Assay Mixture

| | <u>Plasma</u> (ml) | <u>Column Eluate</u> (ml) |
|---|-----------------------|------------------------------|
| Substrate (all reagents except phosphate) | 1.00 | 0.50* |
| Sample | 0.05 | 0.50 |
| Reconstituted starter (creatine phosphate) | 0.10 | 0.10 |

* Substrate reconstituted in 6ml distilled water,
not 11.0 ml as recommended.

Calculating the Creatine Kinase Activity

One unit (U) is defined as that amount of enzyme which converts 1 μ mole of substrate in 1 minute under the conditions of the assay. The same units are used for all the enzyme assays in this study.

From the change in absorbance per minute ($\Delta A/\text{minute}$) obtained from the analyser, the activity of the creatine kinase can be derived by using the equation:-

$$\text{Activity} = \frac{\Delta A/\text{minute} \times \text{volume of assay mixture}}{\text{volume of sample}} \times \frac{1000}{\text{millimolar extinction co-efficient of NADPH at a wavelength of 340 nm}} \text{ U/l}$$

For plasma this becomes:-

$$\text{Activity} = \Delta A/\text{minute} \times \frac{1.15}{0.05} \times \frac{1000}{6.22} \text{ U/l at } 37^{\circ}\text{C} = \frac{\Delta A/\text{minute}}{3700} \text{ U/l}$$

$$\text{For eluate } \Delta A/\text{minute} \times \frac{1.10}{0.5} \times \frac{1000}{6.22}$$

$$= \Delta A/\text{minute} \times 354.0 \text{ U/l}$$

Quantitating infarct size

The assessment of infarct size was accomplished using the method of Norris et al. (1975) for serial serum CK activities, and Sobel et al. (1976) for serial CKMB activities.

An explanation of the method is presented for serum CK activities, but applies also to CKMB determinations.

Serum CK activity was determined for each sample. Each result was adjusted by subtracting an assumed baseline CK activity (a mean value within the normal range).

When the serum CK activities were plotted against time, a typical pattern was usually obtained. CK activities increased to a maximum value which was reached after about 24 hours. This was generally followed by a slow decrease in CK activity, then by a more rapid monoexponential decrease.

The CK activity for any sample on the fall curve is governed by the fractional disappearance rate (K_d) of CK. This (K_d) can be estimated as the slope of the regression between log CK and time.

For specimens not included on the monoexponential decay curve, the CK activity is subject to this 'disappearance effect' as well as to an 'appearance effect' ($f(t)$) of CK released from damaged cardiac tissue into the circulation.

Changes in CK activity can therefore be expressed as:-

$$\frac{dE}{dt} = (f(t)) - K_d E$$

$E =$ serum CK activity (U/l)
 $t =$ time after infarct (hours)
 $f(t) =$ appearance function of CK in serum (U/l/hour)
 $K_d =$ fractional disappearance rate of CK from serum (U/l/hour)

The total CK released from damaged myocardium (CK_R) may then be expressed:-

$$CK_R = \int_0^t f(t) dt = \int_0^t \left(\frac{dE}{dt} + K_d E \right) dt$$

For each specimen therefore the CK_R can be determined from the relationship -

$$CK_R = E_t + K_d \bar{E} dt \quad \text{where } \bar{E} = \text{average CK activities between two samples}$$

$$E_t = \text{CK activity measured for that sample}$$

$$dt = \text{time between samples}$$

When the CK_R was plotted against time it eventually achieved a plateau which signified no further release of CK from the damage tissue. The value for CK_R at this plateau is a measure of the total CK released from the damaged myocardium into 1 ml serum, which is, in turn, the measure of infarct size.

Organisation of the atenolol trial

Based on the preliminary studies outlined in Chapters III, IV and V, a trial was designed to assess the efficacy of atenolol, (a B_1 selective adrenergic blocking drug) in limiting infarct size. The next section outlines the organisation and running of the trial.

Trial size

It was 'estimated' that a trial size of at least 200 patients randomised between atenolol (AT) and standard therapy would be required to have a "reasonable chance" of detecting a 30 - 40% reduction in infarct size. The initial study was planned to run from 1st October 1978 to 31st December 1979 at Oxford. Since 1st March 1979, the Wythenshawe Hospital at Manchester, have joined the study.

Drugs

Patients on entry were randomised to receive 5mgm atenolol intravenously followed by 50mgm orally twice daily on the first day and 100 mgm daily during the rest of the hospital stay. The decision to stop or continue atenolol after discharge was left to the physician-in-charge of the patient. Control patients received standard therapy and no placebo was used (see below).

All drugs were supplied by Imperial Chemical Industries (Pharmaceuticals Division) and were stored in the coronary-care unit (CCU).

Standard investigations

Almost all patients admitted to the casualty had a 12-lead ECG taken before transfer to the CCU, and if this was not done, or if it was considered technically

unsatisfactory by the CCU nursing staff, a technically satisfactory 12-lead ECG was taken immediately after entry to the CCU. A blood sample was drawn from each patient immediately after entry to the CCU. The clinical history included (as accurately as possible) the time of onset* of the signs or severe pain which necessitated CCU admission.

Selection of patients

All conscious patients with a probable infarct in the previous 12 hours (symptoms alone or signs alone were sufficient) were considered eligible for randomisation as soon as they entered the CCU as long as:-

- (i) Staffing problems at the CCU (holidays, sickness absence, a large workload, a concurrent crisis) did not make the extra work (of getting the trial duty doctor to enter the patient and taking 12 extra blood samples over the next three days) impracticable though this rarely happened.

* Very often it is difficult to determine the exact onset of pain. In our study we have defined it as the onset of the symptoms which caused the patient to call the general practitioner or the ambulance which eventually lead to the patient's admission. This was not later changed at all.

- (ii) The patient had not been given beta-blockers during the previous 24 hours.
- (iii) The trial duty doctor could attend.
- (iv) The trial duty doctor did not feel that there was a degree of cardiac failure (or some other medical condition) sufficient to constitute an immediate and definite contra-indication to beta-blockade. No exact criterion for this was formulated, and different trial duty doctors interpreted it slightly differently, though a broad consensus emerged from discussion among the physicians who were associated with the study. Generally, moderate cardiac failure, moderate bradycardia (e.g. no worse than 40 beats/minute) alone did not contraindicate atenolol.
- (v) The trial duty doctor did not feel that there was a definite and urgent indication for administration of beta-blockers (again, no exact criterion was formulated, but generally other drugs were used if possible. For example, it was recommended that high BP could be treated adequately with Methyl DOPA and supraventricular tachycardias likewise with other drugs e.g. digoxin or disopyramide. Note: Verapamil was always avoided as dangerous effects with beta-blockers may occur).

Procedure for entry

When a conscious patient with a possible infarct (i.e. a reasonably good history \pm ECG evidence) was admitted to the CCU at a time when pressure on the nursing staff allowed entry to the trial.

- (a) THE NURSING STAFF checked that:
- (i) A technically satisfactory 12-lead ECG had been performed,
 - (ii) An extra 8mls of blood was taken for the study, the time at which it was drawn was recorded and 4mls of serum were spun down for enzyme estimation,
 - (iii) The patient was not apparently on a beta-blocker.
 - (iv) Onset of symptoms was within the past 12 hours.
 - (v) This was not a readmission of a previous trial patient.
- (b) THE NURSING STAFF then called the trial duty doctor. At all times there was a board in the CCU with the name of the doctor who was responsible for admission of trial patients, and details of how to reach him by phone (during the day this was almost always the writer). During evenings, nights and weekends it was usually one of

Professor Sleight's Housemen. The Housemen were covered by me or one of the cardiac Registrars if a second opinion was sought).

- (c) THE TRIAL DUTY DOCTOR came to the CCU. He confirmed that the patient was not already on a beta-blocker. If he felt that beta-blockers must be given, or must be avoided, then the patient was ineligible and no further action was needed. Otherwise,
- (1) If the infarct appeared to be anterior or was only a suspected infarct, the duty doctor or research nurse did a 35-lead ECG, which took about 15 minutes (NB some patients presented at night with an anterior infarct, or suspected infarct and although it was highly desirable to have a 35-lead ECG on these patients there were several cases where the trial duty doctor was unable or unwilling to perform it in the middle of the night. Such patients were randomised anyway. This was unsatisfactory, but was better than losing them entirely from the trial).

- (2) After this (for anterior infarcts) or immediately (for other infarcts), patients were randomised by opening the next in the series of numbered sealed envelopes held in the CCU, and noting the exact time when the envelope was opened .
- (3) If the random allocation was atenolol, 5mgm was given intravenously over 5 minutes followed by the first oral dose of 50mg, either immediately or, if a substantial adverse reaction to beta-blockade was felt to be at all possible, after an observation period of about half an hour after the injection.
- (4) The doctor checked that the indwelling catheter appeared satisfactory.
- (5) The doctor asked the patient if he/she would consent to about a dozen blood samples being drawn for research purposes from the indwelling catheter over the next 3 days. One would be during the next night (disturbing the patient's sleep but all the rest would be by day).

- (d) One of the Nursing Staff was with the patient when the doctor requested consent, to ensure that the patient's real wishes were ascertained. If the patient consented, the nurse marked his notes with the (approximate) times over the next 3 days at which blood samples were due. (This was some or all of 6.30 hrs, 10.30, 14.30, 18.30 and 22.30hrs on the day of entry (day 0) depending on the time of day when the patient entered, and then 2.30 hrs the next night, and 6.30, 10.30, 14.30, 18.30 and 22.30 on the next day (day 1) followed by an unbroken night's sleep and samples at 6.30, 14.30 and 22.30 on day 2 and again on day 3). A preliminary sample of blood was drawn immediately unless one had already been taken in the CCU.

Finally, the trial duty doctor or the nursing staff plugged a 24-hour tape-recorder into the bedside monitor. (The tape needed no further attention from the nursing staff and turned itself off automatically after 24 hours, ready for collection during the daytime).

Management after entry

The only difference in management was that those patients who consented had blood samples taken by the nursing staff during the first 3 days, and spun down for enzyme estimation. Apart from this, half the patients received 100mg of AT orally daily while they were in hospital, and a doctor concerned with the trial (usually I or the research nurse) came once in the daytime two or three days after entry to do a 12- or a 35-lead ECG, and once in the daytime about a week later to do another 12- or 35-lead ECG.

Blood sampling

Blood samples were taken within about half an hour of the time that they were due, and the actual time and date at which they were taken were always recorded (rather than the time when they were due). If it was convenient for the CCU nursing staff to take the samples for trial enzyme estimations then they did so, but if for whatever reason it was not possible, or if the indwelling catheter failed, they called the duty doctor for assistance. If, due to some crisis, it was neither practicable to call the duty doctor nor to take the blood samples at the scheduled times then that sample was delayed (or even omitted entirely, although this rarely happened).

Samples were spun down when taken, and all samples on one patient were stored at -20°C in the CCU until no more were due, when they were taken away for analysis.

Data collected from each patient

At entry: Full name, sex, exact date of birth, address, hospital number, date of entry, exact time of onset of symptoms, current drugs (esp. beta-blockers, antibiotics, heparin, digoxin), blood pressure, presence or absence of cardiac failure, number of previous infarcts.

ECG's: 12-lead initially; if infarct was anterior or unclear, 35 lead as well. During the daytime 48-72 hours after entry, another 12-lead or 35-lead ECG was taken. On entry, if there was a spare 24-hour tape-recorder it was plugged into the bedside monitor and was left to run (for 24 hours) until it stopped.

Enzymes: If the patient consented, blood samples for (MB-CPK) enzyme levels were taken during the first three days.

Estimated intake:

Judging by the actual intake rate during 1977, it was expected that on average about three eligible patients per week would be admitted to the CCU. The best one hoped for was the entry of 200 patients in the period 1 October 1978 - 31 December 1979. Although this would not be sufficient to assess reliably the relevance of these treatments to mortality, it may have sufficed for reliable detection of a 40% decrease in Q wave evolution (or in enzyme release) in response to treatment, and might well have sufficed for the detection of a 25% decrease. If fewer than 100 patients were entered in total, random errors (whereby, by chance, one happens to give active treatment to more or less than average of those who would do badly anyway) might well have seriously distorted the results to the point where they obscured the truth.

Preliminary analysis

Controlled and uncontrolled previous experience with beta-blockers suggested that the treatment was safe, but also unfortunately demonstrated that the benefits would not be enormous. Although one might reasonably have hoped that the further development of infarction might be reduced by about a third, it seemed unlikely that it could be reduced by two-thirds. It was, therefore, undesirable to analyse the data prematurely, with a view

to stopping intake if any marked discrepancies arose as any marked discrepancies arising early in the study were likely to be misleading and would almost certainly be evened out if more data were accumulated. We therefore proposed to continue the fullest possible intake until 31 May 1979. If analysis of the patients entered up to 31 May showed a difference of 3 SD's in favour of AT or 2 SD's against AT then this fact would be published and AT would be given to all or to none of the patients entered during the second half of 1979, or the trial would be stopped. Otherwise, no publication would be issued until the full data was available and analysed for all patients entered between 1 October, 1977 and 31 December 1979.

Prior hypotheses

- (1) It is possible that treatment may be especially useful if given early, and we therefore decided to do a separate analysis among those who were randomised within 4 or less hours of disease onset (Peter et al., 1978).
- (2) Atenolol may be especially helpful in those with initial tachycardia (Heart rate ≥ 80) or high blood pressure.

Bias

If the physicians in the CCU tended to give very different ancillary treatment to trial patients who they knew were on atenolol, then this could bias our results. However, we considered the likelihood of material biases of this nature too small to justify the ethically dubious practice of giving placebo injections.

In addition, all ECG, enzyme data and arrhythmia tape-recordings were analyzed by a 'blinded' investigator to eliminate investigator bias.

Protocol deviations

If the physicians responsible for a trial patient who was receiving oral atenolol felt strongly that treatment should be stopped, then it was stopped. Conversely, if he felt strongly that a trial patient who is not receiving beta-blockers should do so, then this was done. Such protocol deviations were, however, only allowable in response to strong feelings, and were discouraged. Atropine-responsive bradycardia or atropine responsive hypotension was not an indication for stopping AT. If cardiac failure developed but responded to treatment with lasix, or to lasix plus digoxin, AT was usually continued. Very often in patients with low blood pressure or slow heart rate, the daily dose was reduced to 50 mgm instead of the full 100 mgm.

Ethics

Treatment with AT was given in the hope that it would be of direct medical benefit to the patient, and therefore we felt that there was no need to solicit any kind of consent before its administration - just as there would be no need to obtain informed consent for AT usage if, for example, we chose to evaluate AT (unscientifically) by making a policy decision that all patients presenting at the CCU in 1979 were to be given AT, with the intention of comparing the average outcome in 1979 with the average outcome in 1978.

However, the taking of serial blood samples for enzyme estimation cannot benefit the patient from whom they are taken, and we therefore felt that (although they will be taken from an indwelling catheter that would be there anyway for emergency treatment) the patients should be freely allowed to refuse this procedure if they felt so disposed. Nurses were present when the duty doctor requested consent to this and ensured that no pressure was put on unwilling patients to consent to the extra blood sampling. This policy and the protocol were approved by the local Ethics Committee and all the physicians at both hospitals.

Randomisation envelopes

These were numbered in sequence (1,2,3) on their outsides, with the treatments inside arranged in a completely random order by Mr R. Peto and were kept in the CCU. The exact time and date on which each envelope was opened was recorded. Once an envelope was opened for a particular patient then that patient was irrevocably in his assigned group even if he died before treatment could be started or if the diagnosis of M.I. was later refuted. Envelopes were never allowed to be opened prematurely (and were opaque to transillumination).

Recruitment of other Centres

One of the chief determinants of the reliability of such a trial is undoubtedly the total number of patients randomised. It was therefore decided to enlist the help of at least one other centre. Once the trial was well established, the Wythenshawe Hospital (Drs. D. Ramsdale, D. Bennett and C. Bray) agreed to collaborate and since March 1979, fruitful collaboration was possible.

All data were collected on standardised forms in both centres. All ECG and enzyme analysis were done at Oxford in a uniform manner. Evaluation of the effects of treatment on mortality is also being monitored although it is not really likely that we shall have a large enough trial to assess this (on provision of full name, address and exact date of birth, long-term mortality is being monitored through the National Death Register).

Data forms

A copy of all data forms is provided in Appendix I at the end of the thesis.

STATISTICAL METHODS:-

Standard statistical techniques of correlation have been used to compare the relation between two variables. Unpaired 't' tests have been employed to compare data from two different groups of patients and paired 't' tests to compare trends within the same patients. In addition, Wilcoxon's rank test has also been used to compare data between two small groups. Data have been presented as mean \pm standard error of mean. 2P denotes two tailed 't' tests; P denotes one tailed 't' tests.

CHAPTER III

VALUE OF ELECTROCARDIOGRAM IN PREDICTING
AND ESTIMATING INFARCT SIZE IN MAN

In Chapter I, I have discussed that the quantity of necrotic myocardium is the main determinant of immediate and long-term prognosis after myocardial infarction. Experiments in animals now indicate that the size of an infarct may be limited by appropriate interventions (Maroko & Braunwald, 1973). However, the clinical assessment of interventions designed to protect ischaemic myocardium has posed considerable difficulty. Various techniques (Shell & Sobel, 1976; Bliefeld et al., 1977; Poliner et al., 1977; Muller et al., 1978) have been proposed for measuring and following trends in infarct size in patients. Two of these - ECG and enzyme methods - have been discussed in detail in Chapter I.

In the clinical situation, comparison of any method of measurement of infarct size (e.g. ECG or enzyme) with direct anatomical measurements is not possible in the majority of patients. The alternative is to compare a particular method (e.g. ECG) with another independent method (e.g. enzyme, Technetium scanning, myoglobin release). In this chapter I propose to study the relationship between ECG and enzyme methods of infarct size measurements. If these two show good correlation with each other, it is likely that both are reliable measures of myocardial damage.

Further, most workers have assessed the value of individual waves of the electrocardiographic complex (Norris et al., 1976; Selwyn et al., 1977a & b), and there are few data on the QRS complex as a whole and its relation to ST segment changes in the same patient. The present study was undertaken to investigate further the value of changes in the QRS complex and the ST segment elevation as a guide to infarct size in the coronary care unit. The main aims were to study the relation of the magnitude and extent of Q wave development, R wave loss and ST segment elevation to each other and to infarct size estimated by calculating the total release of myocardial isoenzyme of creatine kinase (CK MB) into the plasma.

Patients

Forty-one patients, aged between 46 and 75 years (mean 62.5 years), admitted to the coronary care unit (CCU) of the Radcliffe Infirmary with definite evidence of a recent myocardial infarction on a 12 lead electrocardiogram and significant increase in cardiac enzymes, were studied. Patients with intraventricular conduction defects (QRS duration >100 ms) including hemiblocks and second and third degree AV blocks were excluded. All patients had normal mean frontal axes (0° to $+90^{\circ}$).

Of the 41 patients, 37 gave no history of a previous infarct, and a previous electrocardiogram was available in 14 of these. Twenty-seven patients had anterior infarcts and 14 inferior infarcts; none of the 4 with a history of previous infarction had pathological Q waves on their initial electrocardiogram. Four patients developed reinfarction as shown by new electrocardiographic and enzyme changes. Routine management of the patient was not altered by the study procedure; diuretics and antiarrhythmic drugs were administered as clinically indicated. Lignocaine was given to 8 patients, 11 patients received oral beta-blockers, and disopyramide was used in only 1 patient. No patient had a systolic blood pressure less than 90mmHg. Three patients required cardioversion for ventricular fibrillation, none of whom showed a further rise in CK MB.

Methods

The methods used in this study are praecordial mapping in patients with anterior infarction, 12-lead standard ECG in patients with inferior infarction and serial CK MB in all patients. These are described in detail in Chapter II.

ECG recordings were made during quiet breathing and great care was taken to reposition the patient at the same angle on each occasion. The first recording was obtained at a mean time of 6 hours after the onset of pain (at less than 4 hours in 19 patients, at 4 to 6 hours in 12 patients, and at 6 to 12 hours in 10 patients). Subsequent recordings were obtained at 8-hour intervals during the first 24 hours, at 12-hour intervals on the second day, and thereafter daily.

Initial studies showed that praecordial electrocardiographic mapping was of limited value in inferior infarction. Therefore, in order to record changes from the inferior surface of the heart, the standard 12 lead electrocardiogram was recorded serially, the V lead positions being marked on the chest wall to obtain reproducible recordings.

Reproducibility Studies in Control Subjects

Four groups of control subjects were studied:

(i) A group of patients aged between 45 and 75 years admitted to the ophthalmic and ENT wards, with no history, clinical evidence or ECG changes of ischaemic heart disease (n = 10).

(ii) A group of normal healthy male volunteers (n = 10).

(iii) A group of patients admitted to the CCU, with a typical history suggestive of acute myocardial infarction in the previous 12 hours but in whom there was no ECG or enzyme evidence (from 4-hourly CK MB) of proven infarction. None of these patients had a previous history of myocardial infarction (n = 9).

(iv) Five patients 2 to 4 weeks after infarction, likely to have a stable electrocardiographic pattern.

The patients were studied to obtain "normal values" (group i to iii) for comparison with patients suffering infarction and to confirm the reproducibility of praecordial mapping and the standard 12-lead electrocardiogram. Recordings were examined for beat-to-beat variations during sinus rhythm and atrial fibrillation, variations during quiet and deep breathing, variations caused by electrode repositioning, and those resulting from changes in patient position.

The beat-to-beat variation of measurements of the QRS complex and of ST segment elevation in the same recording during sinus rhythm was small (mean 2.2%), compared with a mean of 15 per cent and 20 per cent in 2 patients who were in atrial fibrillation (belonging to group iv). The variations resulting from changes in posture and during deep breathing were considerable (mean 12.2% and 18.5% respectively). In contrast, the

variation caused by electrode repositioning, day-to-day variation, and variation during quiet breathing with the patient at 45 degrees and in sinus rhythm was less than 5.3 per cent. All patients were in sinus rhythm except two who were in atrial fibrillation in whom 10 consecutive beats were averaged.

Results

(i) Control subjects

There was no significant difference in ΣR , ΣQ , $\Sigma ST +$ or $\Sigma R/\Sigma(Q+S)$ between the first two control groups (i.e. patients without cardiac disease and normal volunteers). They were therefore combined as a normal group. The ΣR was 217 ± 14 mm; ΣQ was 5.05 ± 1.6 ; $\Sigma R/\Sigma Q+S$ was 1.72 ± 0.21 mm and $\Sigma ST +$ was 12 ± 2.3 mm in this group (mean \pm S.E.M.).

Patients admitted to the CCU and diagnosed as having unstable angina had similar ΣQ and $\Sigma ST +$ values (2.11 ± 1.4 mm and 10 ± 2.5 mm respectively) compared to the normal group. The ΣR and $\Sigma R/Q+S$ were slightly lower than in the normal group (178 ± 14 mm and 1.15 ± 0.11 ; $2p = 0.10$).

(ii) Relation between cumulative CK MB and Praecordial Map in Patients with Anterior Infarction

ST segment elevation (Fig. 1)

The maximum Σ ST observed during the first three days was found to correlate significantly with cumulative CK MB ($r = 0.733$; $p < 0.001$). There was no significant correlation between Σ ST at any other time and cumulative CK MB. The maximum number of recording sites with ST segment elevation more than 1 mm or more than 2 mm also did not correlate with cumulative CK MB.

Q waves

Correlation between the maximum Σ Q and cumulative CK MB was highly significant ($r = 0.827$; $p < 0.001$; Fig. 2). No correlation was observed between the number of recording sites showing pathological Q waves ($r = 0.265$; $p > 0.1$), or QS waves ($r = 0.363$; $p > 0.1$) and cumulative CK MB.

R wave and $R/(Q+S)$

The inverse relations between minimal Σ R (Fig. 3) and minimal $\Sigma R/(Q+S)$, and cumulative CK MB were less significant ($r = -0.623$; $p < 0.01$ and $r = -0.624$; $p < 0.01$, respectively) than the relation between maximum Σ Q and cumulative CK MB.

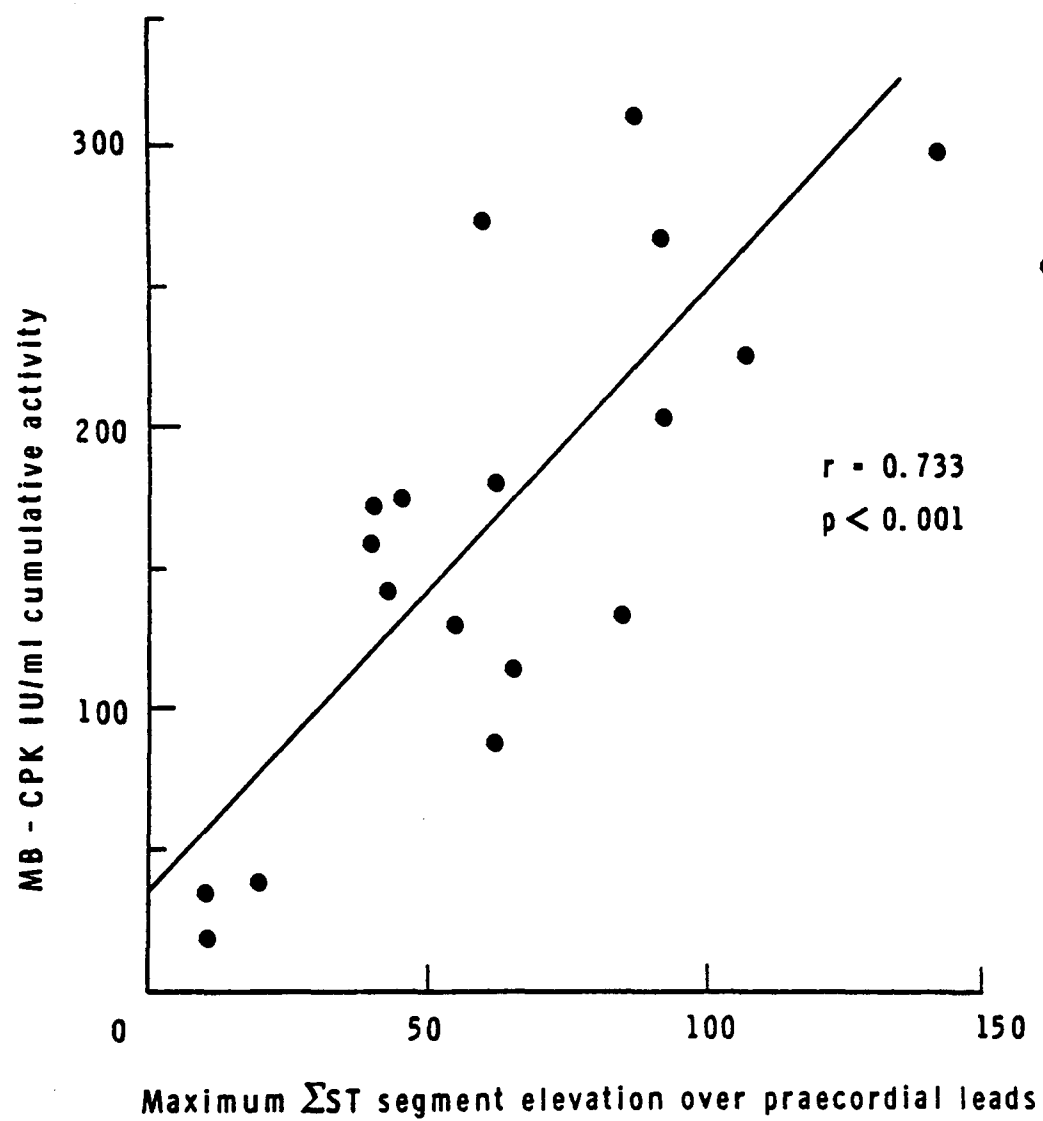


Figure 1: Maximum Σ ST from the preaecordial map is plotted against cumulative release of CKMB in patients with anterior infarction. A good correlation is seen.

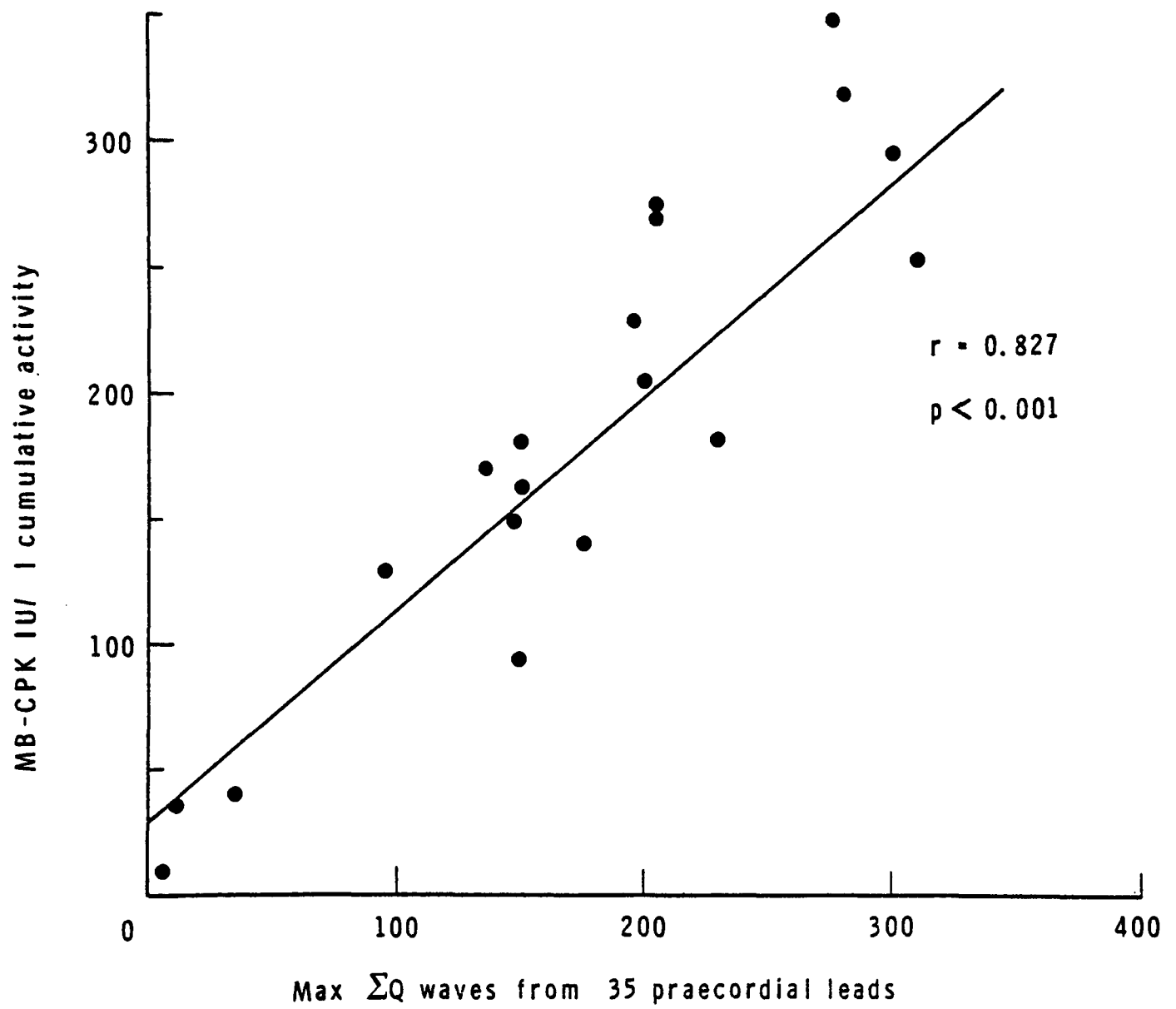


Figure 2: Maximum ΣQ is plotted against cumulative release of CKMB in patients with anterior infarction. A highly significant correlation is seen.

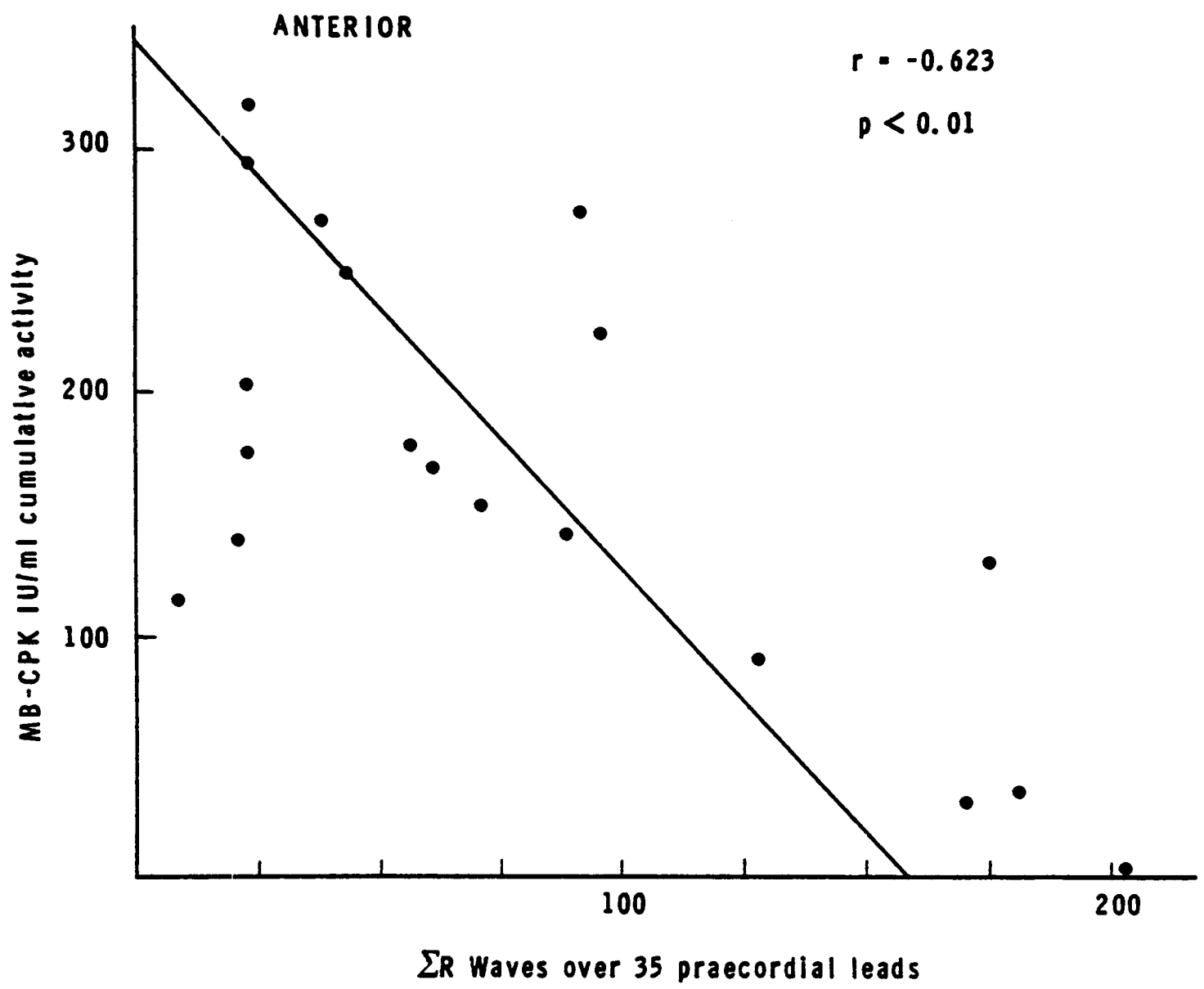


Figure 3: Minimum ΣR is plotted against cumulative release of CKMB in patients with anterior infarction. A fair correlation is seen.

(iii) Inferior Infarction

Preliminary studies not surprisingly failed to show any significant relation between infarct size estimated from CK MB and the praecordial electrocardiogram in patients with inferior myocardial infarction. However, the sum of the ST segment elevations and of Q wave amplitudes in leads II + III + aVF correlated with cumulative CK MB ($r = 0.505$; $p < 0.05$ and $r = 0.745$; $p < 0.01$, respectively; Fig. 4). There was no significant relation between the sum of R wave amplitudes in leads II + III + aVF and cumulative CK MB.

(iv) Interrelation of waves in electrocardiogram

In patients with anterior infarcts, the maximum Σ ST was found to predict maximum Σ Q at a time when electrocardiographic evolution of infarction was not complete ($r = 0.820$; $p < 0.001$; Fig. 5). The number of sites with ST segment elevation more than 1 mm and sites with ST segment elevation more than 2 mm predicted the number of sites developing QS waves ($r = 0.602$; $p < 0.01$, and $r = 0.635$; $p < 0.01$, respectively; Fig. 6). In addition, in individual patients the maximum ST segment elevation recorded at each of the 35 sites correlated well with final Q wave and final R wave amplitude at the same site ($r = 0.764$; $p < 0.001$, and $r = -0.746$; $p < 0.001$, respectively). Maximum Σ Q, not

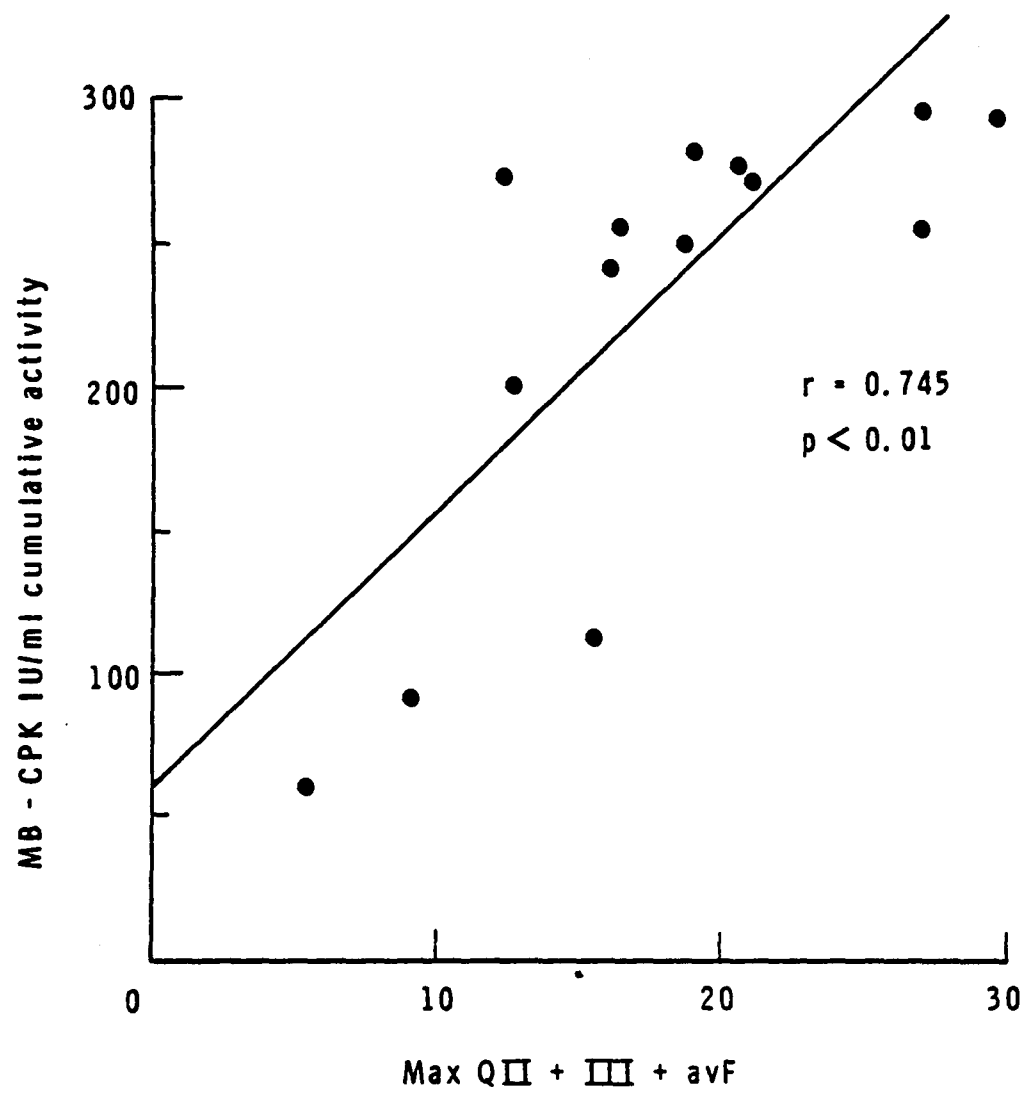


Figure 4: Maximum QII + III + aVF is plotted against cumulative release of CKMB in patients with inferior infarction. A fair correlation is seen.

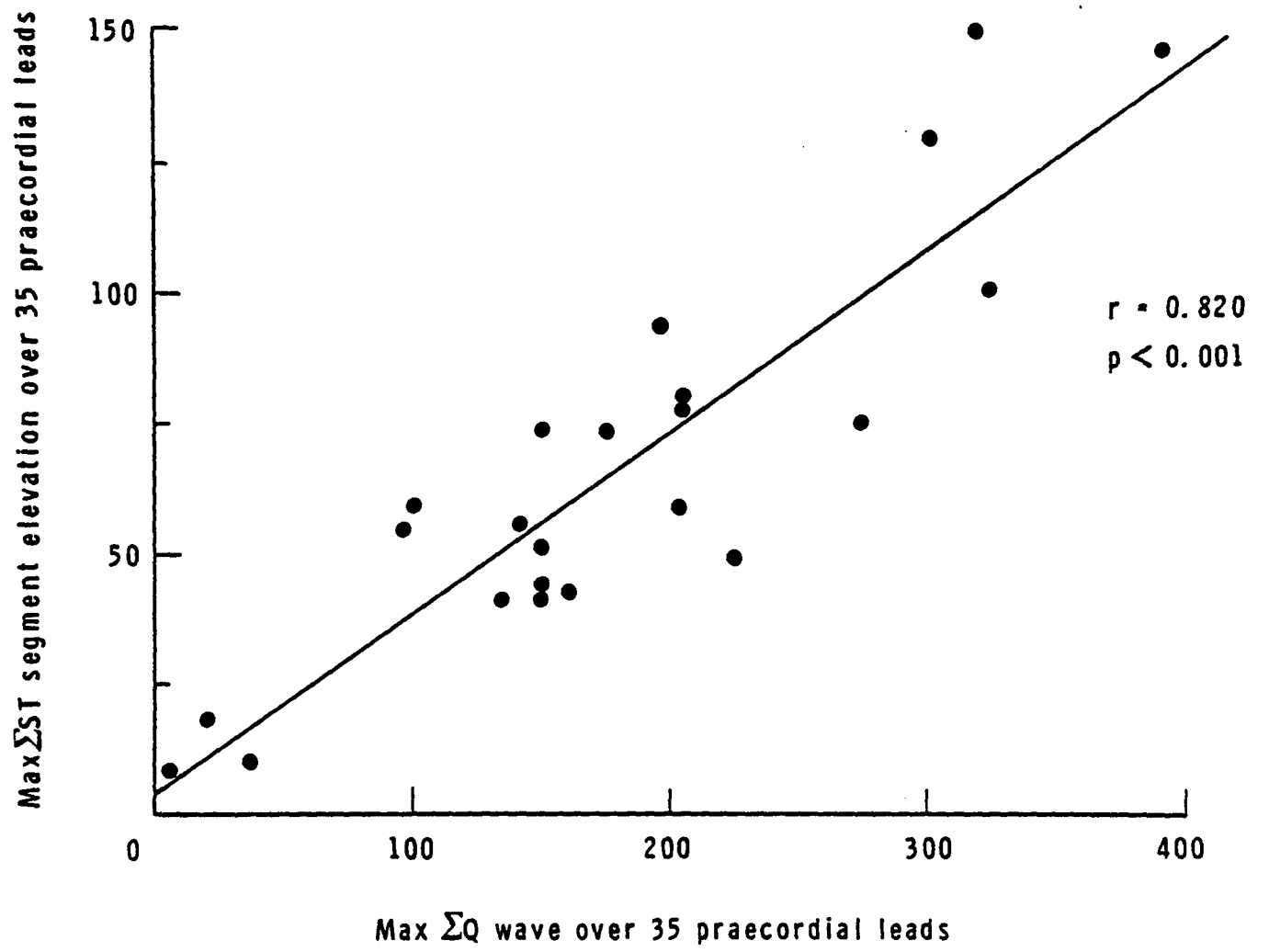


Figure 5: Maximum Σ ST is plotted against maximum Σ Q in patients with anterior infarction. A good correlation is seen.

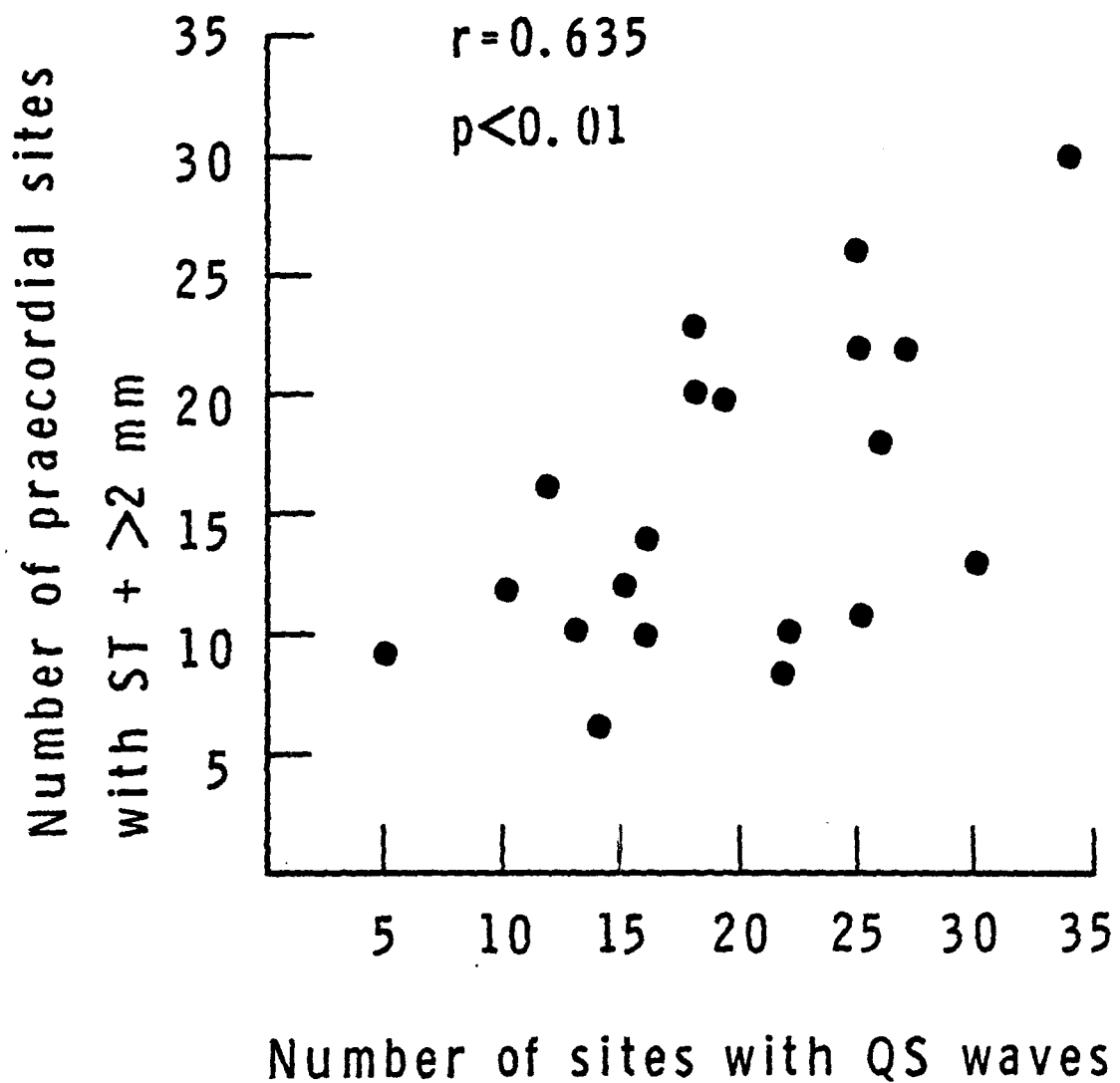


Figure 6: The number of sites with ST segment elevation more than 2mm is plotted against the number of sites with QS waves in patients with anterior infarction. A fair correlation is seen.

unexpectedly, correlated inversely with minimum ΣR in patients with anterior infarcts ($r = -0.824$; $p < 0.001$).

There was no relation between maximum ST segment elevation and maximum $Q_{II} + III + aVF$ in patients with inferior infarcts.

DISCUSSION

Since Maroko and Braunwald (1973) first described ST segment mapping, considerable interest has been focused on the electrocardiographic method for estimating infarct size. Experimental work in dogs with coronary artery occlusion (Maroko et al., 1972a,b) established the validity of the method. In their animal experiments, the site and to a certain extent, the size of the infarction was determined by the site of occlusion of a particular coronary artery. However, in the clinical situation, varying sizes of infarct are encountered more than one wall of the heart may be involved, and evolution of the infarct may be more variable in time (Yusuf et al., 1978). Further infarction in man may be due to several different mechanisms and the process may not necessarily be similar to experimental coronary artery ligation (Baroldi, 1975; Hellstrom, 1979).

The development of the enzyme method of estimation of infarct size has provided the clinician with another index of the extent of infarction. Electrocardiographic assessment may be influenced by factors other than infarct size, such as site of infarct, presence of arrhythmias or conduction defects, or changes in local ion concentration; the enzyme method does not have these drawbacks. The amount of CK released has been shown to bear a close relation to total CK depletion in rabbits (Kjekhsus & Sobel, 1970), and to infarct size measured morphologically at necropsy in patients who died of acute myocardial infarction (Bleifeld et al., 1977). Though the model for the basis for calculation of infarct size from enzymes has been criticised (Roe et al., 1977) the enzyme method nevertheless provides an empirical estimate of infarct size by a totally independent method, with which electrocardiographic assessment of infarct size can be usefully compared.

ST segment elevation

The reliability of ST segment elevation in measuring infarct size is controversial (Chapter I). In our study we have observed a strong positive correlation between maximum Σ ST and cumulative CK MB ($r = 0.7333$;

$p < 0.001$) in patients with anterior infarcts, and a weaker but significant correlation in inferior infarcts using the sum of ST segment elevation in leads II, III and aVF ($r = 0.505$; $p < 0.05$). Several factors may be responsible for the different results obtained by different workers. Firstly, praecordial mapping reflects only changes affecting the anterior and anterolateral wall of the left ventricle and it is possible that in some studies the patients may have had involvement of other walls of the heart. In our study, none of the patients with anterior infarction had any fresh electrocardiographic changes in the inferior leads, though a small true posterior infarct may have been undetected. Secondly, variations in chest shape and size and localisation of infarction may lead to differences between patients. Thirdly, ST segment elevation is known to increase or decrease rapidly in some patients (Selwyn et al., 1977a) and variable intervals between onset of pain and time of electrocardiographic recording will introduce further error. To minimise this source of error we have taken recordings at regular intervals in all our patients.

R wave

A decrease in the amplitude of R waves during experimental myocardial infarction was reported by Wilson et al. (1935). Muller et al. (1978) showed a

good correlation between loss of R wave amplitude and infarct size in experimental infarction. Recently, Selwyn et al. (1977b) have demonstrated a good correlation with estimates of infarct size from CK release.

In our study, we have observed only a fair inverse correlation between minimal ΣR and cumulative CK MB release ($r = -0.623$; $p < 0.01$). This may be partly the result of the large variation in ΣR observed in our control group of normals (ΣR varies from 150 to 300 mm). Though this may limit the value of ΣR in comparing infarct size in different patients, it is still useful in following the course of infarction in an individual patient (Yusuf et al., 1978), and in comparing infarct size in 2 large groups.

Q wave

Data relating Q waves during infarction to other indices of myocardial damage have consistently shown a good relationship (see Chapter I).

In our study, ΣQ from praecordial maps correlates well with cumulative CK MB in patients with anterior infarcts ($r = 0.827$; $p < 0.001$). The range of variation of ΣQ in our control group was between 0 and 12 mm in the 35 lead map. In contrast, ΣQ in most patients with anterior infarcts was several times greater. Though the

correlation between QII + III + aVF and cumulative CK MB in patients with inferior infarcts is less impressive ($r = 0.745$; $p < 0.01$), this is hardly surprising as these data were obtained from 3 electrocardiographic leads only. This may detract from its value in comparing infarct size in different patients but QII + III + aVF is useful in comparing groups of patients and in studying the evolution of an infarct.

Relation of number of sites with electrocardiographic abnormalities to cumulative CK MB

Although several workers have used the number of sites (or area) with ST segment elevation or pathological Q wave development as an index of the extent of ischaemia or necrosis and to evaluate the efficacy of interventions (Maroko et al., 1972a,b; Muller et al., 1975; Selwyn et al., 1977a,b; 1978), we found no relation between the number of sites with ST segment elevation greater than 2 mm, ST segment elevation of any degree, or pathological Q or QS waves, and enzyme estimates of infarct size. A similar experience was reported by Nielsen (1973), who observed that the sum of ST segment elevations from an ordinary 12 lead electrocardiogram was a good prognostic indicator, whereas the number of leads with ST segment elevation was not related to prognosis. This is not surprising as the number of sites showing abnormalities does not provide information

about the magnitude of change at a particular praecordial site. We believe, therefore, that Σ ST or Σ Q are better indices of infarct size than the number of sites with abnormalities.

Prediction of Infarct Size

In patients with anterior infarcts, maximum Σ ST has been shown to be related to final Σ Q and Σ R, and one could therefore use this measurement to predict infarct size. This relation could also be exploited in assessing interventions aimed at decreasing infarct size, as the slope of the line relating Σ ST and Σ Q would be difficult in control subjects and in subjects on beneficial treatment. Henning et al. (1978) have used a formula based on Σ ST obtained from the first map and the rate of loss of R wave amplitude to predict cumulative CK MB. However, these authors stress that this observation was made in a highly selected group of patients. We have also shown a relation between number of sites with ST segment elevation and those with QS waves. This confirms the work of Askenazi et al. (1977) and supports the view that the number of sites with ST segment elevation can be used to predict Q wave extent.

We observed no significant relation between the sum of ST segment elevations in II, III and aVF, and $Q_{II} + III + aVF$ in patients with inferior infarcts.

In conclusion, measurements of ST segment elevation, Q wave development, and R wave loss from praecordial maps, can all be used to assess infarct size in patients, with anterior infarcts. Measurements of Q waves and ST segment elevation in leads II, III and aVF also provide useful but less accurate information about infarct size in patients with inferior infarcts.

CHAPTER IV

VARIABILITY OF ELECTROCARDIOGRAPHIC
AND ENZYME EVOLUTION OF MYOCARDIAL
INFARCT SIZE IN MAN

Introduction

Studies in experimental animals have suggested that ischaemic injury after coronary occlusion can be altered by different pharmacologic, metabolic or mechanical interventions (Maroko et al., 1971). With the exception of two studies (Hillis et al., 1977; Miura et al., 1979) these reports have been based on initiating the test therapy either before or within the first 30 minutes after coronary occlusion. Data obtained from such animal experiments cannot be extrapolated to man since myocardial infarction may not be due to a single coronary occlusion (Baroldi, 1975), and the test therapy may be administered late because of the delay between the onset of symptoms and the call for medical aid (Armstrong et al., 1972).

If interventions designed to limit infarct size are to be successful in clinical practice, these measures must be applied before muscle death is complete. In the previous chapter I have demonstrated that the maximal loss of R waves and development of Q waves are reliable indices of myocardial necrosis in man. The aim of this study is to quantify the evolution of these ECG markers of myocardial necrosis in a group of patients admitted to the coronary care unit. I have also examined the time course of the ST segment evolution in relation

to R wave and Q wave changes and related the duration of these changes to the duration of enzyme release.

Patients and Methods

See previous Chapter)

Results

(i) Loss of R waves

Figure 7 shows the decrease of ΣR waves in patients with anterior infarction. The ΣR was significantly lower at recordings obtained less than 6 hours in these patients compared to the normal controls. ΣR decreased from 154 ± 25 at recordings obtained within 6 hours; to 86.08 ± 12.8 mm at 6-12 hours; the decrease in R waves continuing thereafter at a slower rate to 69.73 ± 13.2 mm at 12-24 hours and 48.19 ± 7.1 mm at 24-48 hours after the onset of chest pain. No further change in R wave was observed except in the 4 patients who **developed reinfarction.**

Figure 8 shows the percentage loss of R waves in the entire group of patients studied. This was calculated from the proportion of R wave lost at a

LOSS OF R WAVES IN PATIENTS AFTER ACUTE ANTERIOR INFARCTION

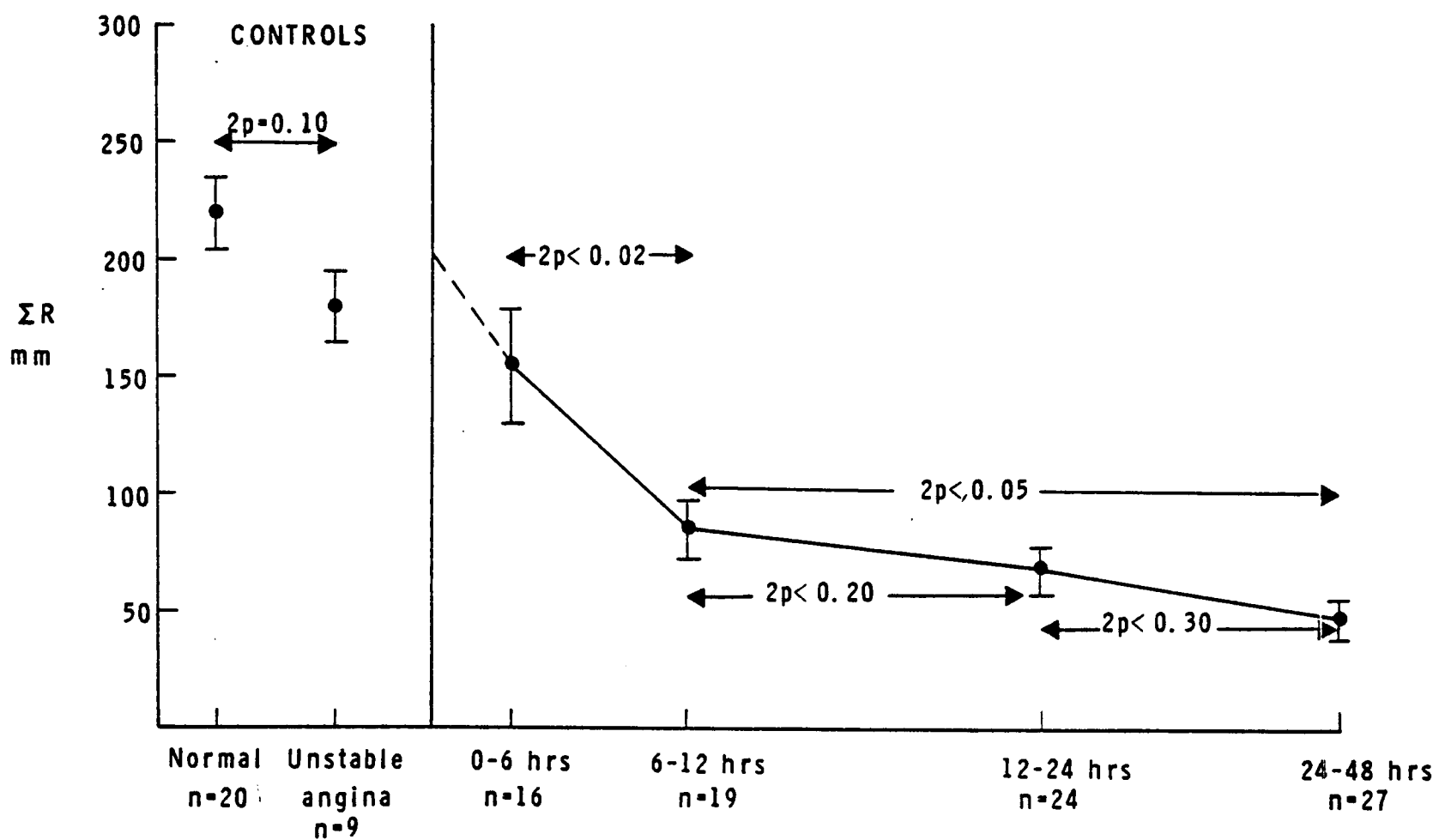


Figure 7: demonstrates the R wave loss over 35 preacordial leads in patients with acute anterior infarction. The interrupted line is drawn from the mean of control patients to the first recording.

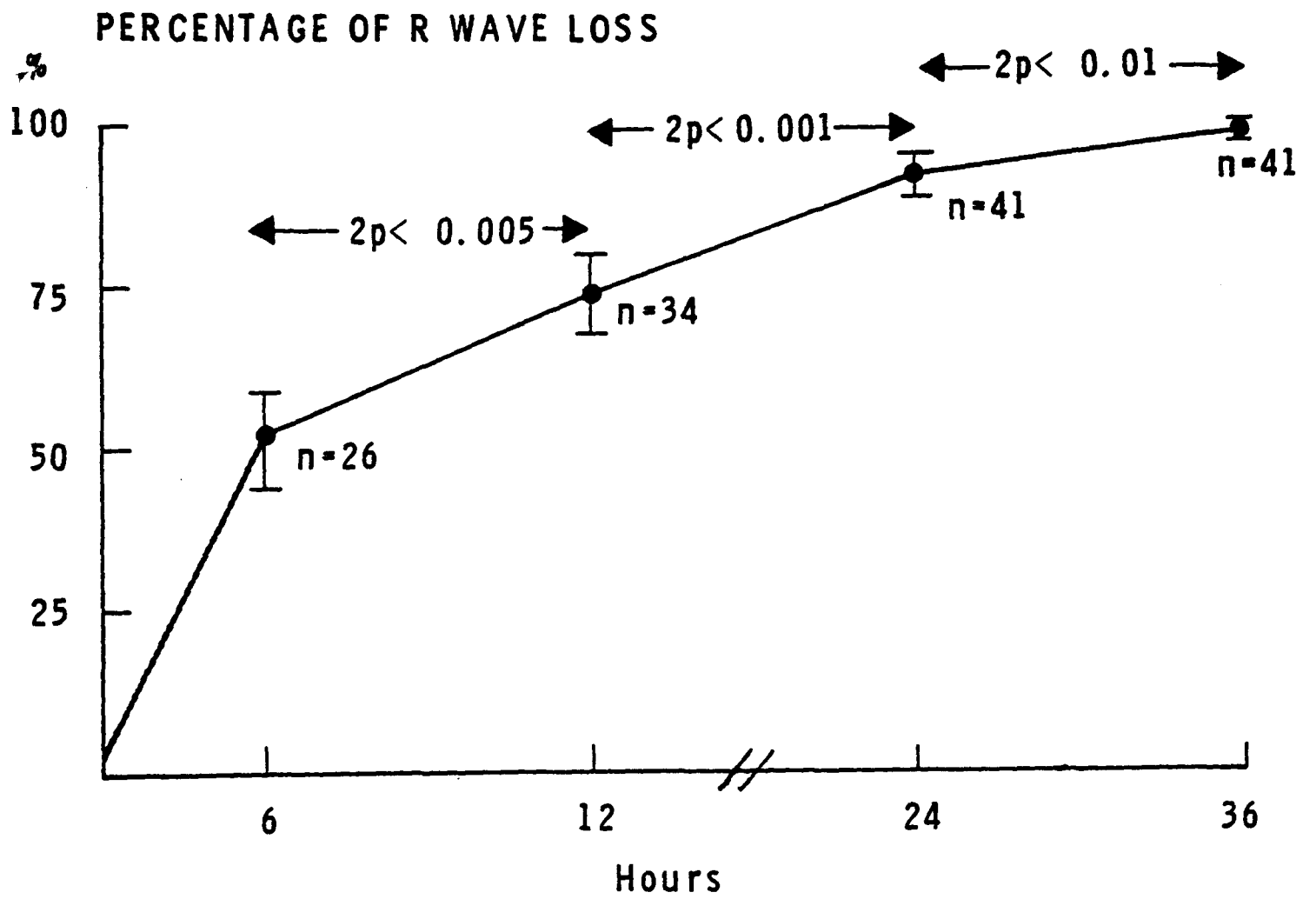


Figure 8: demonstrates the percentage loss of R waves in patients with both anterior and inferior infarction.

particular time of recording expressed as a percentage of total decrease in R waves. 52% of R waves were lost at 6 hours; 74% at 12 hours; 95% at 24 hours and 99% at 36 hours after chest pain.

(ii) Q wave development

Figure 9 shows the ΣQ wave development in patients with anterior infarction. At 6 hours the ΣQ is already greater than in control patients. ΣQ increased from $52.4 \pm 9.75\text{mm}$ at 6 hours to $112.20 \pm 15.5\text{mm}$ at 6 to 12 hours; to $165 \pm 19.4\text{mm}$ at 12 to 24 hours and to $180.6 \pm 18.8\text{mm}$ at 24 to 48 hours after chest pain. Again no further Q wave development occurred in any patient except in the 4 patients who reinfarcted.

Figure 10 shows the percentage development of Q waves in the total group of patients studied, and it parallels the changes in the R waves. The proportion of final Q waves developed at 6 hours was 42%; 72% at 12 hours; 93% at 24 hours and 98% at 36 hours.

(iii) ST segment changes

ST segment elevation was maximal at 6 hours in the whole group and decreased significantly at 12 hours. No further change was observed in the first 24 hours.

Q WAVE DEVELOPMENT IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION

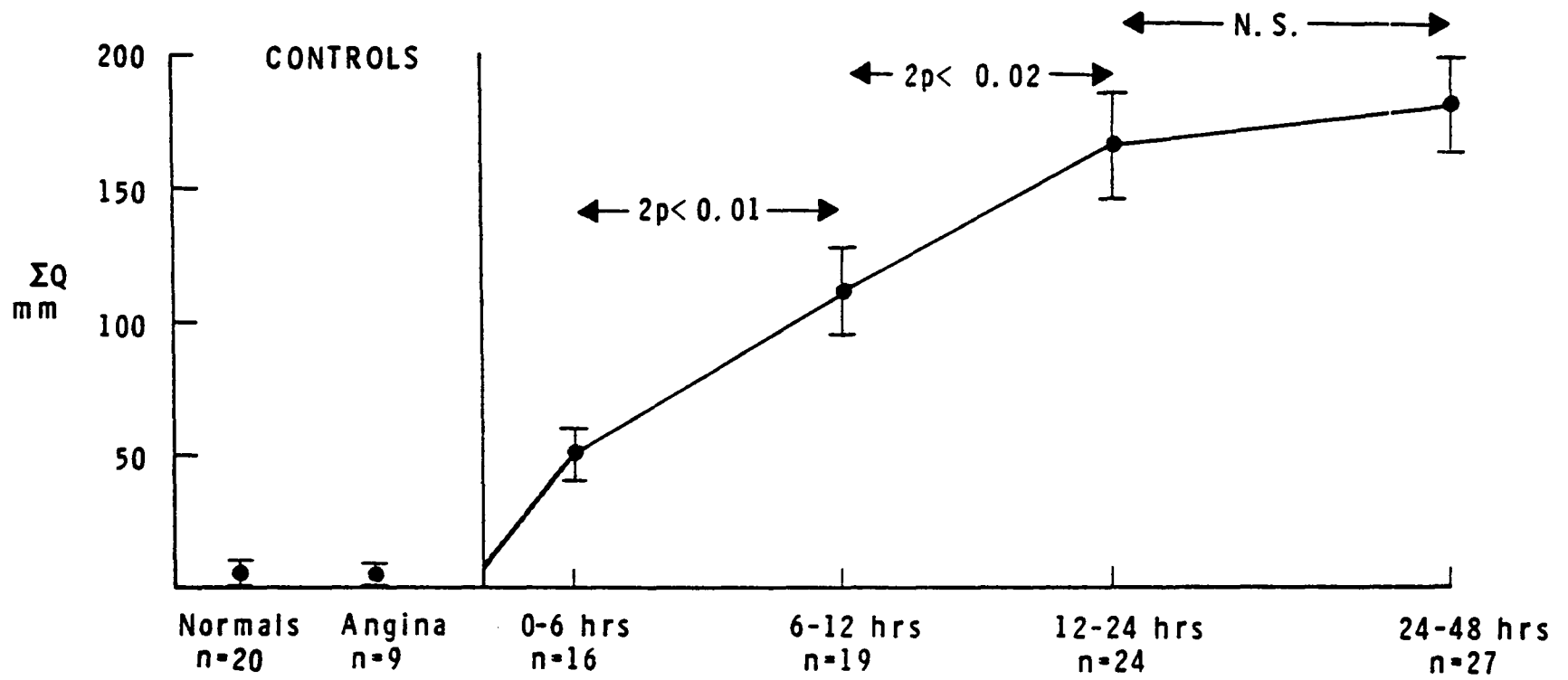


Figure 9: demonstrates Q wave development from 35 praecordial leads in patients with acute anterior infarction. The interrupted line is drawn from the mean of the controls to the first recording.

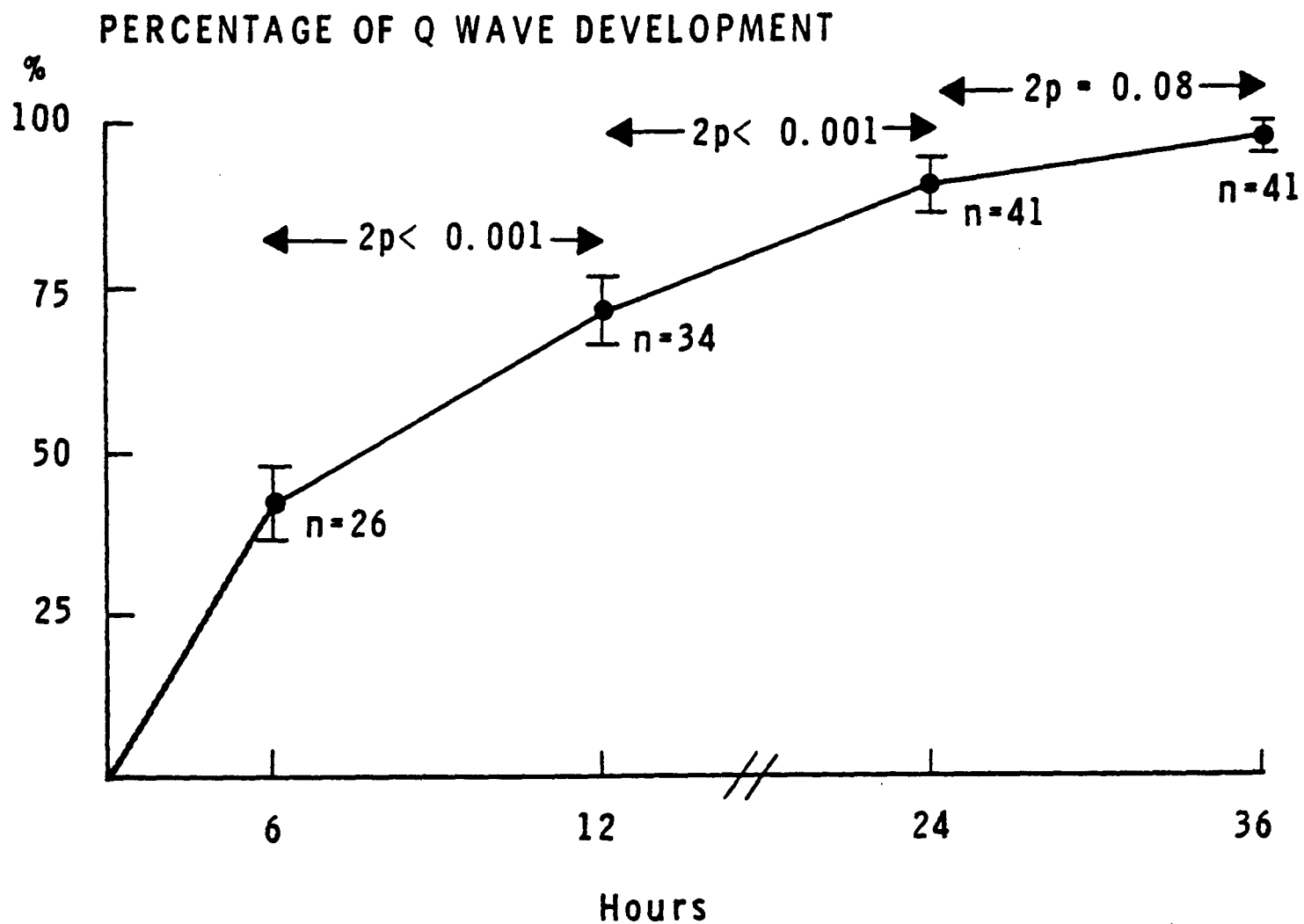


Figure 10: demonstrates the percentage of final Q wave developed at a particular time in patients with both anterior and inferior infarction.

ST SEGMENT ELEVATION IN PATIENTS WITH ANTERIOR MYOCARDIAL INFARCTION

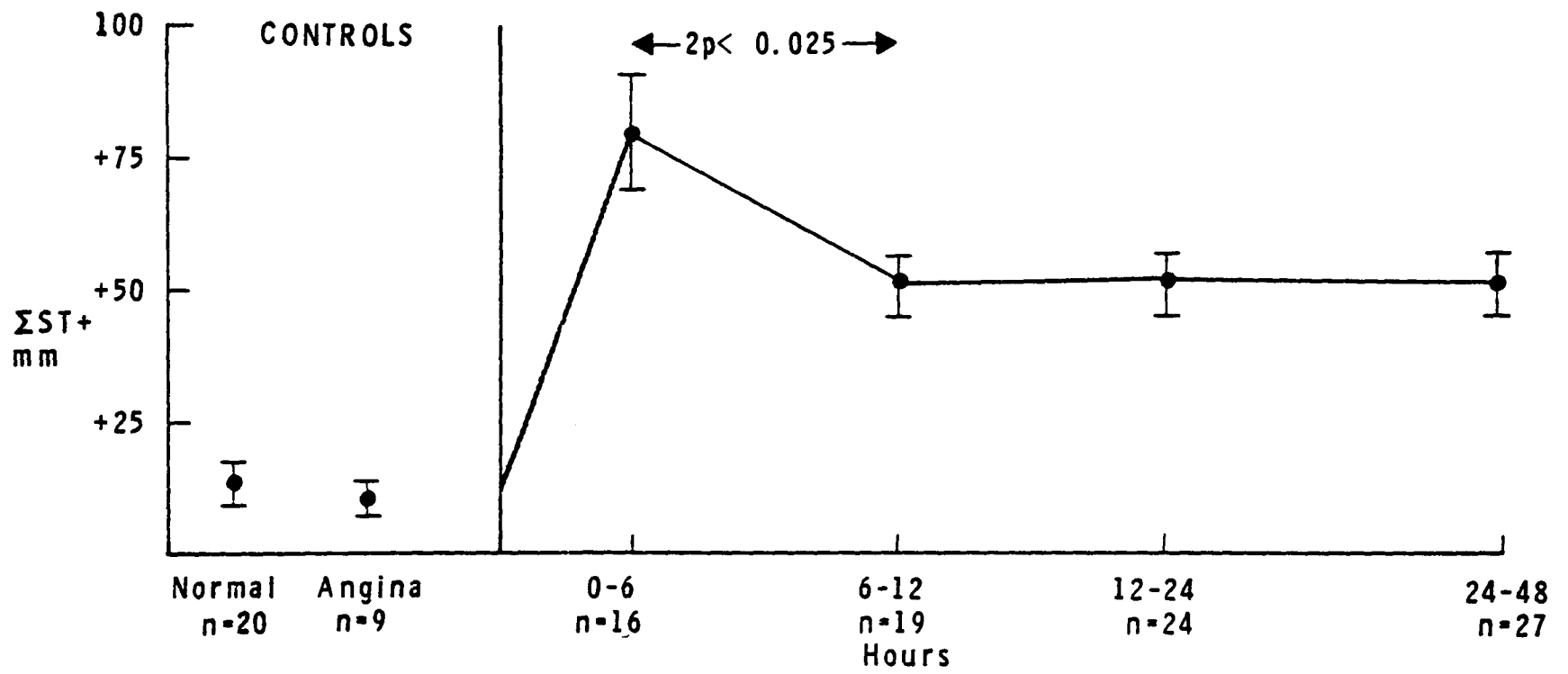


Figure 11: demonstrates the ST segment elevation from 35 praecordial leads in patients with anterior infarction. The interrupted line is drawn from the mean of the controls to the first recording.

Figure 11 demonstrates ST segment changes in the patients with anterior infarction. ST decreases from 80.13 ± 11.5 mm at recordings obtained under 6 hours; to 51 ± 6.3 at 6 to 12 hours; little change occurring in the group after this.

Patterns of Infarct Evolution

Considerable variation in the rate of infarction was observed between individual patients, with some patients showing complete R wave loss and Q wave development in as short a time as 4 hours and some taking as long as 48 hours. To present this variation best, all patients can be broadly divided into 3 categories:-

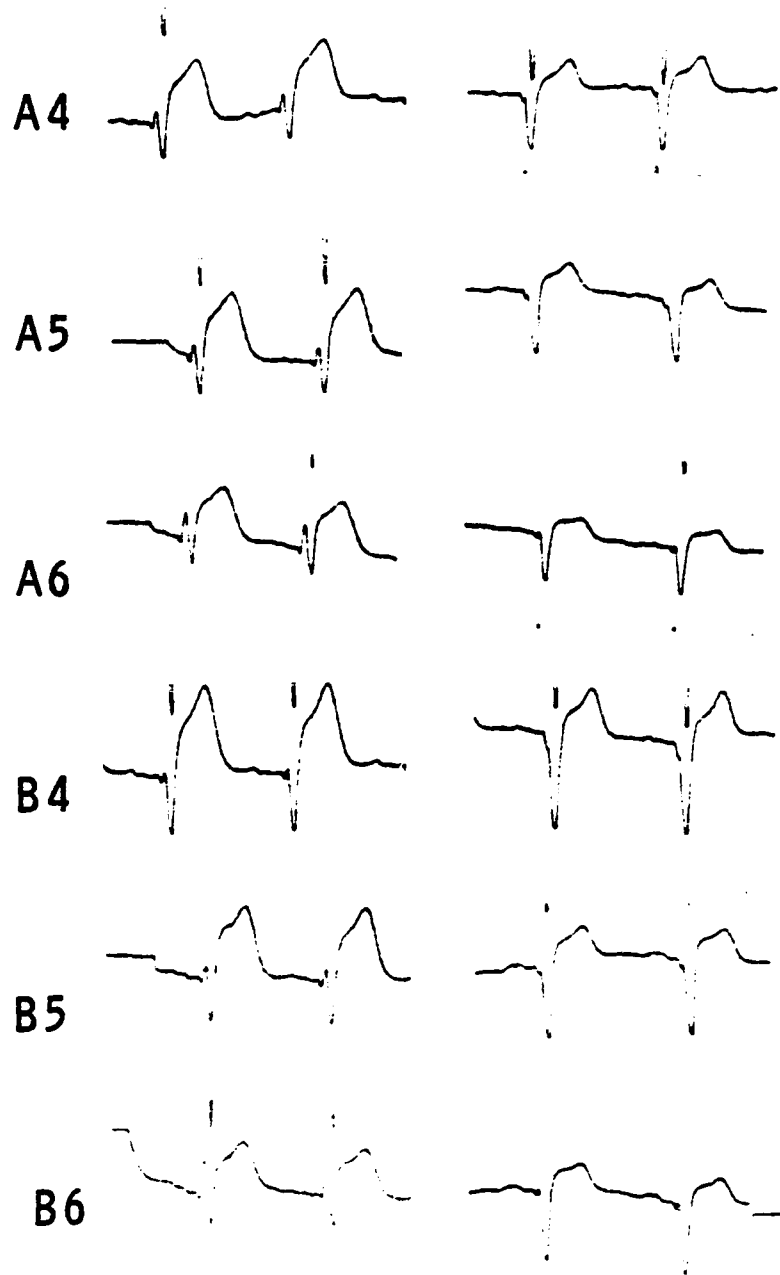
(1) Type A or rapid infarction (n = 17)

All patients completing ECG evolution within 12 hours of chest pain have been arbitrarily included in this group. Figure 12a and 12b demonstrates these changes in an individual patient and it can be observed that R wave loss and Q wave development were rapid. In addition, the degree of ST elevation at the initial recording was high and decreased rapidly when R loss and Q development were complete. These patients also showed quicker release of CK MB (Fig. 12c and Fig. 15) (mean of 19.30 ± 0.85 hours after chest pain) compared to the next group.

Type A pattern of M. I.

4 hrs.
after pain

8 hrs.
after pain



Note rapid R wave loss
Marked initial ST elevation
falls at 8 hours

Figure 12a: ECG recordings demonstrating the rapid R loss, Q development and ST segment changes in a patient with Type A infarction.

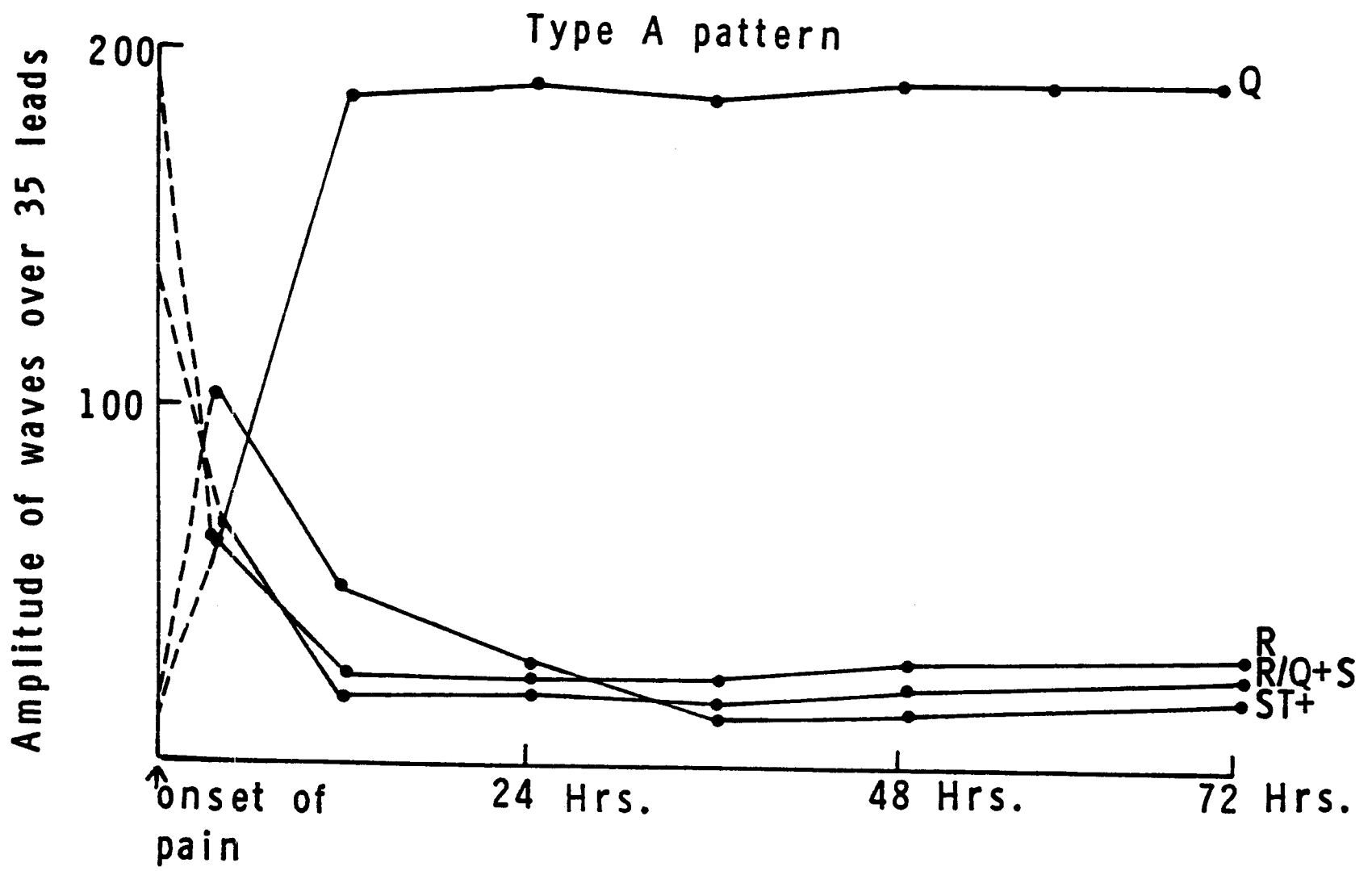


Figure 12b: is a schematic presentation of the rapid R loss, Q development and ST segment changes in a patient with Type A infarction.

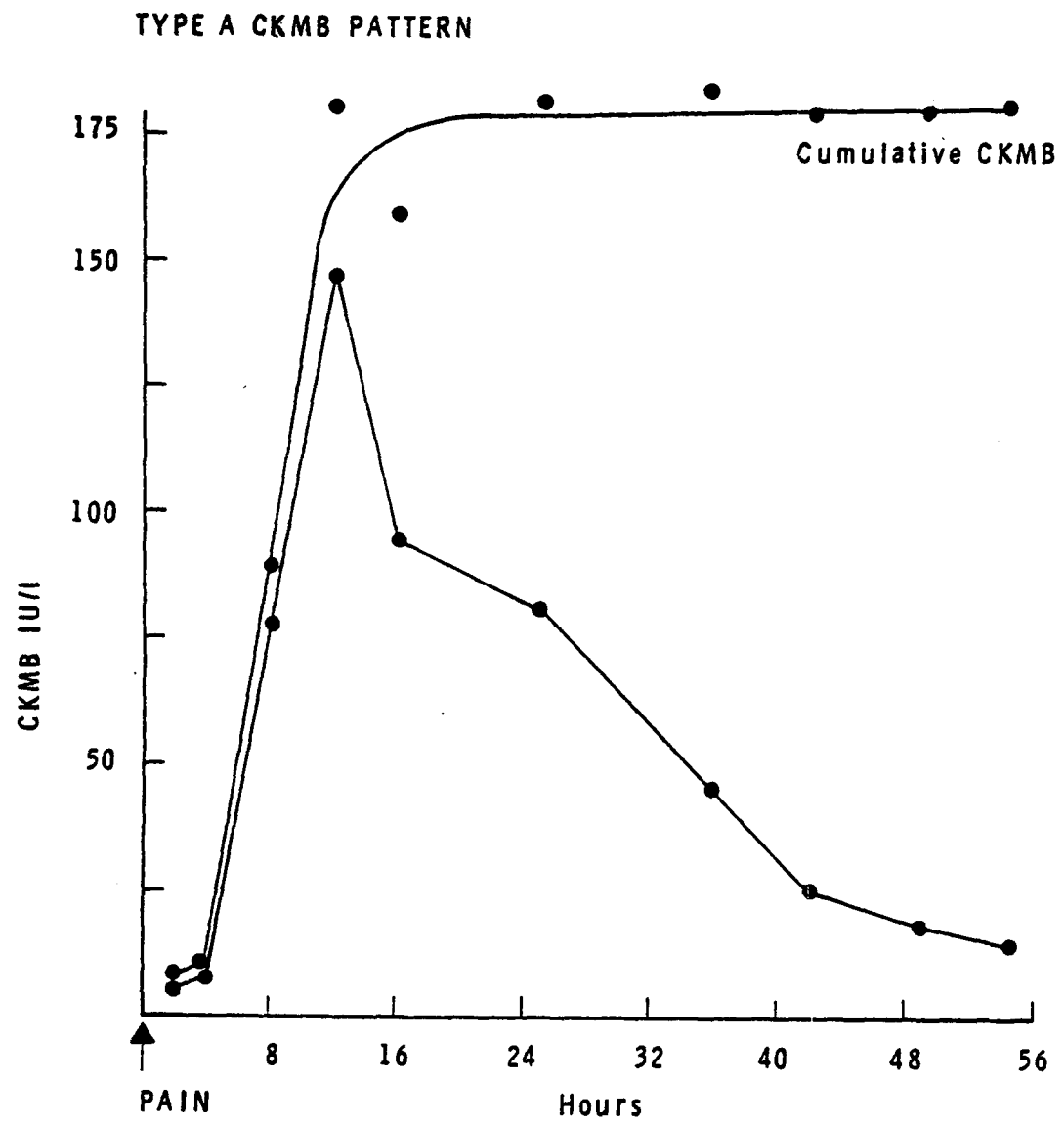


Figure 12c: demonstrates the enzyme release in the patient with Type A infarction.

(2) Type B or slow infarction (n = 24)

Included in this group are all patients in whom ECG evolution of Q waves and R waves continued for longer than 12 hours. Figure 13a and b demonstrates these changes in an individual patient; it is clear that R wave loss and Q development are definitely slower than the patient demonstrated in Figure 12. The degree of ST elevation is smaller and persists for longer than in the previous group of patients. Few patients in this group increased their ST segment elevation but in all instances this decreased after complete R wave loss and Q wave development. The duration of CK MB release in this group was longer than in the earlier group (Fig. 13c and Fig. 15) (mean of 29.9 ± 2.41 hours after pain; $2p < 0.001$).

(3) Type C or reinfarction

Four patients from the above groups developed a new episode of typical chest pain and showed further ST elevation, R loss and Q development accompanied by further release of CK MB (Fig. 14).

(v) Relation of Infarct size to duration of enzyme release

No significant relationship was observed when the total enzyme release was compared with the duration of enzyme release as linear variables. However, a trend towards smaller infarcts in patients with slower ECG evolution was observed ($2p = 0.07$) (Fig. 15).

Type B pattern of M.I.
8.45 hrs. 12.45 hrs. 24 hrs.

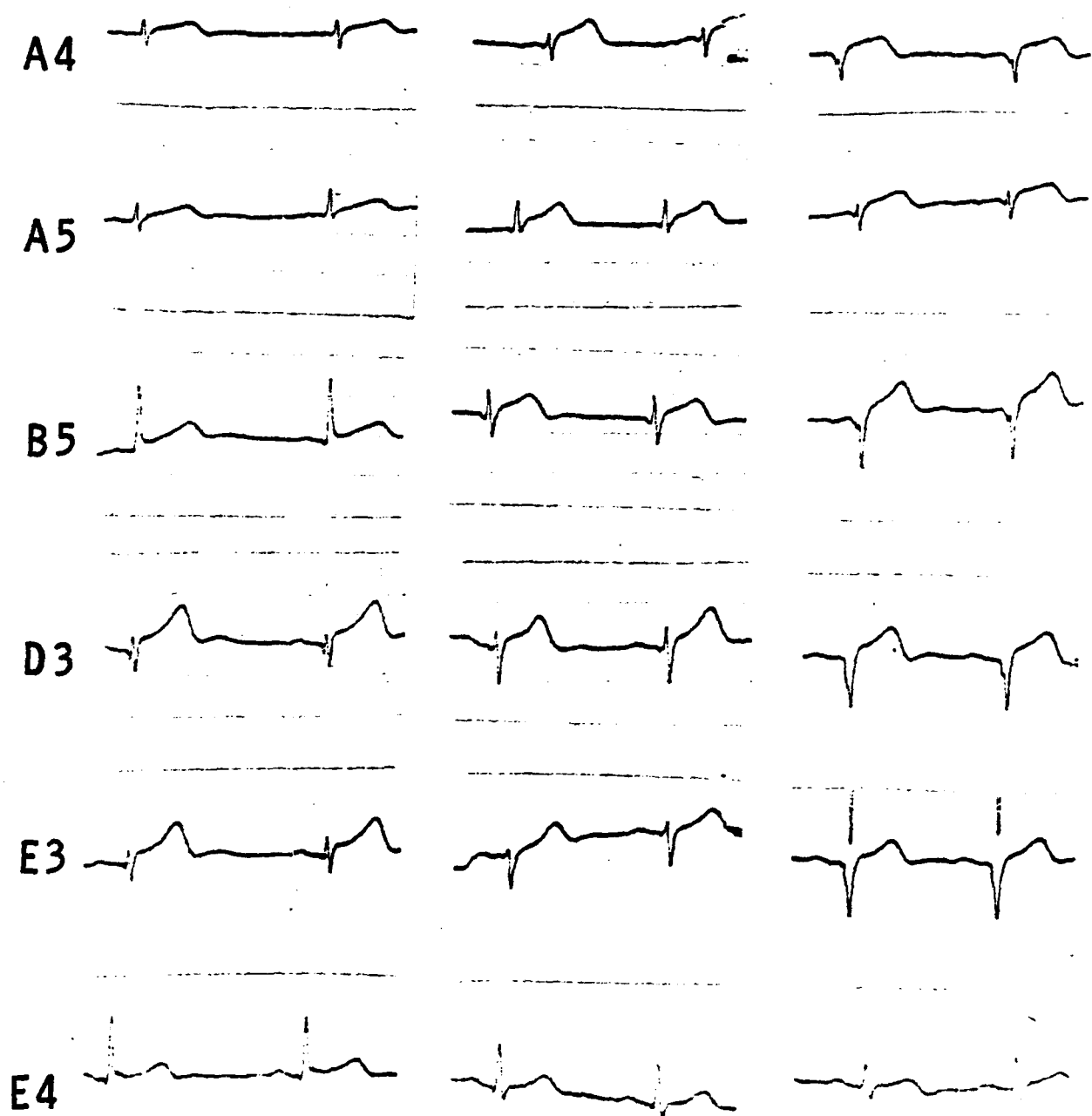


Figure 13a: ECG recordings demonstrating gradual R loss, Q development and ST segment changes in patient with Type B infarction.

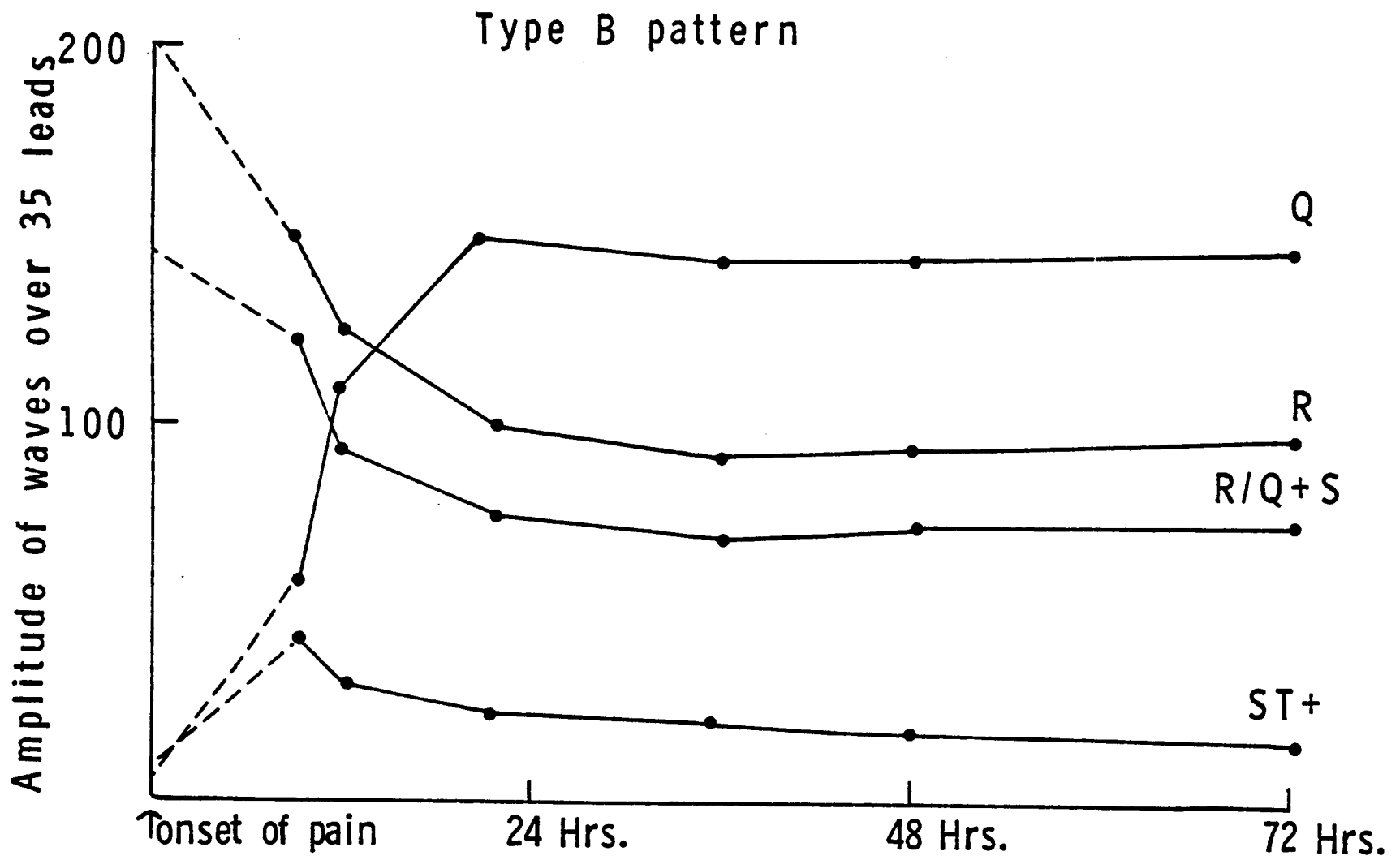


Figure 13b: Schematic presentation of gradual R loss, Q development and ST segment changes in a patient with Type B infarction.

TYPE B CKMB PATTERN

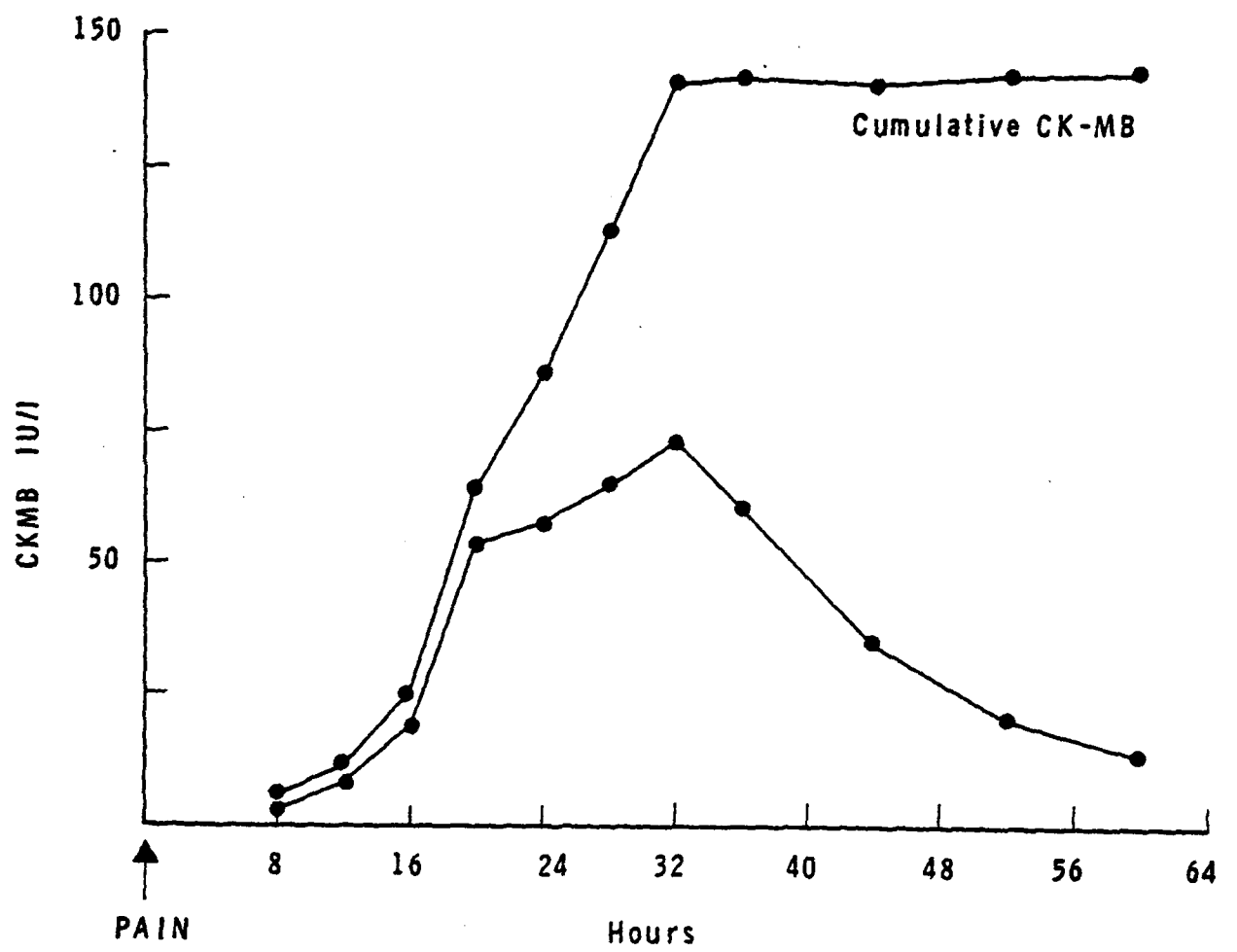


Figure 13c: demonstrates the enzyme release in the patient with Type B infarction.

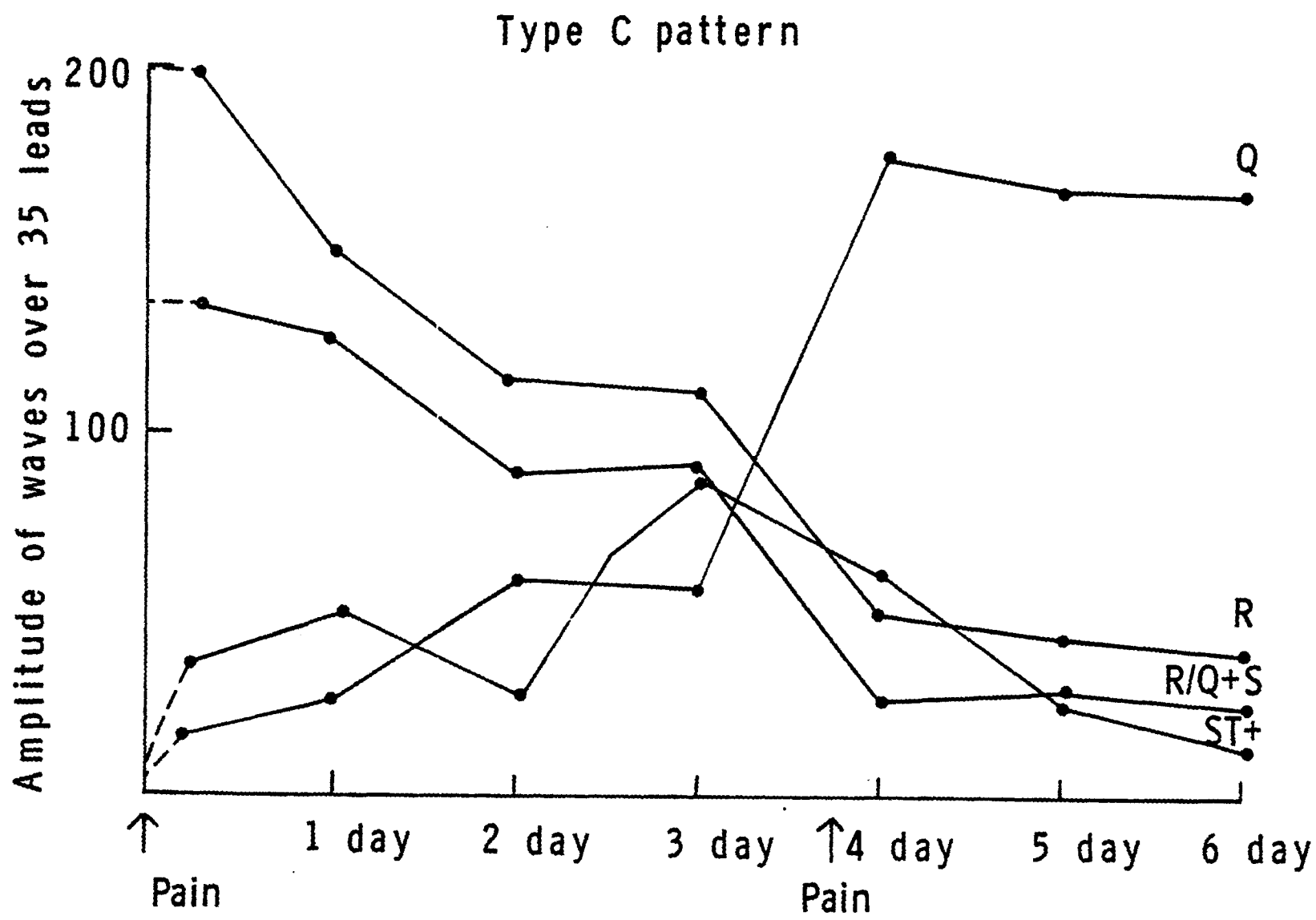


Figure 14: Schematic representation of the ECG changes in a patient with Type C infarction.

Discussion

The main observation of this study is that infarct evolution is very variable in man. In some patients this was complete in as short a time as 4 hours, whereas in others it took as long as 48 hours. Little previous work has been done on the time course of Q wave or R wave development in man. Selwyn et al. (1977, 1978) and Zymslinski et al. (1979) have both reported rapid loss of R waves and development of Q waves; R wave evolution being completed in 6 hours in their studies. In our study we have observed such rapid development of infarct size in less than half the patients, and at 12 hours only 41% of patients studied had completed infarct evolution. In 59% of patients, however, Q wave and R wave evolution continued for longer. In addition, patients with slower ECG evolution also demonstrated longer duration of enzyme release. This suggests that myocardial necrosis proceeds at a slower rate in these patients.

When the group as a whole is considered, 74% of R wave loss and 68% of Q wave development were complete at 12 hours after chest pain. The rate of ECG evolution continues less rapidly after this and is complete on average by 24 hours. The reasons for the longer duration

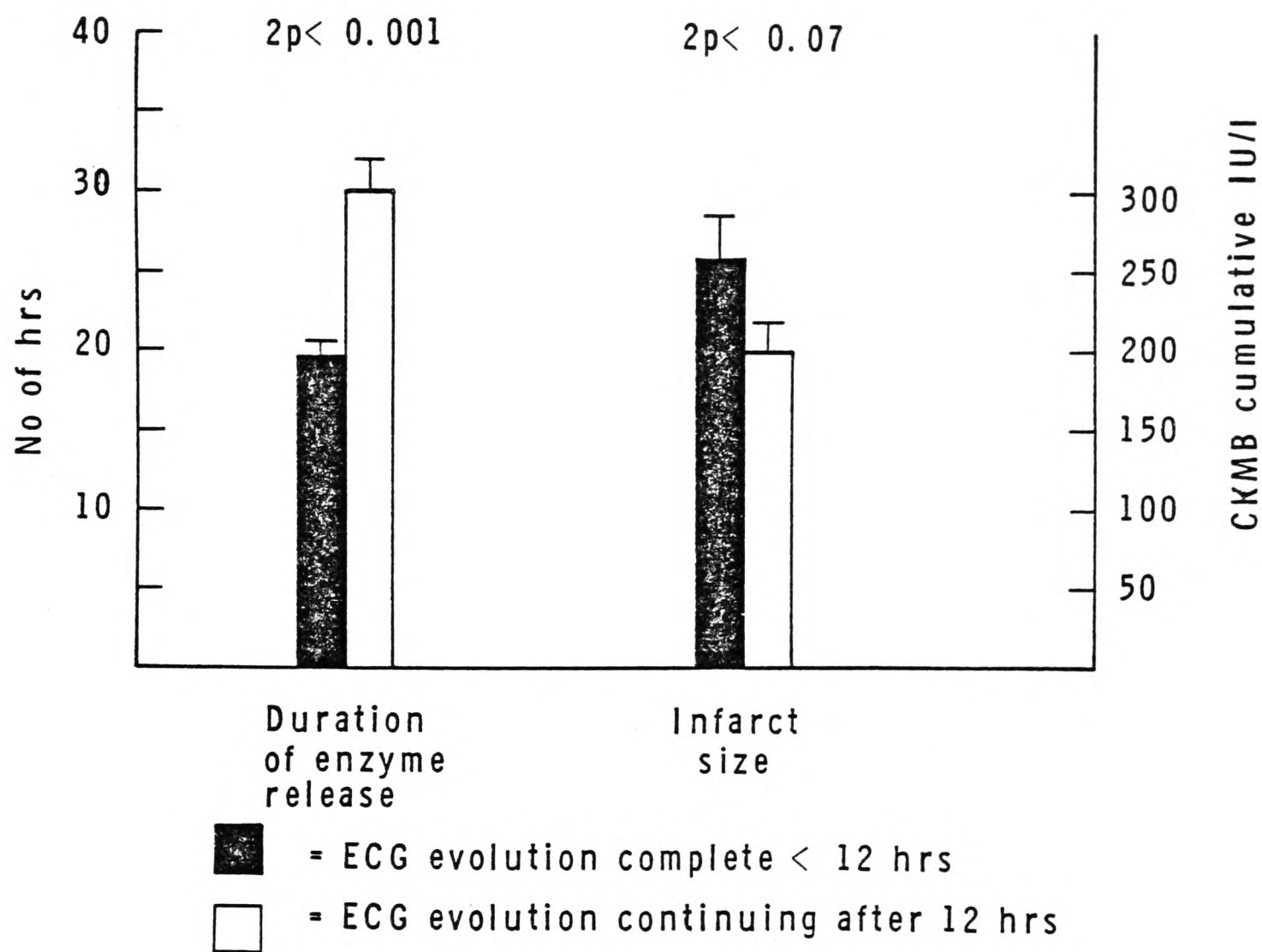


Figure 15: shows on the left, the duration of enzyme release and on the right, infarct size in Type A and Type B patients.

of ECG changes seen in the Type B patients compared to Type A must be considered. Whether the patients with the slower ECG evolution represents a slowly extending infarct, or multiple infarcts occurring in rapid succession is uncertain. None of these patients (except those who reinfarcted and designated as Type C) had repeated episodes of chest pain. No further re-elevation of the ST segment or a separate peak of CK MB release was seen. However, Cobb et al. (1979) have shown in experimental models that very early reinfarction may not produce a separate enzyme peak and may only be manifest by a higher enzyme level and longer duration of enzyme release.

Our data is consistent with the reports of Askenazi et al. (1977) and Henning et al. (1978) Although the above studies were not designed to study the time course of ECG evolution, data provided in their papers suggest that in many patients R wave loss and Q wave changes proceeded for longer than 12 hours and was only complete by 24 hours. In addition, Inoue et al. (1977) have shown that in patients with inferior infarction, Q wave changes occurring in leads II, III and aVF continued for as long as three days even in the absence of reinfarction. These authors also showed a good correlation between the duration of Q wave development and the duration of enzyme release. Bleifeld and co-workers (1976) have shown 3 different patterns of creatine kinase release which correspond to the 3 patterns

of ECG and enzyme release demonstrated in our study. Further, we have observed the same variation and different patterns of infarct evolution in this group of patients using serum myoglobin (unpublished data).

Comparison of infarct size (cumulative CK MB) and the duration of enzyme release did not show a significant correlation. However, a weak trend ($2p = 0.07$) towards larger infarcts in patients with rapid infarction was observed.

Some controversy exists regarding the time course of ST segment elevation. Maroko et al. (1975), Madias et al. (1977) and Flaherty et al. (1975) have reported that ST segment elevation is stable and changes little in the first 24 hours. In contrast, Selwyn et al. (1977) Zymlinski et al. (1979) and Essen et al. (1979) have shown that ST elevation is maximum in the first few hours and then declines considerably by 6 to 12 hours. Our study provides data to support both view points. Although as a whole, the group showed a significant decrease in ST segment elevation from 6 hours to 12 hours, several patients especially those showing gradual infarction showed a relatively stable ST elevation for 24 hours. Importantly, however, the ST segment remained elevated while Q wave and R wave evolution were continuing and always decreased significantly after these were complete.

In all 4 patients with reinfarction, ST segment elevation preceded further Q wave development and R wave loss or re-elevation of CK MB. In two other patients who developed pericarditis, ST re-elevation was not accompanied by further R wave or Q wave changes. In addition to the temporal relationship between ST segment and R wave and Q wave changes, I have demonstrated earlier that maximum Σ ST elevation correlates well with final Σ Q wave or Σ R wave amplitude. As Σ ST elevation usually reaches a maximum well before R wave loss and Q wave development are complete, maximum Σ ST may be used as a predictor of final R wave or Q wave development.

This study only provides an approximate time when infarct evolution was complete. The interval between recordings or blood sampling in individual patients may have led to some over-estimation of both the ECG and enzyme time estimates of infarct evolution. Although maximum Q waves and minimal R waves have been shown to be related to total enzyme release, used as an index of infarct size, whether evolving Q waves and R waves bear the same quantitative relationship to the amount of infarct developed at a particular time is not known. However, the information obtained has practical relevance as the changes in R waves, Q waves and ST segment are being used to evaluate the efficacy of

interventions designed to limit infarct size in man (Muller et al., 1978). In this study, the onset of chest pain has been taken to indicate the onset of infarction; but this may not be a valid assumption. In many instances, accurate timing may not be possible either due to repeated episodes of pain, atypical symptoms or due to prolonged pain. In such instances, onset of pain was taken to be the time of the episode of pain which led to the patient calling his doctor or the ambulance. Although this approach may be inaccurate in some instances, it is practical as this is the major factor causing delay before the patient is admitted to hospital (Armstrong, 1972).

The degree to which drugs (i.e. betablockers or lignocaine) influenced our results is uncertain. No consistent ECG pattern was seen with any particular drug; however, to assess the effect of any drug, randomised prospective studies are required. We have retained all patients who needed these drugs as they may have more severe complications of infarction like arrhythmias; exclusion of these patients may create bias in patient selection.

In conclusion, infarct evolution in man has a more varied time course than that reported earlier. In our study over 50% infarct evolution occurred after admission to hospital and suggests that salvage of ischaemic myocardium is feasible in such patients.

CHAPTER V

DELAY IN BETABLOCKADE AFTER ORAL ATENOLOL IN
ACUTE MYOCARDIAL INFARCTION.
COMPARISON WITH INTRAVENOUS ADMINISTRATION

INTRODUCTION

Beta adrenergic blocking drugs have been used in the acute phase of myocardial infarction in an attempt to decrease mortality and "malignant" ventricular arrhythmias (see Chapter I, page 22). Apart from Snow's (1965) initial report all other studies using oral beta blockers have failed to demonstrate a beneficial effect on mortality or ventricular arrhythmias (Norris et al., 1968; Reynolds & Whitlock, 1972; Balcon et al., 1966; Clausen et al., 1966; Roland et al., 1979). The possibility that adequate betablockade may not have been achieved early enough was raised by Pentecost (1966). Rutherford et al. (1976) reported that oral propranolol 20mgm 6 hourly (dose comparable or larger than some of the above studies; Norris et al., 1968; Reynolds & Whitlock, 1972; Balcon et al., 1966; Clausen et al., 1966) did not produce adequate plasma levels or significant beta-adrenoceptor blockade in the early stages of myocardial infarction in man. This was attributed to the first pass effect in the liver seen with propranolol (Rutherford et al., 1976) and not to poor gastrointestinal absorption or inadequate dosage.

The main aims of this study are:-

- (i) Firstly to assess if oral atenolol in doses equivalent to that used in the above studies produces early and adequate betablockade in patients with acute myocardial infarction.
- (ii) Secondly to compare the effect of oral and intravenous atenolol on the onset and degree of beta-adrenergic blockade by measuring the reduction in heart rate in such patients.

Atenolol is not metabolised by the liver (McAinsh, 1977), therefore any delay in betablockade after oral atenolol is likely to be due to delayed absorption and/or inadequate dosage. Since heart rate is known to vary spontaneously in patients with acute myocardial infarction, due to changing autonomic neural tone and haemodynamic alterations, a group of control subjects were also studied (Jewitt et al., 1969).

SUBJECTS AND METHODS

The data reported consists of two studies:

(i) Randomised double-blind study using oral atenolol

Twenty-eight patients with definite ECG and enzyme evidence of myocardial infarction seen within 12 hours after chest pain were randomised to receive 50 mgm of atenolol 12 hourly, or equivalent placebo tablets on admission to the CCU of the Radcliffe Infirmary. All patients were suitable for beta adrenergic blockade. Twelve patients received atenolol and 16 patients received placebo.

For the purposes of this report, the first heart rate recorded by the nurses before administration of the study drug was taken as control for that patient. Heart rate was subsequently recorded at 1 to 2 hourly intervals for the next 48 hours. The routine management of the patient was unaltered by the study protocol. Diuretics, digoxin and anti-arrhythmic drugs were administered as indicated. A note of the exact time of drugs administered was obtained in all patients from the nurses' records. Lignocaine was used in two atenolol and 3 control patients; 2 atenolol and 4 control patients received diuretics.

EFFECT OF ORAL ATENOLOL ON HEARTRATE

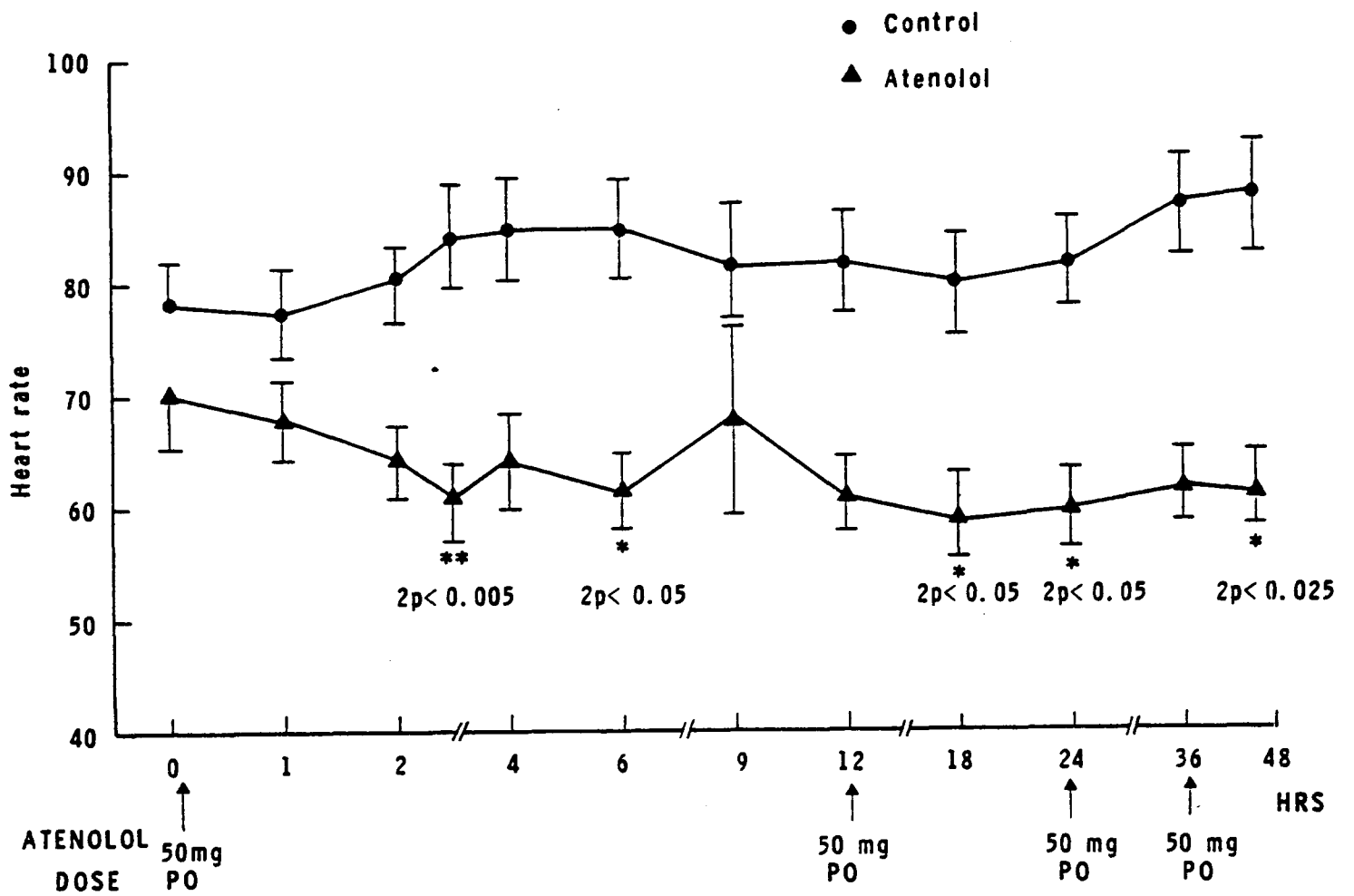


Figure 16: Heart rate response after oral atenolol. A significant decrease only occurs at 3 hours after administration.

(ii) Randomised controlled study using an initial dose of intravenous atenolol

The first 53 patients admitted to the study at the Radcliffe Infirmary have been included in this study. All patients entered the study within 12 hours of chest pain and were suitable for beta-adrenergic blockade. On admission, the heart rate was noted and patients were randomised to receive 5 mgm IV atenolol given slowly over 5 minutes followed 30 minutes later by 50 mgm orally b.d. Control patients received standard therapy and no placebo was used. Twenty-six patients received atenolol and 27 patients were controls. Heart rate was measured at 1 to 2 hourly intervals as mentioned above. Six treated and 5 control patients received lignocaine; 7 treated and 13 control patients received diuretics and one patient from each group received atropine and digoxin.

RESULTS

(i) Oral Atenolol

Figure 16 demonstrates the heart rate over 24 hours in the 12 patients receiving oral atenolol compared to the 16 patients who received placebo.

EFFECT OF AN INITIAL IV DOSE FOLLOWED BY ORAL ATENOLOL ON HEART RATE

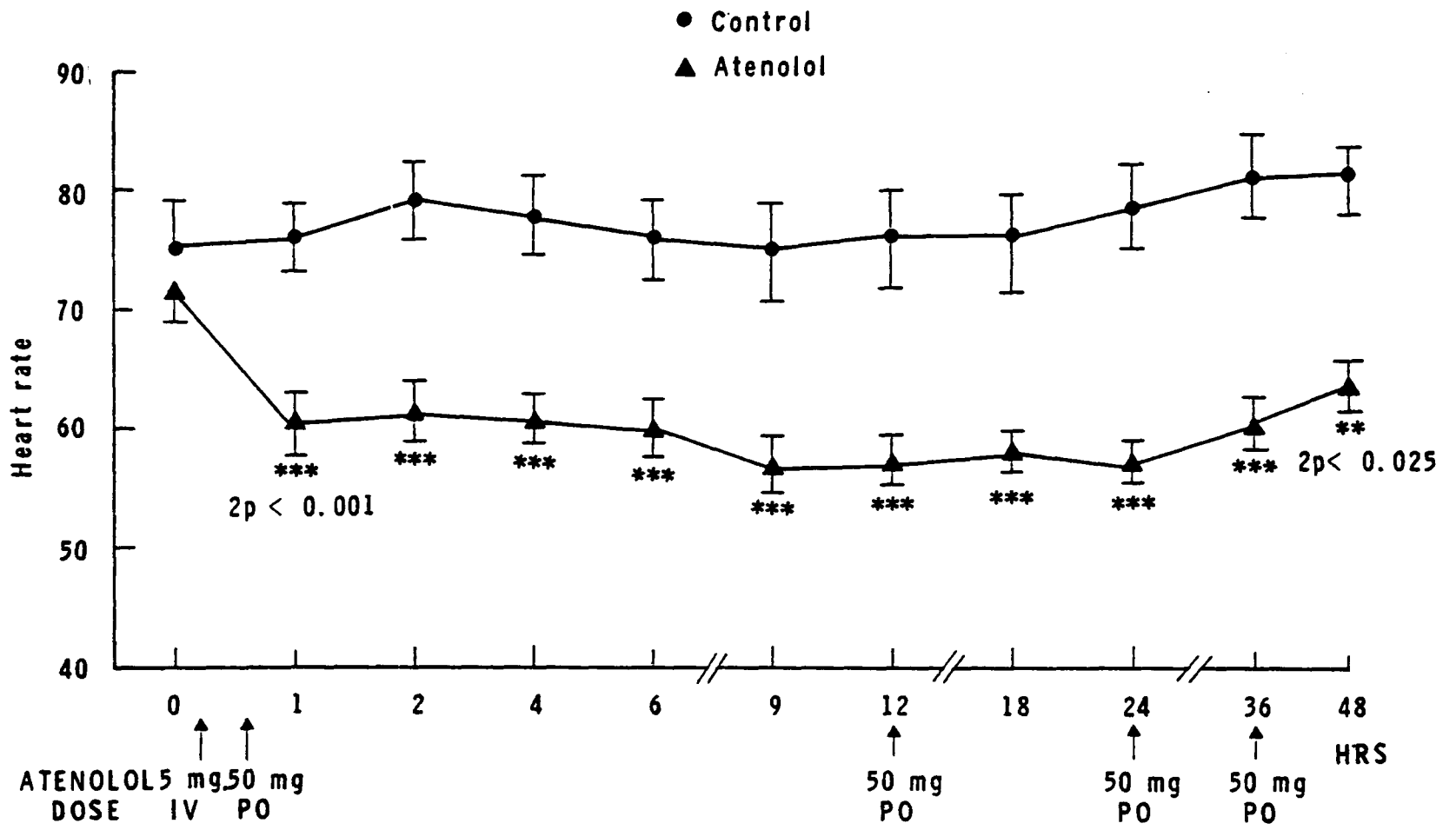


Figure 17: Heart rate response after intravenous + oral atenolol. Note early reduction in heart rate.

A significant decrease in heart rate occurred 3 hours after administration of the drug but only after 12 hours does a stable bradycardia occur.

(ii) Intravenous atenolol (Fig. 17)

It can be seen that after 5 mgm of IV atenolol significant bradycardia is immediately achieved. Further, the fluctuation in heart rate is considerably less than that seen when oral atenolol is used alone. In addition, the degree of bradycardia produced is more marked compared to the bradycardia when oral atenolol is used alone (Fig. 18).

(iii) Control patients

Figure 18 demonstrates the heart rate from both studies (n = 43). In the first 18 hours, heart rate is only slightly elevated in both control groups (see Fig. 16 and 17). However, there is a further increase in heart rate at 36 and 48 hours by a mean of 8 to 10 beats ($2p < 0.05$ and $2p < 0.02$ compared to the initial heart rate). This trend towards increasing heart rate is also seen in both the atenolol groups after 18 hours. Figure 18 compares the reduction in heart rate in the two groups of treated patients (corrected for variations in individual initial heart rates) and demonstrates the earlier onset, greater and more stable bradycardia achieved by an initial dose of IV atenolol preceding oral administration.

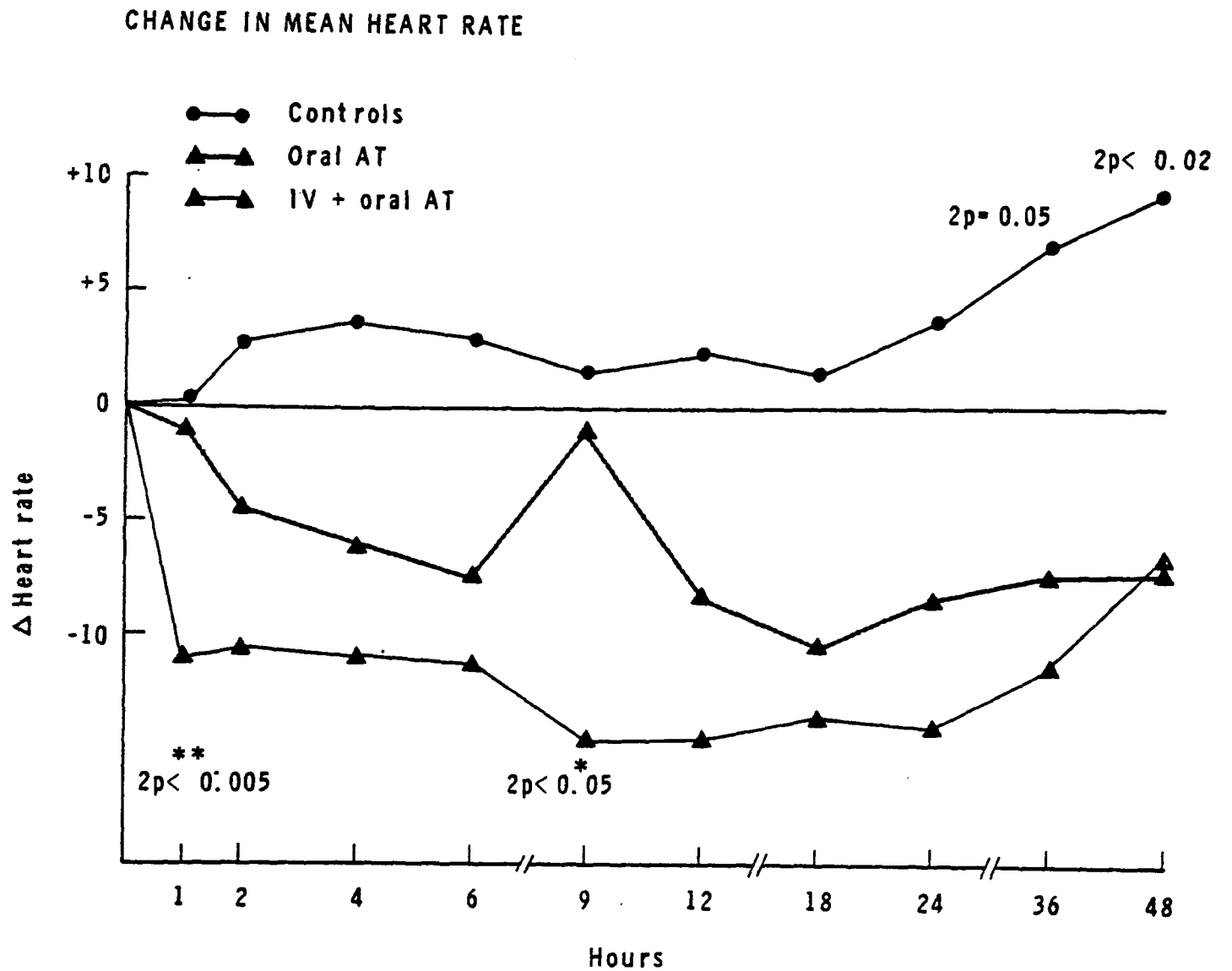


Figure 18: Mean heart rate in control patients, patients given oral atenolol and those given IV + oral atenolol. There is a small but significant increase in heart rate in control patients at 36 and 48 hours compared to initial values. At 1 hour and at 9 hours, the patients given an initial IV dose of atenolol show significantly lower heart rates than patients given oral atenolol only.

DISCUSSION

The most important observation of this study is that considerable delay occurs in achieving adequate reduction in heart rate after the administration of oral atenolol in doses comparable to several studies (Norris et al., 1968; Reynolds & Whitlock, 1972; Balcon et al., 1966; Clausen et al., 1966; Roland et al., 1979). In contrast, initial intravenous administration of atenolol followed by the same oral dose results in earlier and stable bradycardia.

The dose of oral atenolol we used was similar to the dose in the recent study of Roland et al. (1979) which reported that atenolol did not influence early ventricular arrhythmias after acute myocardial infarction. In the studies of Norris (1968), Balcon et al. (1966) and Clausen et al. (1966), no reduction in mortality after myocardial infarction in propranolol treated patients was observed; these studies used comparable or lower doses of oral propranolol.

Malignant arrhythmias and a substantial proportion of muscle death occur within 6 to 12 hours after chest pain (Selwyn et al., 1978; Yusuf et al., 1978; Adgey et al., 1971). It is therefore imperative to achieve early and adequate beta blockade if mortality and morbidity are to be influenced. This delay in beta-

blockade after oral administration may in part explain the negative results of earlier studies (Norris et al., 1968; Reynolds & Whitlock, 1972; Balcon, 1966; Clausen et al., 1966; Roland et al., 1979). Preliminary studies using a loading dose of intravenous beta-blockers have demonstrated a reduction in infarct size estimates (Peter et al., 1978) and a reduction in ventricular arrhythmias (Ahumada et al., 1978).

The cause of the delay in beta-blockade after oral administration of atenolol in acute myocardial infarction is uncertain. Rutherford et al. (1976) reported that oral propranolol 20 mgm 6 hourly did not produce any significant bradycardia in the first 24 hours. The differences between our study (where we found oral atenolol to produce some bradycardia after 3 hours) and that of Rutherford et al. (1976) may be in part due to the lack of first pass effect and the longer half life of atenolol (McAinsh, 1977). Although the total daily dose of propranolol (80 mgm) used by Rutherford is only slightly less than the total dose of atenolol (100mgm), higher doses were used at each administration (atenolol and propranolol are approximately equipotent in the same dose; Barrett et al., 1977). Further, our patients may not be entirely comparable to those entering Rutherford's study.

We have also found that after oral atenolol, bradycardia is slower in onset in our patients with acute myocardial infarction compared to the normal controls studied by Fitzgerald (1977) who found the lowest heart rates 45 minutes after the oral dose. In our patients with myocardial infarction, significant bradycardia did not occur until 3 hours after oral administration. This may be due to one of three reasons. Firstly, it is likely that in patients with acute myocardial infarction some delay in gastrointestinal absorption of oral beta blocker may occur compared to normal individuals either due to reduced blood flow to the gut or delayed transit of the tablets caused by drugs like morphine. Secondly, Fitzgerald used a larger dose (200 mgm). Further his subjects were normal volunteers and may have had less generalised atherosclerosis (which may also affect the blood flow to the gut), compared to patients who develop infarction.

An increase in heart rate after 18 hours was observed in all patients. This was most marked in the controls but the same trend was also observed in the beta blocker groups. This may be due to a reflex increase in heart rate secondary to extensive myocardial necrosis and a drop in cardiac output.

In conclusion, it is necessary to give the first

dose intravenously, to achieve adequate and early beta-blockade in myocardial infarction. The subsequent oral dosage is likely to be more effective if a beta blocking drug is not extensively metabolised by the liver e.g. atenolol may be preferable to propranolol.

CHAPTER VI

PREVENTION OF INFARCTION, REDUCTION IN INFARCT
SIZE AND MORBIDITY BY EARLY INTRAVENOUS ATENOLOL
IN SUSPECTED ACUTE MYOCARDIAL INFARCTION

Introduction

The amount of infarcted myocardium determines early and late morbidity and mortality after acute myocardial infarction (Sobel et al., 1972). In experimental infarction, beta-adrenergic blocking agents have been shown to reduce eventual infarct size when given soon after coronary artery ligation (Miura et al., 1978; Jennings & Reimer, 1974) and there has been one previous report based on a small number of patients that intravenous administration of propranolol within 4 hours of infarction reduces the release of creatine kinase (CK) into the serum (Peter et al., 1978).

Fifty per cent of electrocardiographic (ECG) evolution occurs more than 6 hours after the acute onset of pain, suggesting that worthwhile myocardial salvage may still be feasible in patients admitted to a coronary care unit early after pain (Yusuf et al., 1978). Since there may be a delay in the absorption of oral beta blocker and if such drugs do effect myocardial salvage an initial intravenous dose is essential to obtain early adequate beta-blockade.

The present chapter reports the preliminary findings from a randomised trial of beta-blockade among patients entering the CCU within 12 hours of the onset of chest pain. Our main aims were to discover:

(i) whether, among patients who already have definite ECG evidence of infarction on entry to the CCU, immediate beta-blockade could produce a worthwhile reduction in ECG or enzyme estimates of eventual infarct size. We have earlier demonstrated that both the ECG and enzyme methods of measuring infarct size are reliable indices of the severity of infarction (Yusuf et al., 1979).

(ii) whether, among patients who did not yet have any definite ECG evidence of infarction on entry to the CCU, immediate beta-blockade could materially reduce the probability of definite ECG or enzyme evidence for infarction materialising over the next few days.

A subsidiary aim of this study was to compare the clinical course in treated and control patients to ascertain if morbidity is also reduced in treated patients.

Patients and Methods

The design, organisation and methods used in this trial are detailed in Chapter II (pages 69-84).

All patients entering the CCU of the Radcliffe Infirmary and the Wythenshawe Hospital from October 1978 onwards were assessed for eligibility for the study. All patients with a clinical history strongly suggestive of myocardial infarction within the previous 12 hours, suitable for beta-blockade were considered eligible whether or not ECG abnormalities were already evident. Criteria for exclusion are detailed in Chapter II. At entry an ECG was taken and the following were written outside the randomisation envelope before opening it: (1) Time from onset of pain; (2) Heart rate and blood pressure; (3) Evidence of heart failure.

The patient was then randomised by opening the envelope with patients randomised to active therapy immediately receiving 5 mgm atenolol intravenously followed by an oral dose of 50 mgm twice daily for 10 days or until the patient died or was discharged. Control patients were not given placebo tablets or injections and received the usual care of the unit. At discharge or at 10 days, the decision to stop or continue the beta-blocker in the active treatment group or to give a beta-blocker in the control patients was left to the physician responsible for the patient.

At entry, 8ml of blood were drawn; subsequent 4 hourly samples were drawn for the next 48 hours and 6 hourly for the subsequent 24 hours. The blood samples were centrifuged, plasma separated, stored at -20°C and were analysed for total CK and CK MB blind of treatment and clinical details. Cumulative CK MB was calculated for each patient by the method of Sobel et al. (1972) as modified by Norris (1975).

Standard 12 lead ECGs were done prior to randomisation and repeated daily for the first 3 days and every 2 or 3 days thereafter until discharge. For the purposes of the study, the pre-randomisation ECG, the ECG on the 3rd day and the final ECG were measured in the usual way (Chapter II). Thirty-five lead praecordial ECGs were performed in patients with suspected or definite anterior infarction.

Based on the initial ECG, patients (all of whom by definition to have a good clinical history of chest pain with onset in the past 12 hours) were subdivided into two groups:

Group I: Definite ECG evidence of infarction before randomisation:- ST elevation of at least 1mm in the limb leads or 2mm in the praecordial leads with or without Q waves.

Group II: Threatened infarction.

(a) Patients with a good history plus a suspicious ECG (ST depression and/or T wave inversion).

(b) Patients with a good history and a normal ECG. Evidence of infarction was considered to have materialised later if at any subsequent time during their hospital stay they showed at least a 20% reduction in R wave amplitude or enzyme levels twice the upper limit of the normal range for CK MB.

Routine management of the patients was not altered by the study protocol. Other beta-blocking drugs (or administration of a beta-blocker to control patients) was avoided in general. In a few cases, a beta-blocker had to be given to control patients when the physician-in-charge of the patient considered this absolutely necessary. Conversely in patients randomised to atenolol, an occasional dose was missed or the drug was completely stopped when side effects were suspected (e.g. severe bradycardia, severe heart failure not responding to diuretics, or complete heart block). A careful record of all protocol deviations, of the clinical course and of all drugs administered was kept (Tables XI and XII). Post-hospital death is being monitored through the National Health Service Central Register, by courtesy of the Office of Population Censuses and Surveys (OPCS).

This report deals with the 215 patients admitted up to December 1979.

Statistical Methods

Standard unpaired 't' tests have been used to compare groups of data. A one tailed 't' test has been used on the prior assumption that atenolol treated patients will do better i.e. a reduction in infarct size and morbidity. Levels of significance with the two-tailed 't' test (2p) have also been calculated. The Chi square test with and without continuity correction have also been used.

Enzyme data have been analysed using both actual values and \log_{10} values. When actual values are used, patients with large infarcts exert the greatest influence on the analysis. When \log_{10} values are used, small infarcts exert the greatest influence on the analysis.

Results

- (i) Results of the preliminary analysis of enzymes on all patients admitted by May 31st, 1979:

A preliminary analysis of the enzyme estimates of infarct size was carried out on the 99 patients admitted until May 31st 1979. There was a slight but (as yet at

least) wholly nonsignificant tendency for the mean \log_{10} cumulative CK MB to be lower in the atenolol group than in the controls. Six patients had incomplete data, 22 patients (11 atenolol and 11 controls) had no infarcts (as judged by peak enzyme levels) and of the remainder 34 were treated with atenolol and 37 were controls. Among these latter 71 patients, the mean \log_{10} cum CK MB differed by only 0.037 ± 0.099 (mean differences \pm SE of the difference) in favour of atenolol (not statistically significant). A difference of 0.037 in \log_{10} corresponds to a ratio of 0.92 i.e. suggesting an 8% reduction. However, the range of uncertainty is enormously wide with the 95% confidence interval corresponding to the atenolol infarct size being 59% to 143% of control.

Moreover, when the data was subdivided at 4.0 hrs (prior hypothesis in the protocol and based on the observations of Peter et al., 1978) and analysed similarly, there was on average a one third reduction in infarct size in favour of atenolol in the early entry group (non-significant but encouraging: 95% confidence interval = $-0.1844 \pm 1.96 \times 0.136$; mean \log_{10} difference $\pm 1.96 \times$ SE of difference; when converted to antilogs = 35% to 121%; $p = 0.10$). The difference in those admitted over 4 hours was somewhat in the opposite direction. We, therefore, decided to continue until larger numbers accrued.

TABLE VIIICALCULATION OF TRIAL SIZE

| Number of patients | Reduction in infarct size | Chances of | |
|--------------------|---------------------------|------------|-------------|
| | | $p < 0.05$ | $p < 0.001$ |
| 200 | 25% | 33% | - |
| | 33% | 50% | - |
| | 40% | 66% | - |
| 400 | 25% | 55% | 30% |
| | 33% | 80% | 60% |
| | 40% | 90% | 80% |

Based on the data analysed, the trial sizes required to demonstrate various degrees of benefit were calculated (Table XIII). As a result of this, preliminary evaluation, we decided to publish our results on the first 200 patients as originally planned, but also to extend the study to 400 patients as it was thought that although we may have a 50% probability (or thereabouts) of detecting a benefit, the degree of benefit (i.e. the confidence interval) would be very large and the real benefit of treatment therefore questionable.

(ii) Second analysis on patients admitted to the trial until December 1979.

Complete enzyme data were available in 211 of the 215 patients randomised until December 1979. In three patients blood samples were lost during transportation and in one patient blood sampling was not done to protect the investigators (from infection of syphilis). At the time of this analysis (early January 1980), complete 12 lead ECG data and morbidity data were available in 195 patients (the remaining 20 still being en route). 35 lead maps were recorded in only 45 patients and are ignored in this report. For purposes of interpreting the ECG evolution during the days following randomisation, our fundamental measure has been what we have called the "R wave score". Leads showing ST segment deviation $>1\text{mm}$

TABLE IXENTRY DATA ON PATIENTS

| | <u>Atenolol</u> | <u>Controls</u> |
|---|-----------------|-----------------|
| Number of patients | 100 | 95 |
| mean age | 57.2 | 55.3 |
| Number of women | 9 | 13 |
| Previous H/O infarction | 12 | 9 |
| Heart Failure at entry | 11 | 9 |
| Time to randomisation from chest pain: | | |
| \leq 2 hrs | 4 | 10 |
| > 2-4 hrs | 45 | 39 |
| > 4-6 hrs | 24 | 22 |
| > 6-8 hrs | 14 | 12 |
| > 8-12 hrs | 13 | 12 |

were classified as vulnerable leads based on the pre-randomisation ECG. In patients with initial threatened infarction, leads showing ST depression or T inversion at any recording were considered vulnerable. The lowest R wave amplitude was expressed as a percentage of initial R wave amplitude in vulnerable leads. Our R wave score takes a value of 100% for patients who suffer no infarction and takes a value of 0% for patients whose R wave disappears in such leads. Since this cannot be reliably assessed for patients with bundle branch block or major axis deviations and in those patients dying before a second ECG was recorded, an arbitrary score was given to such patients:

- (1) Right or left bundle branch block or major axis deviation - 25%.
- (2) Two of the above - 10%.
- (3) ECG not available because of patients death - 0%.

Clinical details of the patients at entry are given in Table IX.

Threatened Infarction

Seventy-nine patients at entry were classified as belonging to Group II (threatened infarction). Eleven of 35 such patients (31%) randomised to receive atenolol

developed infarction compared to 27 of 44 such patients (61%). (chi square = 6.91 without continuity correction; $p < 0.01$, see Table X). Moreover the mean cumulative CK MB in the 11 patients who eventually infarcted in the atenolol group was slightly but non-significantly lower than in the 27 patients who eventually infarcted in the control group.

Complete ECG data was available for 76 of these 79 threatened infarction patients. The R wave score was $91.7 \pm 3.1\%$ in the atenolol group compared to $79.5 \pm 4.1\%$ in the control group ($t = 2.40$; $p < 0.025$, $2p < 0.05$) (Fig. 19). Patients were subdivided further into two groups based on entry heart rate (< 79 and 80 and above). In patients with entry heart rate less than 79 , the R score was $91.2 \pm 3.5\%$ in the atenolol group ($n = 22$) compared to $76.8 \pm 5.5\%$ in the control group ($n = 24$; $t = 2.23$, $p < 0.025$; $2p < 0.05$). In patients with entry heart rate 80 and above, the R score was $92.5 \pm 6.1\%$ in the atenolol group ($n = 13$) compared to $83 \pm 6.4\%$ in the control group ($n = 17$; $t = 1.05$, $2p < 0.30$).

All group II patients were subdivided into two further groups based on the time of randomisation from chest pain. (< 4 hrs and > 4 hrs). In patients < 4 hrs, the R wave score in the atenolol group ($n = 13$) was $86.2 \pm 7.1\%$ compared to $79.5 \pm 7.3\%$ in the control patients ($n = 17$; $t = 0.66$; not significant). In patients

R WAVE CHANGES IN ATENOLOL AND CONTROL PATIENTS WITH THREATENED INFARCTION

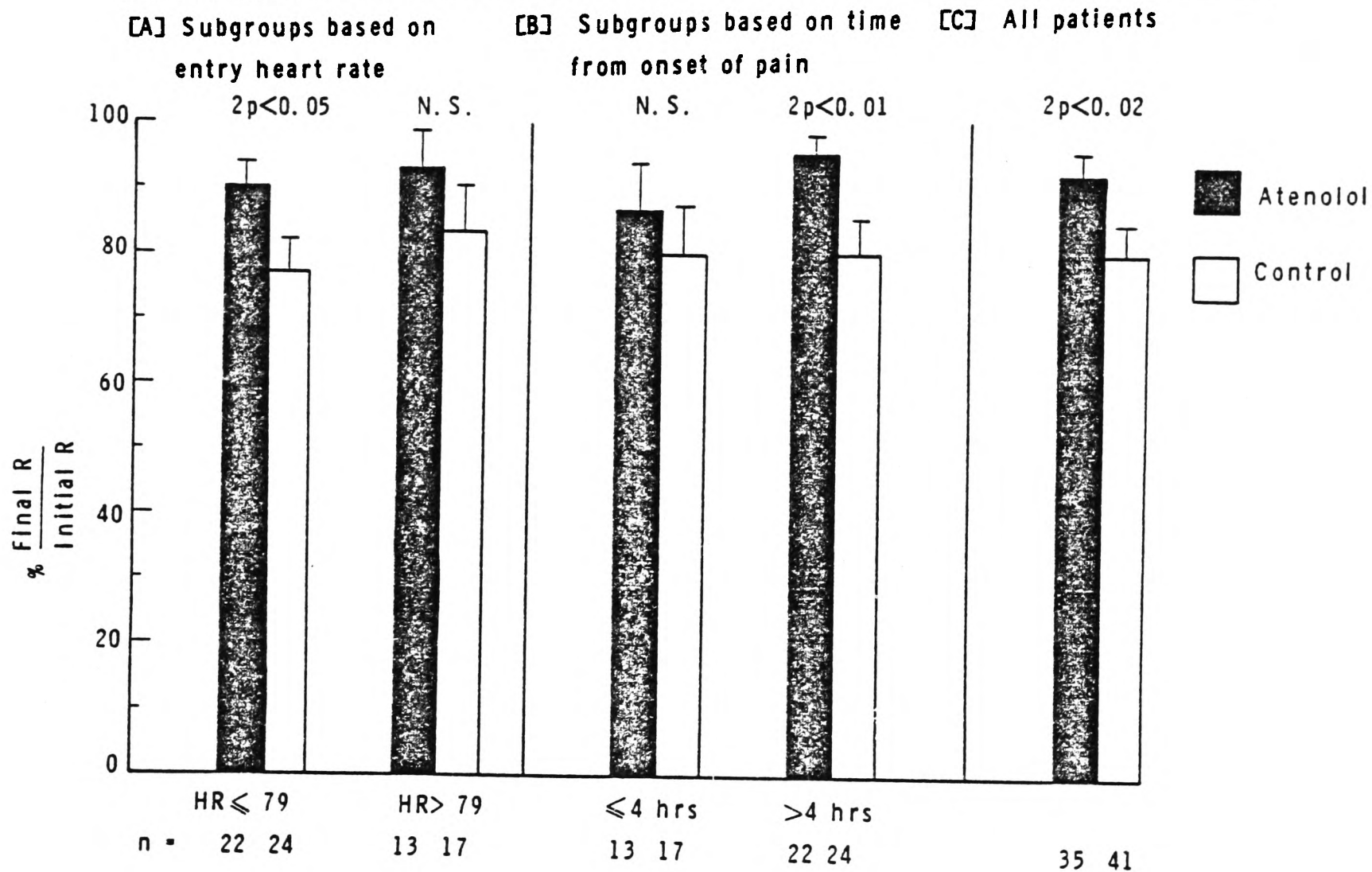


Figure 19: R wave score in patients with initial threatened infarction.

admitted over 4 hours, the R wave score was $95 \pm 2.5\%$ in the atenolol group ($n = 22$) compared to 79.5 ± 4.9 in the control group ($n = 24$; $t = 2.80$; $p < 0.005$; $2p < 0.01$).

Definite Infarction (Group I patients)

Enzyme Data (Fig. 20).

One hundred and thirty-five patients were classified based on their entry ECG to Group I, with 72 randomised to receive atenolol and 63 patients randomised to be controls. The mean cumulative enzyme value was 121.2 ± 9.7 in the atenolol group compared to 177.2 ± 16.7 in the control group ($t = 2.91$, $p < 0.0025$, $2p < 0.005$). This is a ratio of 0.68 and represents a 32% decrease in cumulative enzyme values with a standard 95% confidence interval ranging from 5% to 50%. This means that although we can be fairly certain atenolol has some effect in reducing enzyme levels, there is a tenfold uncertainty regarding the true degree of benefit.

The mean \log_{10} cumulative CK MB was 1.975 ± 0.039 in the atenolol group compared to 2.113 ± 0.048 in the control group ($t = 2.226$; $p < 0.025$, $2p < 0.05$). This suggests a mean reduction in enzyme levels of 27% in the atenolol group.

CUMULATIVE ENZYME RELEASE IN ATENOLOL AND CONTROL PATIENTS WITH DEFINITE INFARCTION AT ENTRY

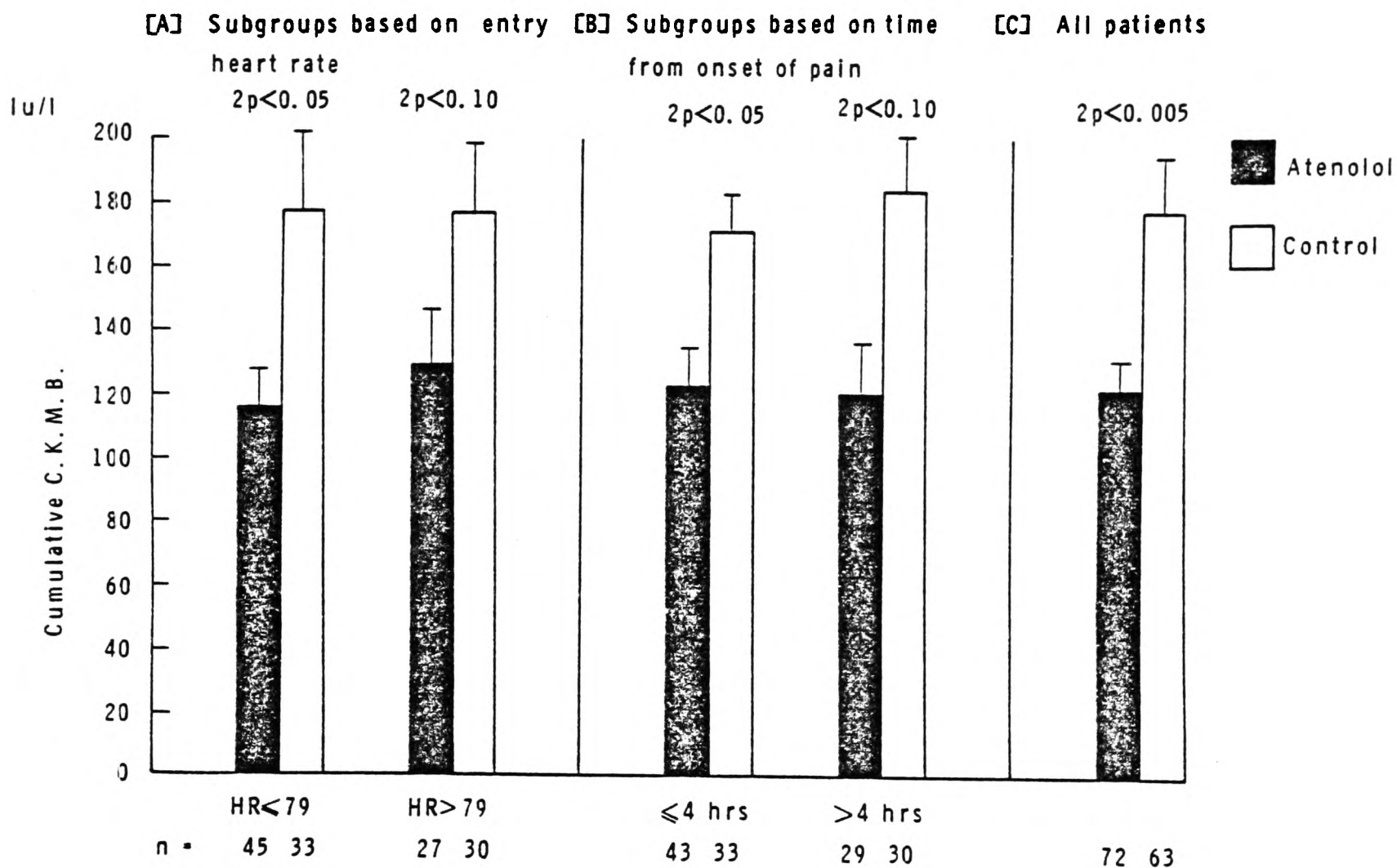


Figure 20: Cumulative CKMB release in patients with initial definite infarction.

As before, we separately analysed patients entering with a low heart rate (≤ 79) and patients with a high heart rate (80 and above); early and late entry patients (≤ 4 hrs and > 4 hrs).

In patients with entry heart rate ≤ 79 the mean cumulative CK MB in the atenolol group (n = 45) was 116.6 ± 11.8 compared to 177.1 ± 25.5 in the control group (n = 33; t = 2.16; $p < 0.025$; $2p < 0.05$). In patients with entry heart rate 80 and above, the mean cum CK MB was 129 ± 16.9 in the atenolol group (n = 27) compared to 177.4 ± 21.4 (n = 30; t = 1.77; $p < 0.05$; $2p < 0.10$).

In patients entering ≤ 4 hrs of pain, the mean cum CK MB was 122.0 ± 12.0 in the atenolol group (n = 43) compared to 171.1 ± 19.6 in the controls (n = 33; t = 2.14; $p < 0.025$, $2p < 0.05$). In patients entering > 4 hrs after pain, the cumulative CK MB was 120.2 ± 16.5 in the atenolol group (n = 29) compared to 184.1 ± 27.9 in the controls (t = 1.97; $p < 0.05$; $2p < 0.10$).

ECG Data (Fig.21)

Complete R wave data was available for 120 of the 135 patients belonging to Group I (66 in the atenolol group and 54 controls). The R score in the atenolol group was $45.5 \pm 2.9\%$ compared to $35.7 \pm 2.9\%$ in the controls (t = 2.40; $p < 0.01$; $2p < 0.02$).

R WAVE CHANGES IN ATENOLOL AND CONTROL PATIENTS WITH DEFINITE INFARCTION AT ENTRY

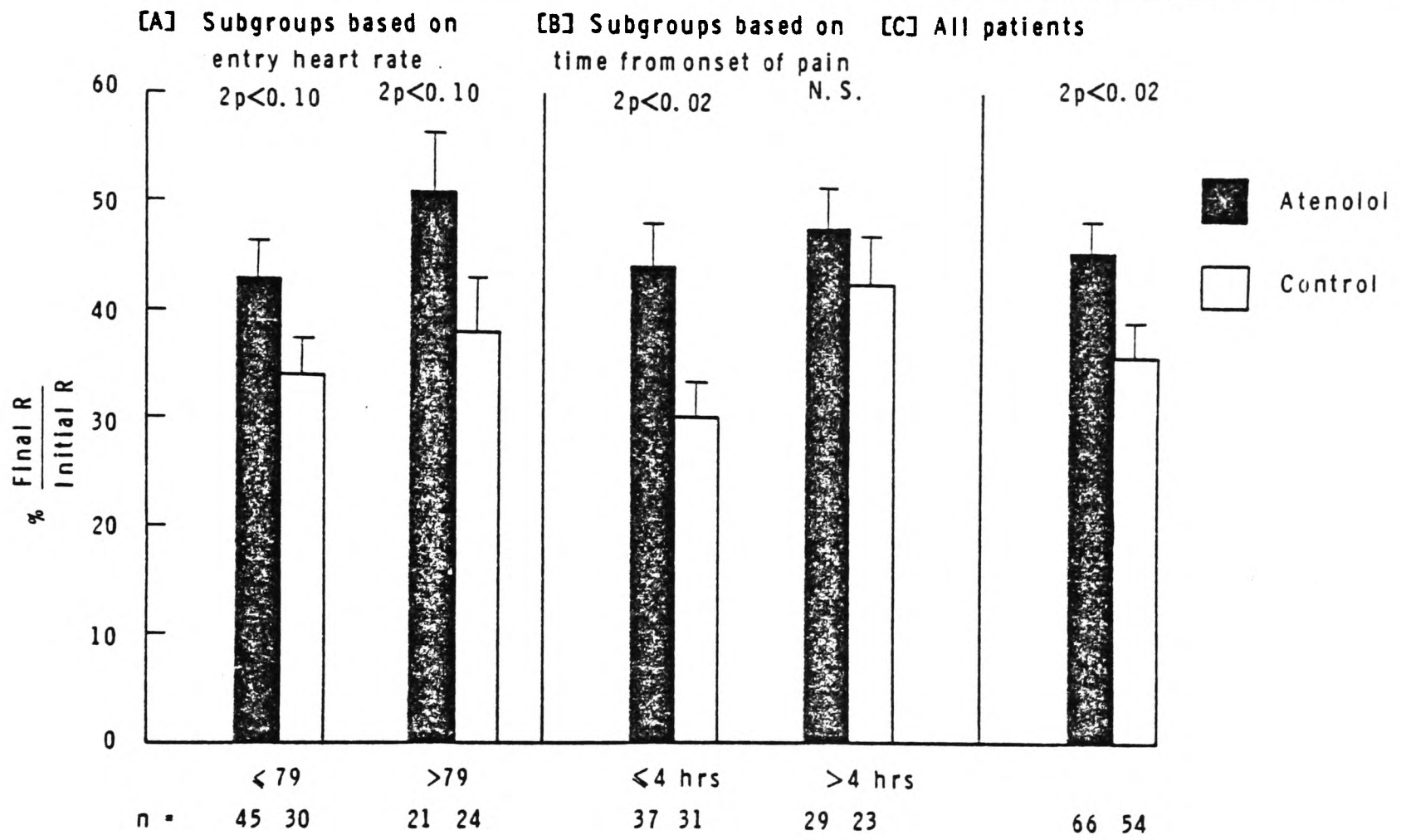


Figure 21: R wave score in patients with initial definite infarction.

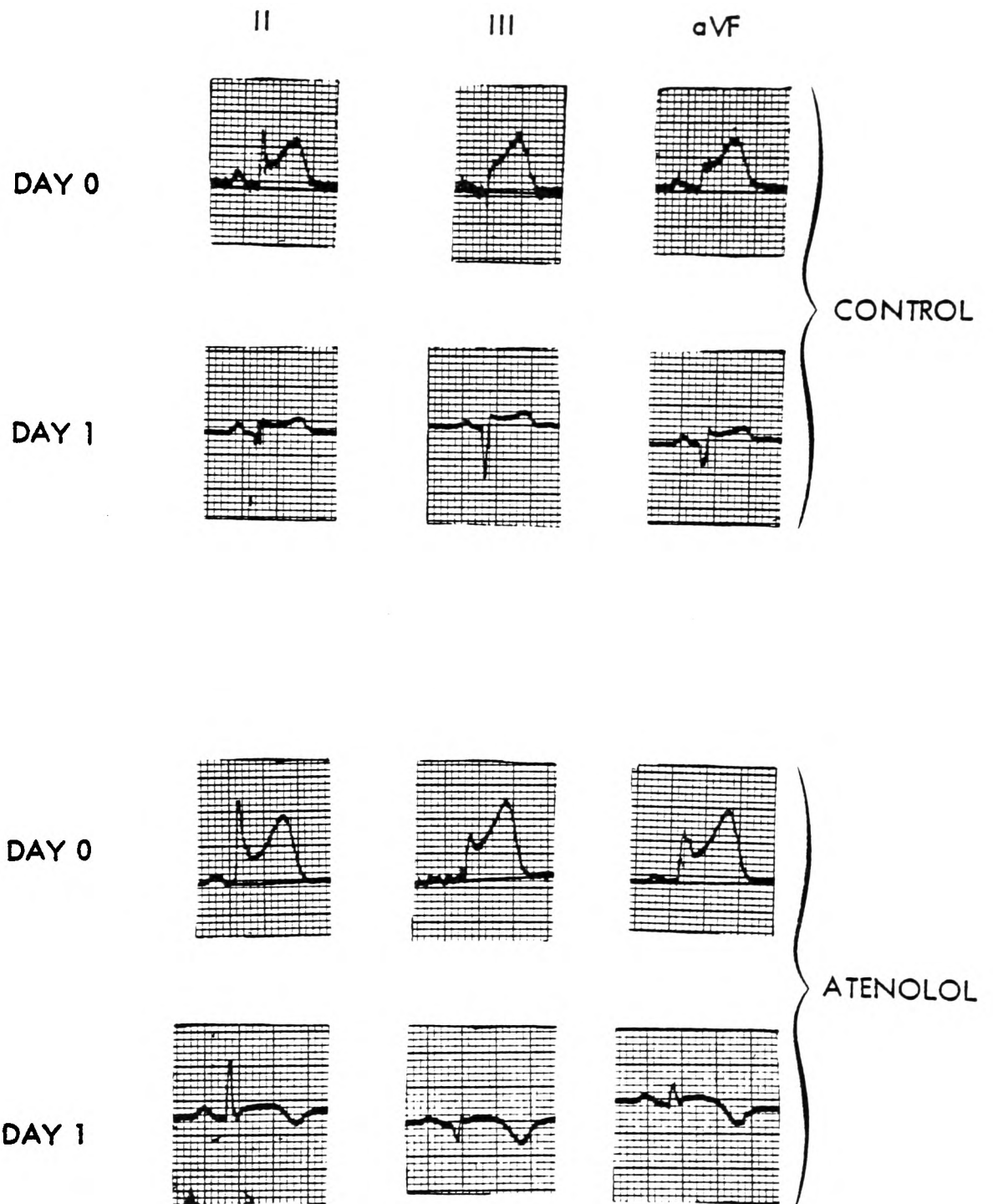


Figure 22: ECG recordings in control and atenolol patients with inferior infarction.

The patients were subdivided as before into high and low heart rate groups and early and late entry groups.

In patients presenting with a heart rate 79 or less the R score was $44.0 \pm 4.2\%$ in the atenolol group ($n = 37$) compared to $30.6 \pm 3.6\%$ in the controls ($n = 31$; $t = 2.43$; $p < 0.01$; $2p < 0.02$). In patients presenting with heart rates above 79, the R score was $47.4 \pm 4.0\%$ in the atenolol group ($n = 29$) compared to $42.4 \pm 4.5\%$ in the controls ($n = 23$; $t = 0.83$; not significant).

The mean R score in atenolol patients admitted 4 hours ($n = 45$) was $43.1 \pm 3.5\%$ compared to $33.7 \pm 3.3\%$ in the controls ($t = 1.96$; $p < 0.05$; $2p < 0.10$). In patients randomised after 4 hours the R score in atenolol patients ($n = 21$) was $50.7 \pm 5.2\%$ compared to $38.2 \pm 5.0\%$ in controls ($n = 24$) ($t = 1.72$; $p < 0.05$; $2p < 0.10$).

Preliminary Data on Clinical Course, Morbidity and Side Effects;

Heart Failure

This data is summarised in Table XI. At entry 11 atenolol and 9 control patients had evidence of heart failure (defined as the institution of anti failure therapy either before or within an hour of randomisation).

TABLE XIDETAILS ON HEART FAILURE

| | <u>Atenolol</u> (n = 100) | <u>Controls</u> (n = 95) |
|---|------------------------------------|-----------------------------|
| 1. No. of patients with failure at entry | 11 | 9 |
| 2. Late failure (no. of patients given diuretics) | 36 $\chi^2=3.61; 2p<0.10$ | 47 |
| 3. No. of patients given digoxin | 3 | 9 |
| 4. Mean Frusemide dose in hospital | 145±33 t=1.659; p<0.05; 2p<0.10 | 247±54 |
| 5. No. of patients on thiazides only | 8 | 9 |
| 6. No. of patients on frusemide + thiazide | 4 | 11 |
| 7. No. of patients on spironolactone | 0 | 2 |
| 8. No. of patients on diuretics at discharge | 19 $\chi^2=4.75; 2p<0.05$ | 31 |
| 9. No. of patients on digoxin at discharge | 3 | 7 |

Thirty-six percent of atenolol patients and 47% of control patients developed heart failure during hospital stay (chi square = 3.61, $2p \leq 0.10$). Nineteen percent of atenolol patients and 33% of control patients were discharged on diuretics (chi square = 4.748, $2p \leq 0.05$), 3 atenolol and 7 control patients were discharged on digoxin.

A detailed analysis of the amount of anti-failure drugs used showed a greater amount of diuretics and digoxin in control patients. Atenolol patients received a mean dose of 144.80 ± 33 mgm of frusemide compared to 247.16 ± 54 mgm in the control patients ($t = 1.659$; $p \leq 0.05$; $2p \leq 0.10$). In addition, 8 atenolol patients and 9 control patients received thiazide diuretics as the only treatment for heart failure. Four atenolol and 11 control patients received both frusemide and a thiazide diuretic. A further 2 control patients received spironolactone.

The proportion of patients receiving diuretics and the amount of diuretics used was greater in the controls compared to the atenolol group.

Arrhythmias, Cardiac Arrests and Mortality

The incidence of atrial fibrillation or flutter (detected by the nursing staff) was higher in the controls compared to the atenolol group (5 treated and 9 controls).

Two atenolol patients and 6 control patients developed nonfatal cardiac arrests in hospital after entry to the study. The in-hospital mortality was 4 in the treated group compared to 9 in the controls. At present our post-discharge mortality data is incomplete; however, we hope to obtain complete follow-up through the Office of Population^{Censuses} and Surveys.

Bradycardia and Hypotension

Table XII shows that bradycardia and hypotension, not unexpectedly, were commoner in the treated group compared to the controls. However, the number of patients receiving atropine was similar in both groups, suggesting that in most instances of bradycardia associated with atenolol, this was treated by stopping all or part of the remaining doses of the drug. Three atenolol and two control patients required inotropic agents. Two of the three atenolol patients had previous infarction and both these patients were discharged alive. The third patient reinfarcted, ruptured his papillary muscle and died inspite of small enzyme release. Both patients in the control group died in cardiogenic shock.

No difference in the development of complete heart block and bundle branch block in the two groups were observed. There were more patients showing axis deviation (left anterior or posterior hemiblocks) in the control group.

TABLE XII ADVERSE EFFECTS OTHER THAN HEART FAILURE

| | <u>Atenolol</u> | <u>Control</u> |
|---|-----------------|----------------|
| 1. Protocol deviations | 17 | 14 |
| 2. Hypotension (systolic less than 90 mmHg/any level at which action was taken) | 24 | 16 |
| 3. Use of inotropic agents (Dobutamine, Dopamine, Noradrenaline) | 3 | 2 |
| 4. Bradycardia (heart rate less than 40 or any level at which action was taken) | 17 | 7 |
| 5. No. of patients receiving atropine | 9 | 7 |
| 6. Complete heart block | 6 | 6 |
| 7. Right bundle branch block | 4 | 4 |
| 8. Extreme axis deviation | 3 | 6 |
| 9. Atrial fibrillation or flutter | 5 | 9 |
| 10. Nonfatal cardiac arrests | 2 | 6 |
| 11. In hospital deaths | 4 | 9 |
| 12. Nonfatal cardiac arrests and/or in hospital deaths | 5 | 14* |

* Although this is highly significant ($2p < 0.03$), it is inappropriate to attribute a p-value to data-derived hypotheses, as we did not initially plan to look at the above combined end point.

Protocol Deviations

Atenolol was stopped in 17 patients allocated to the atenolol group when side effects were suspected (see Table XII). In 14 patients in the control group, a beta blocking drug was given as the physician-in-charge of the patient felt that this was strongly indicated. In 12 of these, this was because of continuing chest pain, uncontrolled by nitrates. All the above patients were retained in their original groups for analysis.

Three other patients merit further consideration. One patient randomised to the control group received atenolol intravenously 30 minutes later as the physician-in-charge thought that this was essential. She was retained in the control group. Two other patients were given atenolol at entry as soon as they were randomised in the mistaken belief that they drew atenolol. It was only at the time of analysis that the mistakes were discovered. We have retained these patients in the atenolol group since the drug was given unbiasedly in both instances. Reanalysis of the data by excluding these patients or even including them in the control group does not materially alter the results.

Discussion

We have demonstrated that atenolol reduces the incidence of completed infarcts in patients with threatened infarcts ($p \leq 0.01$) and reduces both enzyme and ECG estimates of infarct size in patients with definite infarcts at entry ($p \leq 0.0025$ and $p \leq 0.01$ respectively). In addition, subsequent heart failure, atrial fibrillation, in-hospital cardiac arrests and deaths were fewer in treated patients.

Although doubts have been expressed about the reliability of the ECG (Holland et al., 1977) and the cumulative enzyme release as direct estimates of infarct size (Roe et al., 1976), most workers accept their validity as a reasonable estimate of myocardial damage (Sobel et al., 1972; Bleifeld et al., 1976; Maroko et al., 1973). We have earlier shown good correlations between the ECG and enzyme methods, thereby validating both (Yusuf et al., 1979). It has been suggested that the reduction of serum enzyme levels by a beta-blocker may be an artefact by reducing washout from the centre of the infarct zone or by affecting its kinetics (Slutsky et al., 1978). However, this seems an unlikely explanation of our present data as we have demonstrated parallel reduction in both enzyme and ECG estimates of infarct size.

Our results confirm the earlier report of a reduction in serum enzyme levels after administration of propranolol within 4 hours of pain (Peter et al., 1978). We have used similar criteria for entry into our study but unlike them we appear to find a reduction in infarct size in the 4-12 hour group as well. Further analysis of our data (Table IX) shows that 75% of patients were admitted within 6 hours of pain, and 87% by 8 hours. We earlier demonstrated that infarct evolution continues beyond 12 hours in about half the patients admitted to hospital, and it is possible that atenolol may be effective even at this time.

The reduction in the incidence of infarcts in the treated group with threatened infarction at entry, confirms the recent report of Norris et al. (1978).

Of particular interest in this study is the reduction of R wave loss in the treated group. Although this has not been demonstrated before in man, Miura et al. (1978) reported a parallel reduction in R wave loss and decrease in anatomical infarct size in dogs treated with propranolol. We subdivided our patients based on entry heart rate into those with high and low entry heart rates as we expected the greatest benefit in patients with initial tachycardia. However, our data do not support this hypothesis. This may be, in part, due to the small number of patients who entered the study with substantial tachycardia (e.g. over 100/min).

We should note certain points in trial design and analysis. First, we 'estimated' initially that at least 200 patients would be required to give us a reasonable chance of detecting a 30 to 40% benefit. Had we stopped our study at 100 patients (trial size of Peter et al.), we may not have detected any benefit. Only after the first analysis did we have enough data on the differences between groups and their standard error. We could then calculate that 200 patients would give us only a 55% chance of detecting a 30% benefit at $p \leq 0.05$; we therefore planned to continue the trial until at least 400 patients were entered. We may have therefore been rather fortunate in detecting such significant benefit at the 200 patient stage. On the other hand, the sensitivity of the analysis was improved by separate analysis of definite infarction and threatened infarction.

The second design feature to note is that all subdivision of patients into subgroups based on time from pain, entry heart rate and entry ECG were prior hypotheses in our protocol. Third, the number and times of analysis were determined beforehand. If analysis of data occurs too frequently, misleading results may be reported unless sequential methods of analysis are used (McPherson, 1974; Peto et al., 1977).

Although beta-blockade is thought to be potentially harmful when cardiac function is impaired, reduction in infarct size would be expected to reduce subsequent morbidity (especially cardiac failure, atrial fibrillation, late ventricular arrhythmias, secondary cardiac arrests). We found in our study a lower incidence in the severity of heart failure in the atenolol group. In this report, we defined heart failure based on the need for anti-failure therapy. We believe this is possibly the best available criteria in our study as the decision to give diuretics or digoxin was left entirely to the physician-in-charge of the patient and was not influenced in any way by the investigators. Further the amount of diuretics used may be an approximate indication of the severity of heart failure. We accept there may be variations between physicians regarding the type and amount of diuretics or even if a diuretic has to be used in an individual patient. However, it is unlikely that the physicians were biased in their ancillary treatment given to controls or atenolol patients; it is therefore reasonable to expect any variations between physicians to be random.

Our study (and all published randomised controlled trials - see Chapter I) do not support the common belief that beta-blockers precipitate or worsen heart failure.

In our study we have given atenolol to a few patients presenting with heart failure (some had even interstitial oedema on their chest X/ray) and there was no clinical or radiographic worsening of failure in these patients. Overall, fewer atenolol patients required antifailure therapy during hospitalisation; the amount of diuretics and digoxin used was less in treated patients and fewer patients required antifailure therapy on discharge. Studies by Mueller et al. (1977), have demonstrated that intravenous propranolol given within 12 hours of pain induces only a modest increase in left ventricular filling pressure in those with low pretreatment values and a decrease in those with initial elevated values. This may be due to improved compliance of the left ventricle secondary to reduction of ischaemia by beta-blockade.

Bradycardia and hypotension were commoner in atenolol treated patients. However, the number of patients receiving atropine and inotropic agents was similar in both groups suggesting that stopping the beta-blocker was sufficient in most cases. Analysis of the data of patients with later troublesome bradycardia did not identify any factor that could predict this. This is important as our lower limit of heart rate for entry into the study was 40/min and it is possible that even such patients may have benefited by beta-blockade. Some control patients with low entry heart rates later demonstrated tachycardia and signs of heart failure.

The measured PR interval showed no prolongation in the treated group. The incidence of complete heart block and bundle branch block did not differ in the two groups. We therefore believe that the role of betablockers ⁱⁿ producing or worsening heart block needs to be re-evaluated. Extreme right or left axis deviation were commoner in controls.

Despite the encouraging results thusfar, we are still not even certain whether beta-blockade has any substantial enough effect on enzymes or ECGs to justify its widespread use. The lower confidence limit for our enzyme improvement is a mere 5% (the 95% confidence interval being 5% to 50%), and if this is the real truth then the treatment is so unpromising that most clinicians would choose not to use it. To determine whether the real benefit is of a worthwhile magnitude, our present trial is being continued for at least one more year.

However, the chief aim is to reduce mortality rather than to reduce infarct size, and this we have not demonstrated, nor could we reasonably hope to do so with only a few hundred patients. A serious study of the effects of early beta-blockade on mortality should involve randomisation of some thousands of patients. If one year hence, our data continue to indicate a worthwhile reduction in infarct size, then there will be a strong case for undertaking a trial of mortality.

Although it is even possible that myocardial salvage might preserve harmful tissue which will act solely as a focus for arrhythmias, it is certainly plausible to hope for sound net benefit.

In conclusion, the early intravenous administration of atenolol prevents the development of infarction in a proportion of patients with threatened infarction, reduces infarct size in patients with acute infarction and reduces subsequent morbidity in these patients. Widespread use of this drug must await confirmatory evidence from other similar trials in progress - Myocardial Infarct Limitation Study; MILIS from the National Heart, Lung and Blood Institute and the Goteborg, metoprolol study - and clear reduction in mortality and morbidity.

CHAPTER VII

EFFECT OF LONG-TERM BETA ADRENERGIC
BLOCKADE ON THE HEALING OF CLINICAL
AND EXPERIMENTAL INFARCTION

INTRODUCTION

This study extends the earlier work on the electrocardiographic evolution of acute myocardial infarction. Many interventions have been used to prevent the further development of Q waves and loss of R waves in experimental and clinical infarction (Maroko et al., 1973). Little quantitative work has been done on the ECG changes after hospital discharge. Although the regression of Q wave changes after acute myocardial infarction has been reported earlier (Pyorala & Kentala, 1974), little is known regarding the changes in R wave amplitude. No study has been performed aimed at investigating the factors which may affect the recovery of the QRS complex of the ECG in the chronic healing phase after myocardial infarction.

I report here a series of clinical and experimental studies on the long-term changes that occur after myocardial infarction.

Section I. Initial Study of the Chronic Phase After Myocardial Infarction

As part of a trial of beta-blockade after myocardial infarction I routinely recorded 35 lead praecordial maps at discharge, and then at three, six and twelve months after discharge. We were surprised

to find that the subjects on beta-blockers showed a greater and faster recovery in the ECG.

Subjects and Methods

Twenty-two patients aged between 46-70 years admitted to the coronary care unit of the Radcliffe Infirmary with definite evidence of a recent anterior transmural myocardial infarction (between 4 hours and 24 hours after chest pain) were studied. This was later confirmed by a significant elevation of CK MB. In addition to the exclusion criteria mentioned earlier (patients with conduction defects and extreme axis deviation; see Chapter III), only patients suitable for beta-adrenoceptor blockade were included (pulse $>50/\text{min}$, BP $>100\text{mm}$ systolic and no evidence of left ventricular enlargement or failure on the chest X/ray). On admission (mean time of 8 hours after chest pain) patients were randomised to receive 100mgm of atenolol or equivalent placebo tablets daily for a year.

35 lead praecordial maps (Chapter II) were recorded just before discharge from hospital (between 10 and 14 days after admission) and at 3 months and 6 months for all patients. Recordings were obtained in 17 patients at 12 months after discharge.

TABLE XIII

| | Discharge | 3 months | 6 months | 12 months |
|-----------------|-------------|---------------------------|---------------------------|------------------------|
| Q | 147.4 ± 17 | 118.8 ± 14 2p = 0.11 | 101.6 ± 18 2p = 0.07 | 109.6 ± 19 |
| R | 56.7 ± 9 | 76.3 ± 11 2p = 0.17 | 84.2 ± 11 2p = 0.053 | 98.3 ± 15 2p = 0.02 |
| ST elevation | 37.8 ± 4 | 12.00 ± 1.5 2p < 0.001 | 13.6 ± 1.5 | 11.6 ± 1.2 |
| R/(Q + S) | 0.28 ± 0.06 | 0.42 ± 0.07 2p < 0.1 | 0.65 ± 0.14 2p < 0.025 | 0.74 ± 0.10 |

The amplitude of the various waves obtained during the follow-up period in the total group.

2p = two tailed unpaired 't' test and are for comparisons of the particular value to the initial value.

Statistical Methods

Standard statistical tests of paired and unpaired 't' tests and the nonparametric Wilcoxon rank test were used. All figures are expressed as mean \pm one standard errors.

Results

A. Serial Changes in ECG in the Whole Group (Table XIII)

The ΣQ waves showed a steady decrease of about 33% at six months ($2p = 0.07$). Simultaneously, the ΣR showed a 74% increase at one year in comparison to the discharge recording. The ST segment elevation decreased significantly at three months and then remained unchanged at six and 12 months. The $\Sigma R / \Sigma(Q+S)$ ratio showed a steady increase reflecting a gradual increase in the ratio between positive and negative waves.

B. R wave recovery with Atenolol compared with placebo

The ΣR wave increase was significantly greater in the treated group as compared to the placebo group ($2p < 0.001$, using both Wilcoxon rank tests and the unpaired 't' test). Figure 23 shows the ΣR wave increase per month of follow-up in the treated and untreated groups.

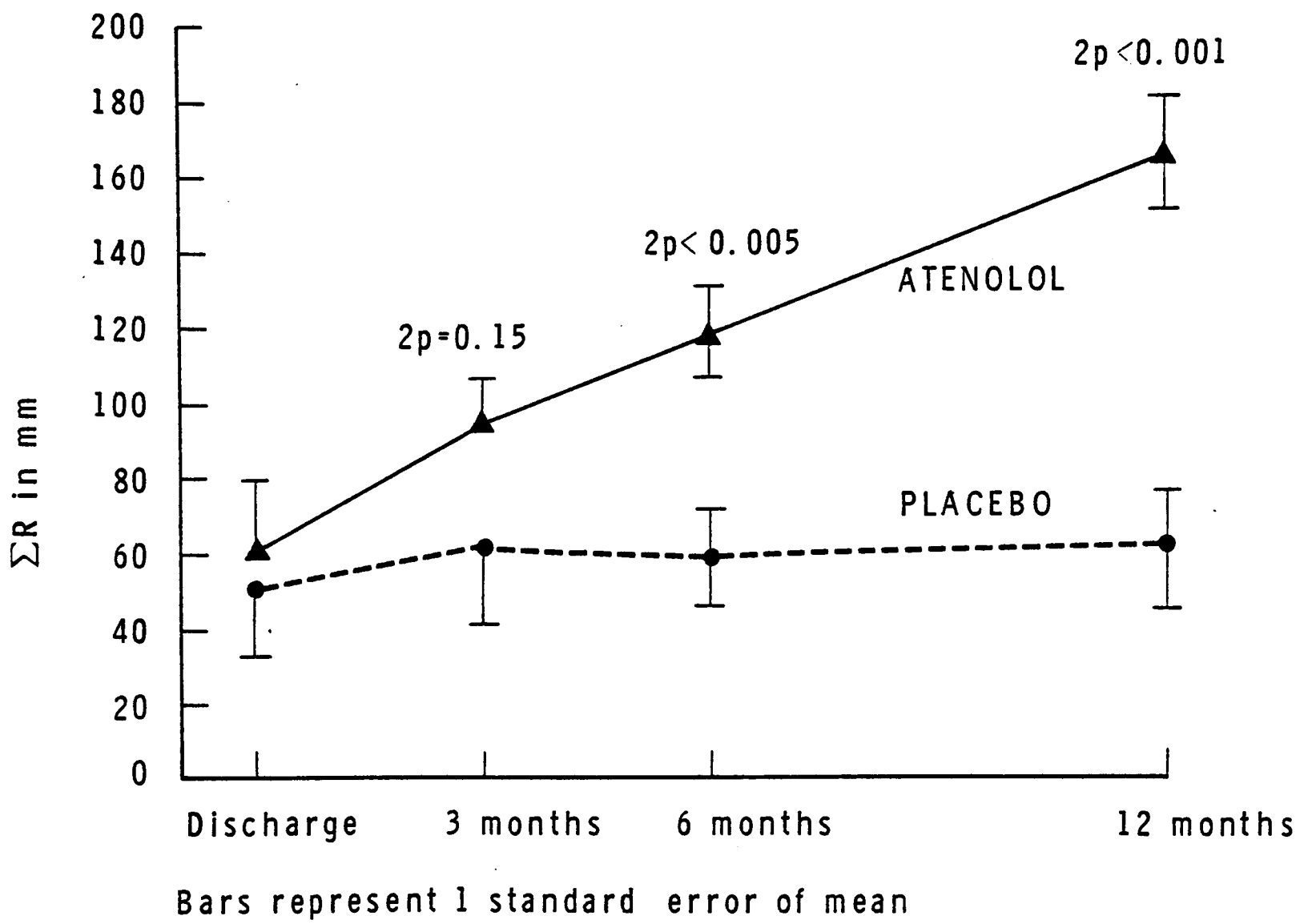


Figure 23: Increase in R waves in the atenolol treated and control groups.

The ΣR changed from an initial mean value of 62.2 ± 8.4 (SEM) in the atenolol treated group and $49.8\text{mm} \pm 14.5$ in the placebo group (difference not significant) to 93.8 ± 9.4 and 61.8 ± 19.6 at three months ($2p = 0.05$), to 118.8 ± 10.5 and 58.3 ± 14.2 at six months ($2p < 0.005$) and to 166.5 ± 15.3 and 61.1 ± 16.2 at one year ($2p < 0.001$) (Figure 23).

C. Q wave changes with Atenolol compared to placebo

Figure 24 demonstrates that the decrease in ΣQ waves per month of follow-up was significantly greater in the atenolol treated group ($-9.06\text{mm} \pm 2.40$) as compared to the placebo group (-1.92 ± 1.20) ($2p < 0.025$; student 't' test).

D. QRS duration

The duration of the QRS wave did not change significantly in the two groups.

Comment on Section I

In the above study I have demonstrated that the electrocardiographic signs of myocardial infarction regress. I have also shown that chronic administration of atenolol (a beta-adrenoceptor blocker) increases the recovery of the R wave amplitude and regression of the Q wave abnormalities.

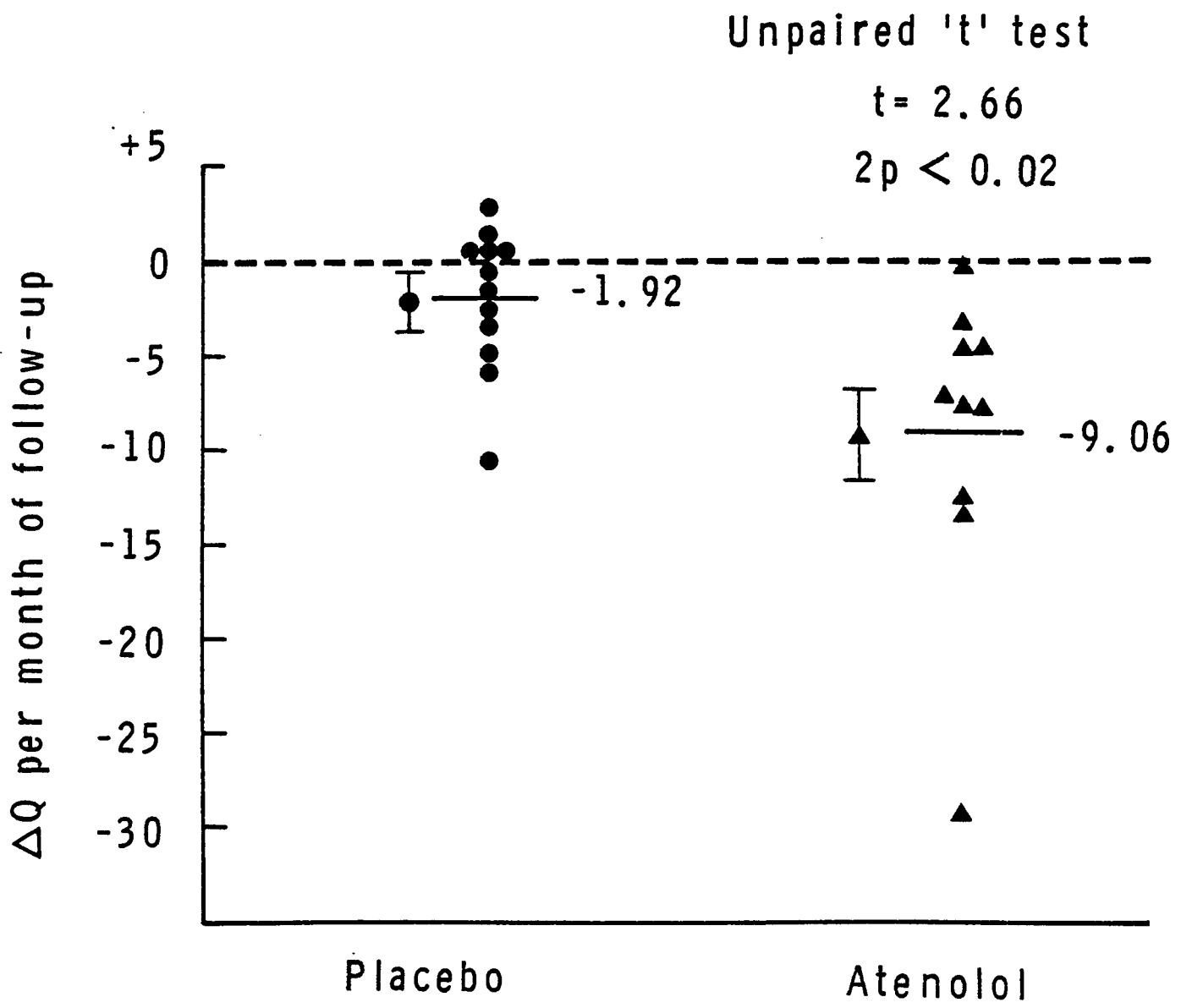
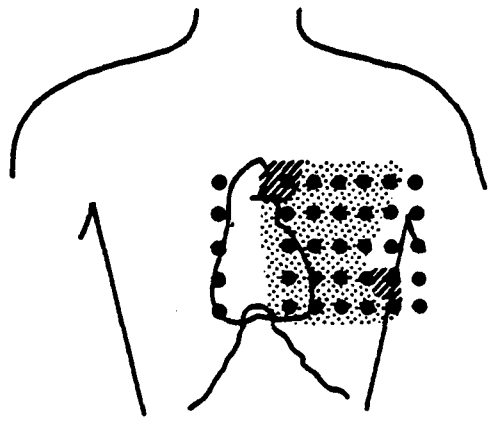
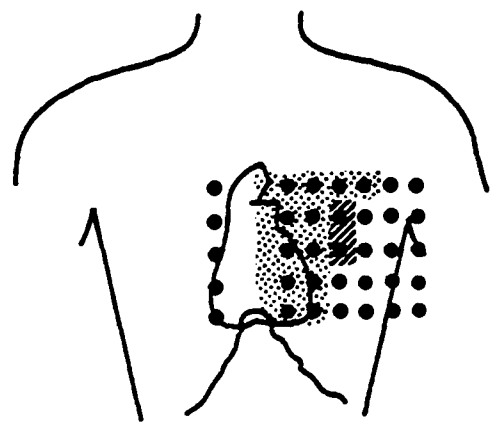


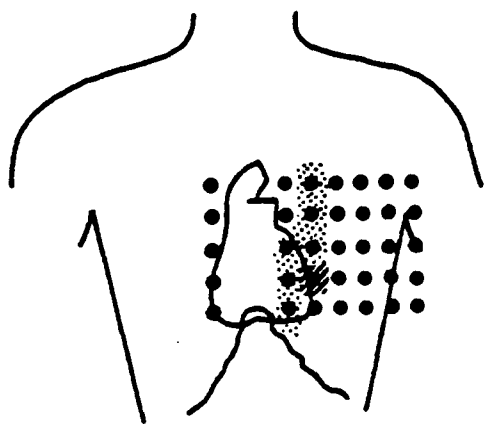
Figure 24: Decrease in Q waves in the atenolol-treated and control groups.



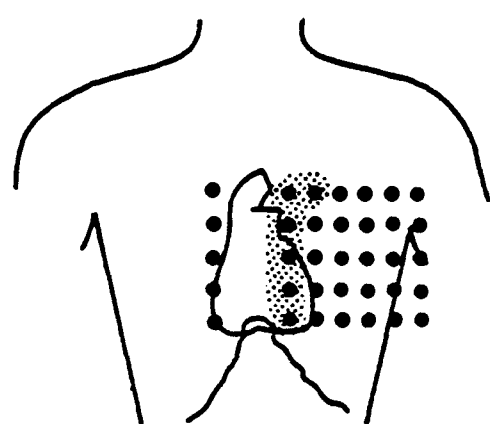
DISCHARGE



3 MONTHS



6 MONTHS



9 MONTHS

Figure 25: Area of QS waves in a patient treated with atenolol.

LONG TERM CHANGES IN ECG AMPLITUDE AFTER ACUTE MYOCARDIAL INFARCTION

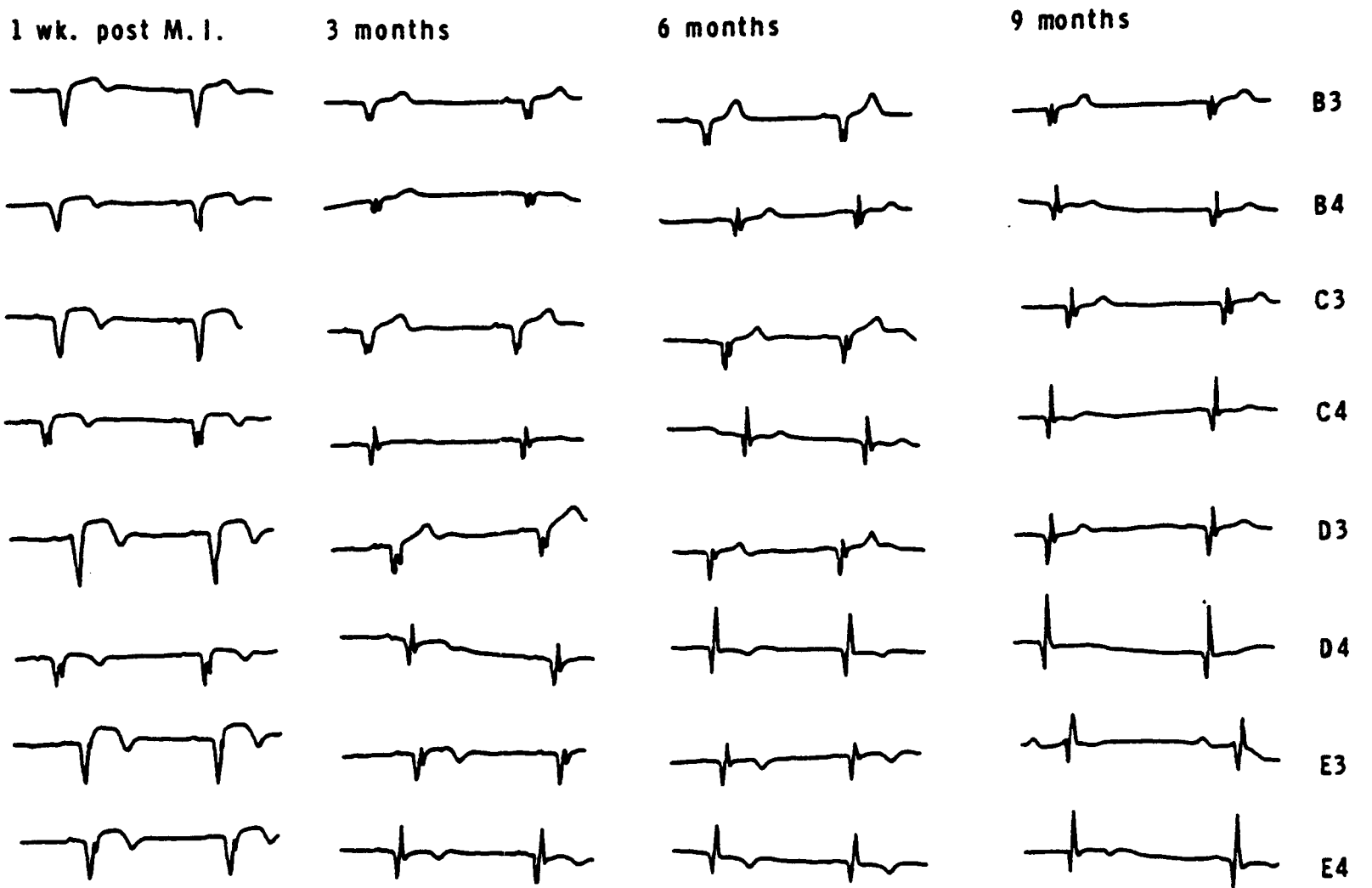


Figure 26: demonstrates the changes in the ECG in a patient treated with atenolol.

To confirm and further investigate this phenomenon I studied a larger group of patients already admitted to a randomized double-blind trial in Göteborg, Sweden. These patient's records were studied retrospectively by me.

Section II. Further Study on ECG Recovery After Myocardial Infarction in Man

A total of 67 patients with recent anterior transmural infarcts (confirmed by enzyme and ECG changes) admitted to the Sahlgrens Hospital at Göteborg were admitted to a randomised double-blind study of metoprolol. All patients showing intraventricular conduction defects, aged more than 75 years and a previous history of acute myocardial infarction were excluded. The mean age was 58 years and all patients were randomised at entry and were treated double-blind - one group received metoprolol 15 mg IV followed by 50 mg 6-hourly orally for 48 hours, and then 100 mg orally twice daily and the other group received a placebo injection and equivalent tablets for 3 months.

Standard 12 lead electrocardiograms were recorded once daily for 4 days and then every two or three days till discharge from hospital (approximately 2 weeks).

The electrocardiogram showing the smallest R wave amplitude was used as the baseline for my study. The ECG was recorded at 3 months after discharge in the post-infarction clinic. All ECGs were recorded on a 4 or 6 channel mingograf ECG recorder (Elema Schonander 34 or 82) at a paper speed of 50mm/sec and standardisation of 10mm = 1mv.

The amplitude of the Q wave and R wave were measured from each V lead and summed per patient. The difference (ΔQ and ΔR) was calculated between the discharge and 3 month recordings. In addition, the QRS width was measured, and the heart rate was calculated from each recording.

LDH levels

Blood was drawn at 12 hourly intervals for at least 48 hours and up to 108 hours (mean 82 hours) for estimation of LDH levels

The peak values were used as an index of infarct size in individual patients.

Results

- (i) R wave increase and R/Q change in the placebo and metoprolol group

The R wave increased from an initial mean of 25 ± 4.9 in the placebo group and 24 ± 6.7 in the

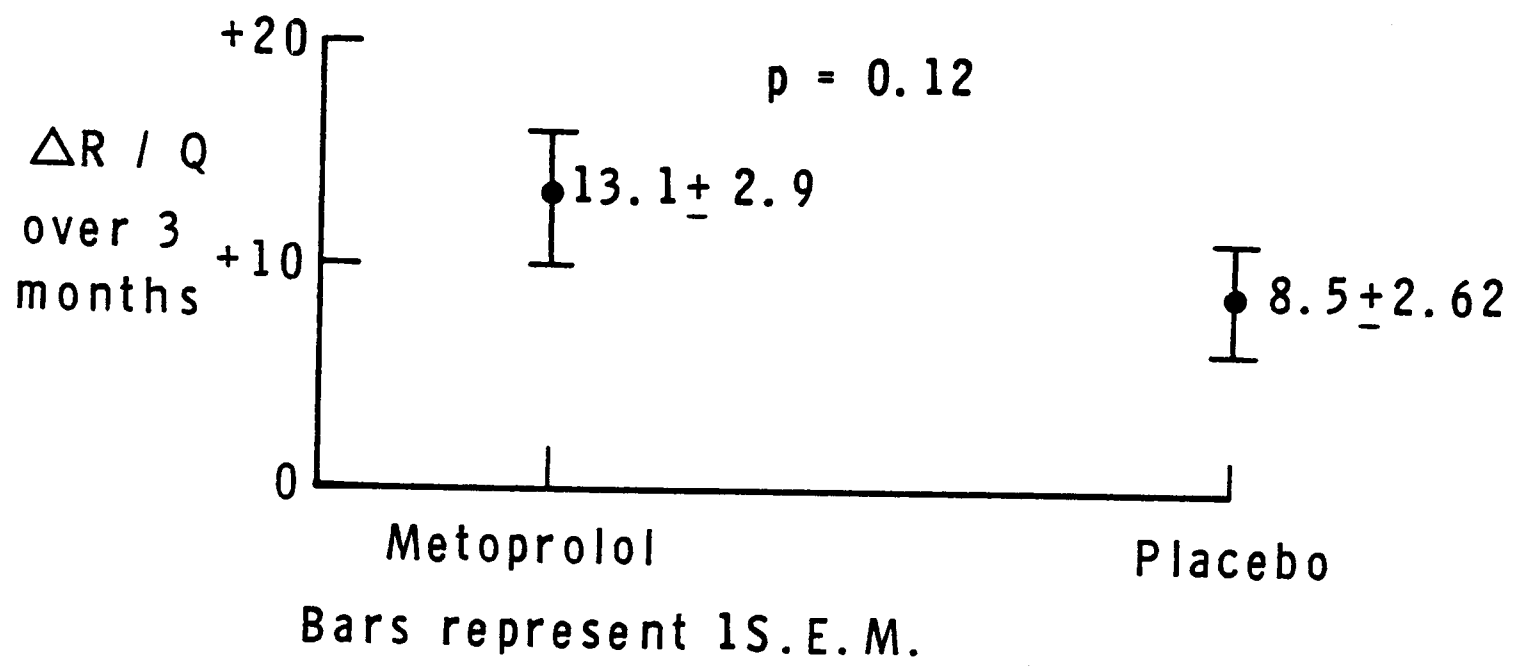


Figure 27: change in R/Q ratios over 3 months in the metoprolol and placebo groups.

metoprolol group to 36 ± 3.66 and 39 ± 4 at 3 months respectively. Although the difference between the two groups was not significant at the 5% level a trend in favour of increasing R wave recovery was observed in favour of the metoprolol group. (N.B. In our study with atenolol, statistical significance was only achieved after 6 months follow-up and not at 3 months) (Fig. 27). Similarly, the R/Q ratio showed a greater improvement in the metoprolol group as compared to the placebo group ($p = 0.1$).

(ii) Influence of heart rate and R wave recovery in metoprolol and placebo patients (Fig. 28)

All patients with anterior transmural infarction were divided into 3 approximately equal groups based on the mean of the two heart rates obtained from the baseline ECG and 3 months ECG recordings.

Group I: A low heart rate group
(n = 22) HR 63 and below/min

Group II: An intermediate heart rate group
(n = 23) HR 64 to 75/min

Group III: A high heart rate group
(n = 22) HR >75/min

HEART RATE AND R WAVE RECOVERY [R_x + CONTROL]

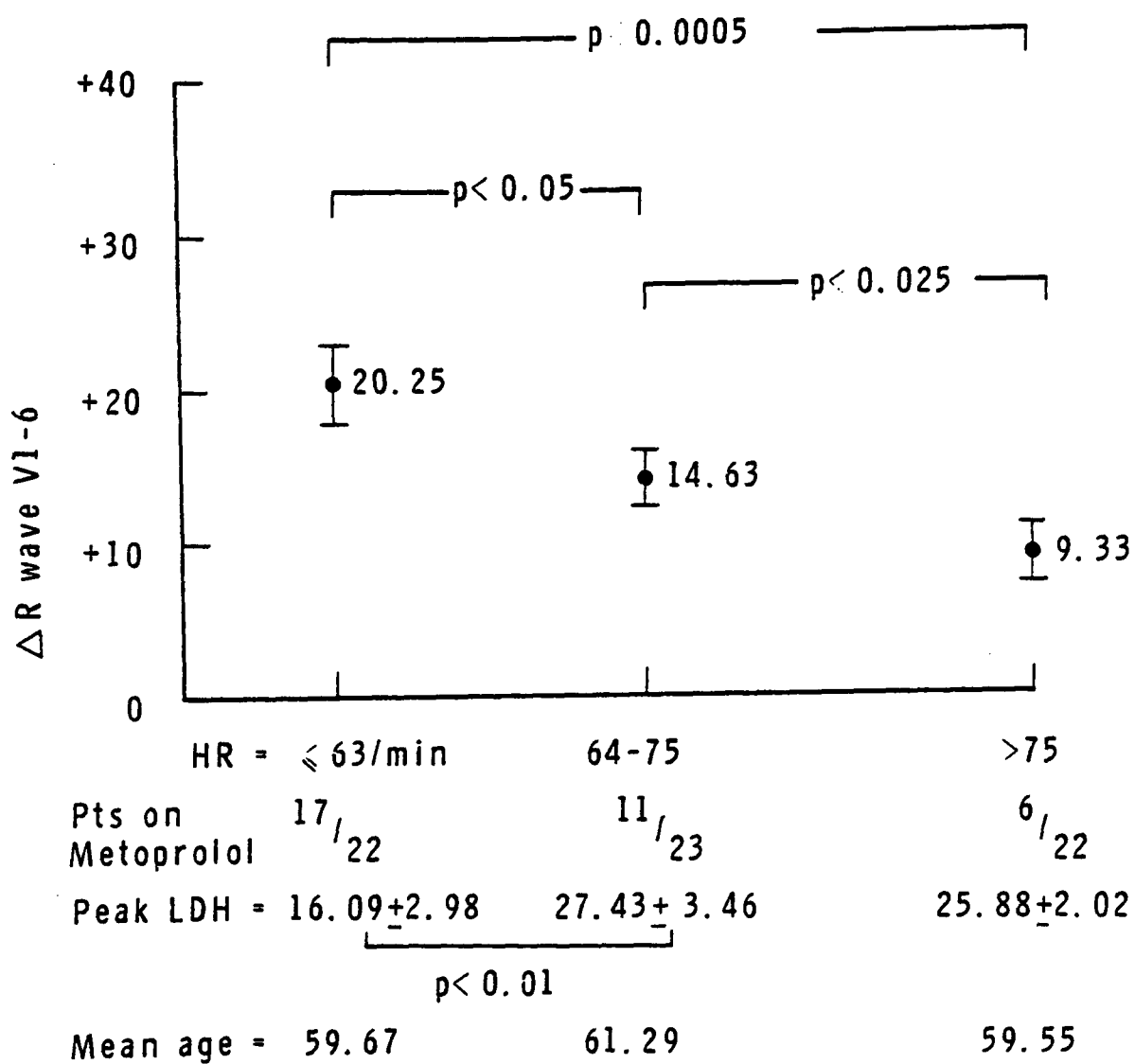


Figure 28: Increase in R wave amplitude in groups with low, intermediate and fast heart rates. Both metoprolol treated and control patients are included.

The increase in R wave amplitude was significantly greater in Group I (mean $\Delta R = +20 \pm 2.34$) when compared to Group II (mean $\Delta R = +14.6 \pm 1.9$; $p < 0.05$) and significantly greater in Group II than Group III (mean $\Delta R = +9.3 \pm 1.9$; $p < 0.025$). The R wave increase in Group I was more significant when compared to Group III ($p < 0.0005$). The number of patients receiving metoprolol was higher in group I $>$ group II $>$ group III (17/22; 11/23; 6/22 respectively). This appears to be indirect evidence that metoprolol administration by lowering heart rate improves R wave recovery.

(iii) Heart rate and R wave recovery in the placebo patients (Fig. 29)

To investigate if a similar trend of increasing R wave recovery at lower heart rates occurred without beta-blockers, the placebo group was in turn divided into 3 groups of 11 patients each:

- Group I: low heart rate, ie below 72/min;
mean 64 ± 6 .
- Group II: Intermediate heart rate, ie 72 to 81/min;
mean 76 ± 3 .
- Group III: High heart rate, ie >82 /min;
mean 92 ± 6.5

The ΔR in Group I ($+ 23 \pm 12$) was significantly greater than in Group II ($+11.44 \pm 8$; $p < 0.01$); the increase in Group II being greater than Group III

HEART RATE AND R WAVE [V1-V6] RECOVERY
IN THE PLACEBO GROUP

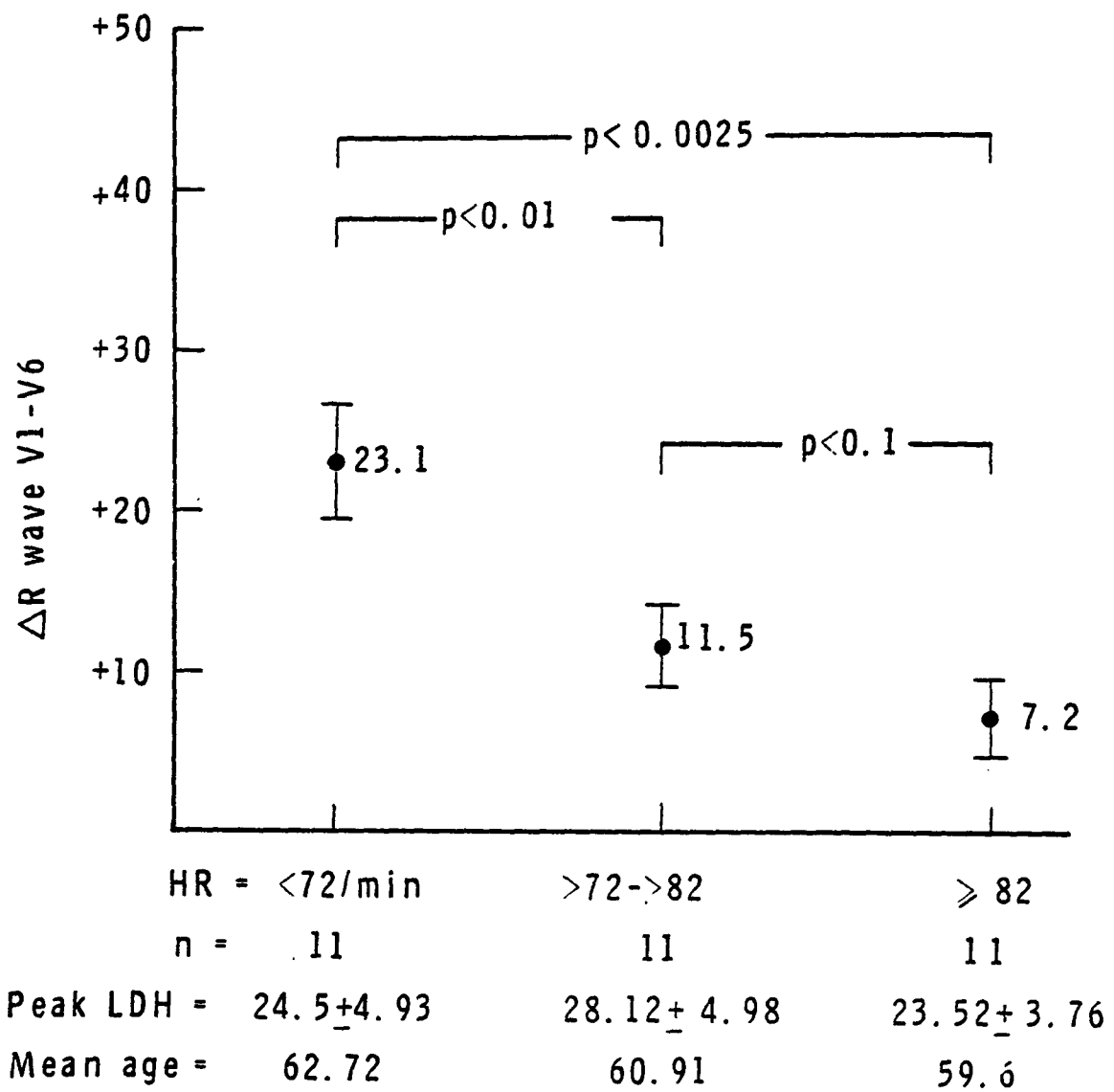


Figure 29: R wave increase related to heart rate in the placebo group.

(+7.21 \pm 8; $p < 0.01$); the difference between Group I and Group III being highly significant ($p < 0.0025$).

(iv) Heart rate and R wave recovery in the metoprolol treated subjects (Fig. 30)

Similarly, patients treated with metoprolol were subdivided into 3 groups:

| | |
|------------|---|
| Group I: | Low heart rate |
| (n = 12) | HR < 59 /min; mean 54.7 \pm 4.03 with a ΔR of +18.0 \pm 8. |
| Group II: | Intermediate heart rate |
| (n = 12) | HR 60-69/min; mean HR of 64 \pm 3 with a ΔR of +16 \pm 10. |
| Group III: | High heart rate |
| (n = 10) | HR ≥ 70 /min; mean HR of 83.1 \pm 11 with a ΔR of +11.0 \pm 10. |

(No statistically significant difference between groups I and II; a trend between groups II and III; $p = 0.12$; and a significant difference between groups I and III; $p = 0.035$).

(v) QRS duration (Fig. 31)

The duration of the QRS was measured in 40 patients and did not change during the study (84 \pm 14 msec initially to 86 \pm 11 msec at 3 months).

HEART RATE AND R WAVE [V1-6] RECOVERY
 IN THE METOPROLOL GROUP

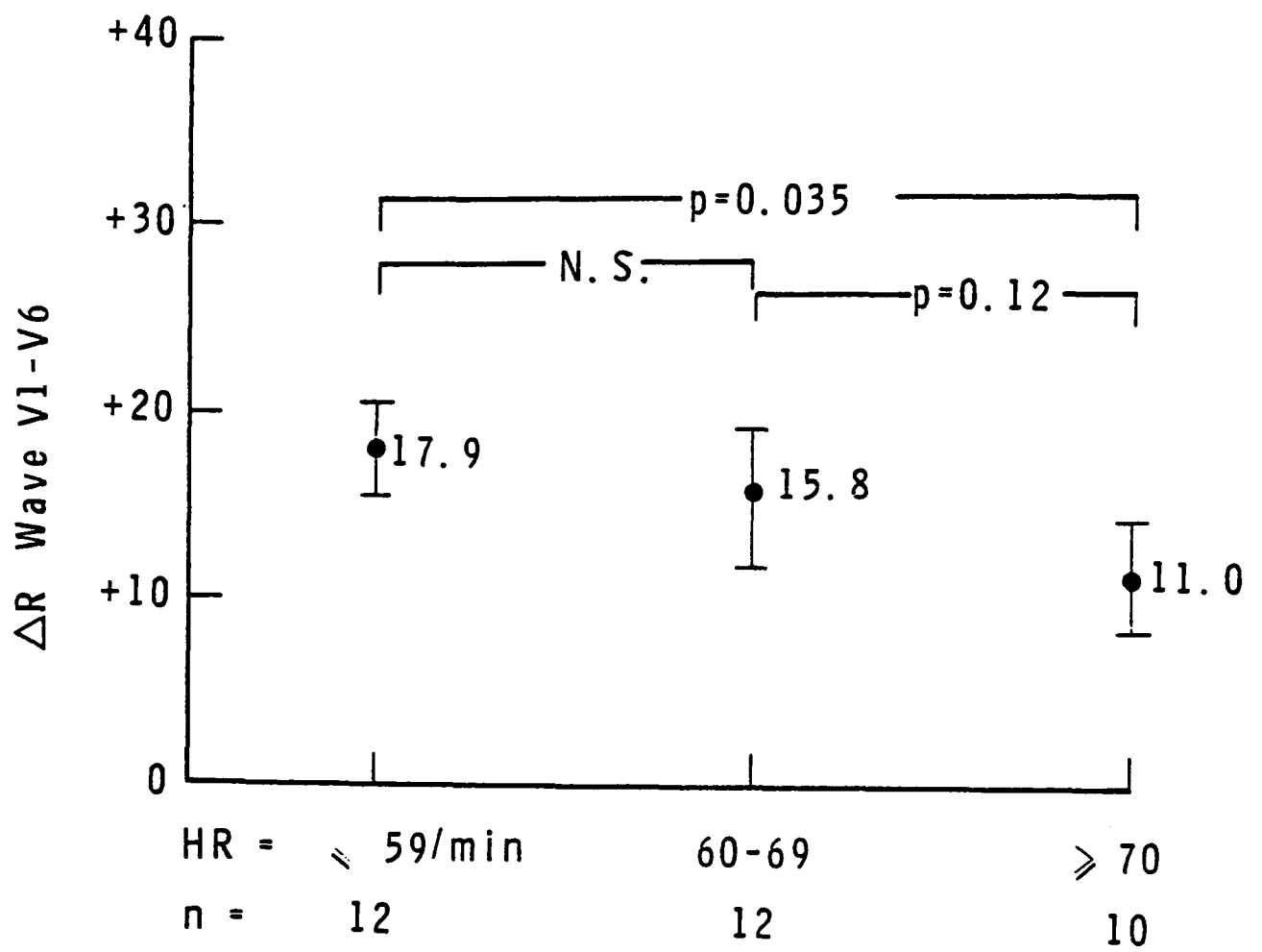


Figure 30: R wave recovery in relation to heart rate in the metoprolol group.

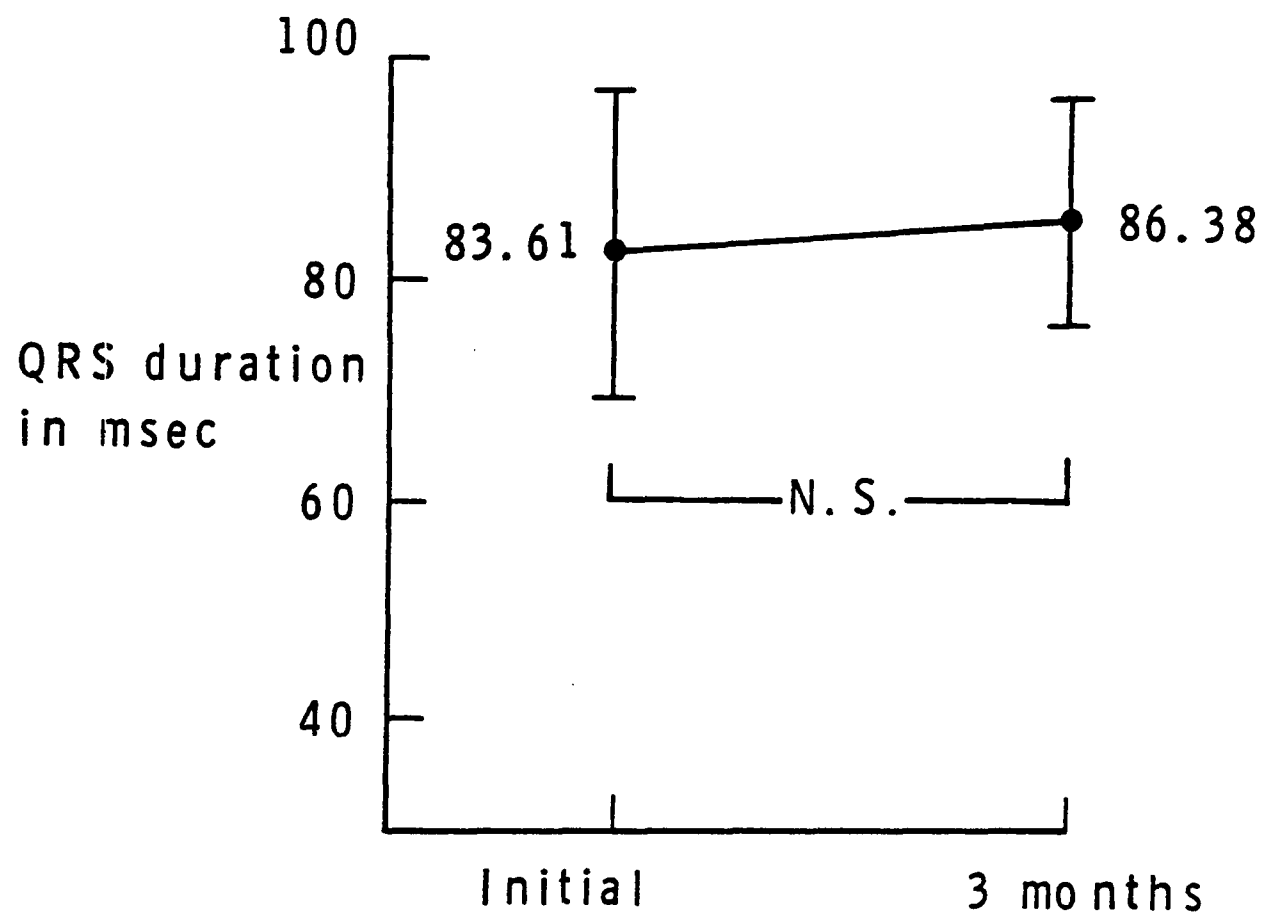


Figure 31: Duration of the QRS complex at the initial and 3rd month recordings.

(vi) Peak LDH and R wave recovery

- (a) Is the heart rate-related R wave recovery dependant on the severity of myocardial damage?

The peak LDH was compared in the three groups of patients with different levels of mean heart rate (Figs. 28 & 29). It can be observed that the LDH peak was lower in the group of patients with the lowest heart rate when all patients were included (Fig. 28). However, no significant difference in LDH levels could be demonstrated in the intermediate or high heart rate groups.

Similarly, when the placebo patients were split into 3 groups based on heart rate no significant difference in LDH levels were observed (Fig. 29). This would indicate that the influence of heart rate on R wave recovery was independent of the severity of myocardial damage.

- (b) Does severity of initial myocardial damage influence later ECG recovery as an independent variable?

To investigate if the extent of myocardial damage was related to R wave recovery independent of a heart rate effect, patients were divided on the basis of peak LDH into 2 groups: large infarcts (>21 units; n = 32)
and small infarcts (<21 units; n = 34)

LDH LEVELS AND R WAVE RECOVERY
IN ANTERIOR INFARCTION

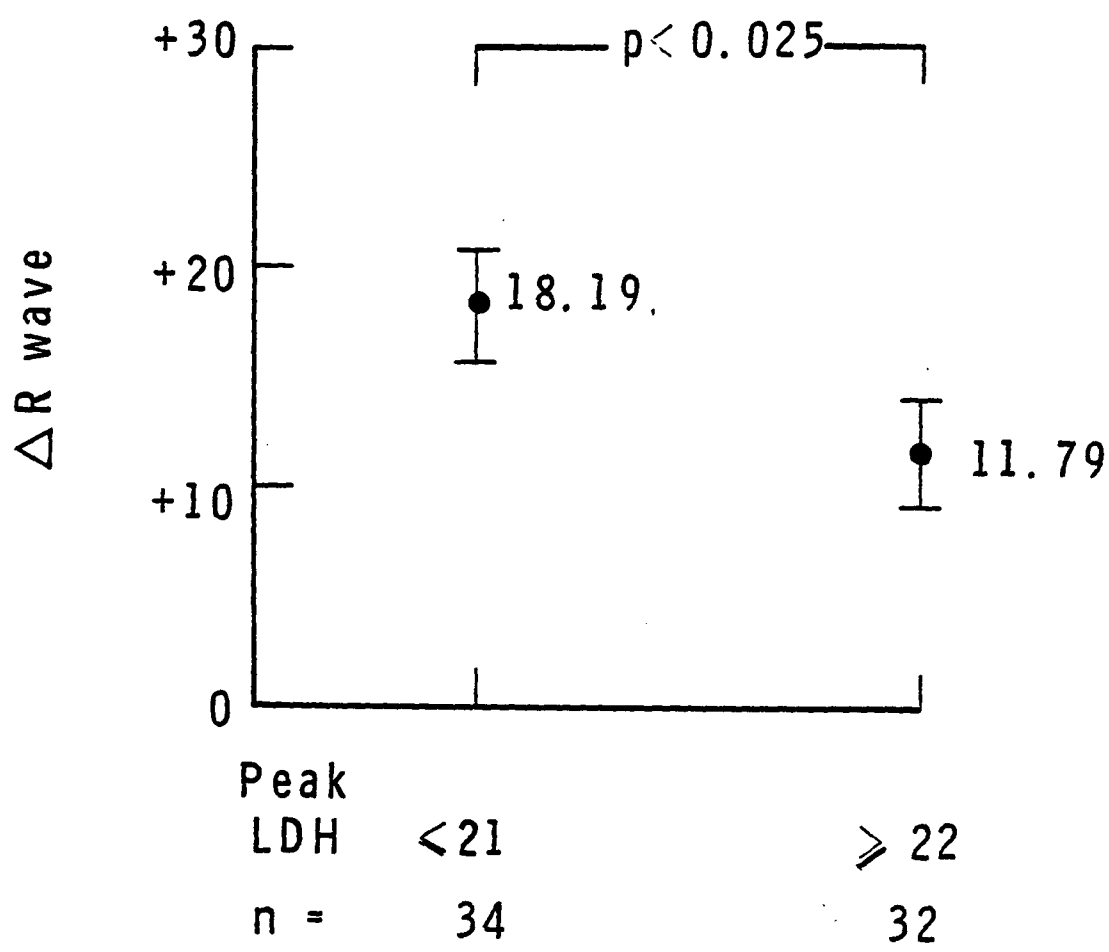


Figure 32: R wave recovery in relation to the size of the initial infarct.

The mean increase in R wave was greater in the patients with smaller infarcts (18 ± 11) as compared to larger infarcts (11.8 ± 11) $p < 0.025$ (Fig. 32).

Comment on Section II

In the above section, I have extended our observations to demonstrate that either spontaneous or beta blocker induced low heart rate improves the recovery of the ECG. This is independent of initial infarct size. However, the extent of initial myocardial damage also influences the R wave recovery as an independent factor i.e. small infarcts being associated with better recovery.

Section III

Experimental work

This section describes the development of an experimental dog model in which the increased recovery of the ECG by atenolol has been reproduced in order to investigate the pathological basis underlying this observation.

Materials and Methods

Myocardial infarction was produced in 14 beagle dogs using a closed chest technique under halothane anaesthesia. A copper coil of approximately 2mm x 5mm was introduced into one of the branches of the left anterior descending coronary artery using a double sleeved catheter passed via the carotid artery under fluoroscopy. Electrocardiographic signs of infarction (ST segment and T wave changes) are usually seen within an hour after introduction of the coil (unpublished data).

ECG's were recorded using a needle electrode from 17 praecordial sites which were marked on the chest wall with an indelible felt pen. Standardisation used was 1mv = 10 mm. The first recording for the study was obtained before infarction followed by recordings on the 3rd day and then twice weekly for 4 weeks. Measurements of the amplitude of the Q wave, R wave and S wave were made from each site as described in Chapter II.

Eight dogs were dosed daily with 60mg of atenolol orally starting on the third day post-infarct; 6 dogs serving as controls. All leads were classified as ischaemic or non-ischaemic on the presence or absence of ST segment deviation, T wave inversion, R wave loss or Q wave development in the first post infarct ECG. All dogs were sacrificed after 4 weeks and the hearts were removed for pathological examination.

Gross pathology was performed with the investigator unaware of the treatment and electrocardiographic findings in individual dogs.

The following were measured:

- (i) The weight of the ventricles.
- (ii) Thickness of the left ventricle (LV) just above the anterior and posterior papillary muscles using a micrometer.
- (iii) Thickness of the LV at the lower end of the anterior and posterior papillary muscles.
- (iv) Thickness of the right ventricle (RV) approximately 0.5cm from its upper edge midway between the two junctions with septum.
- (v) Thickness of the RV approximately 0.5cm from its lower end midway from the septal junctions.
- (vi) Thickness of the septum. Care was always taken to avoid scar tissue during measurements (ii) to (vi). However, this was not possible on two occasions.
- (vii) Scar thickness at the centre of the scar.
- (viii) Scar area was marked on the surface with an indelible felt pen by palpating for the scar edge. The outline of the scar was obtained on thin cardboard which was then cut out and weighed. Knowing the weight per unit area, the area of the scar was calculated.

Results

A. Electrocardiographic Changes

(i) A significantly greater increase in R wave amplitude was observed in the atenolol treated dogs (mean 6.10 ± 8 mm per site) as compared to the control dogs (mean 0.24 ± 3 mm per site) ($2p < 0.0001$). These changes were mainly confined to the ischaemic sites (Fig. 33) with non-ischaemic sites in treated and control dogs showing little change.

(ii) Figure 34 shows the rate of change of the R wave amplitude per site in treated and control dogs. The atenolol treated dogs had smaller initial R wave amplitude than the controls (suggesting a larger infarct) but by 4 weeks they showed greater amplitude compared to the control group ($2p < 0.01$).

B. Gross Pathological Examination

(i) No difference between the two groups of dogs was observed for the following parameters:

- (a) Heart weight
- (b) LV thickness
- (c) High RV thickness
- (d) Septal thickness

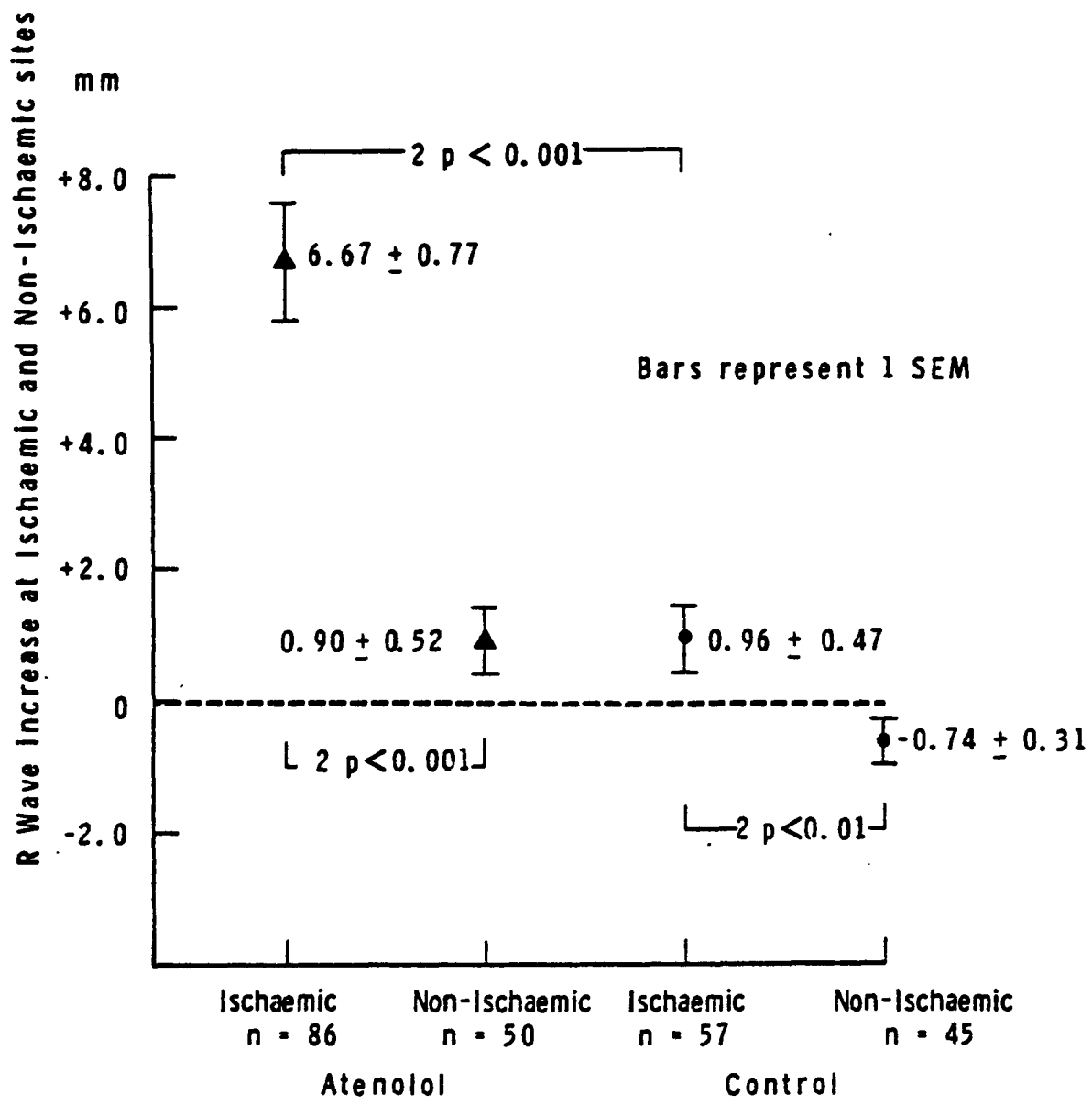


Figure 33: Increase in R wave in ischaemic and non-ischaemic sites in treated and control dogs.

ECG CHANGES IN DOGS

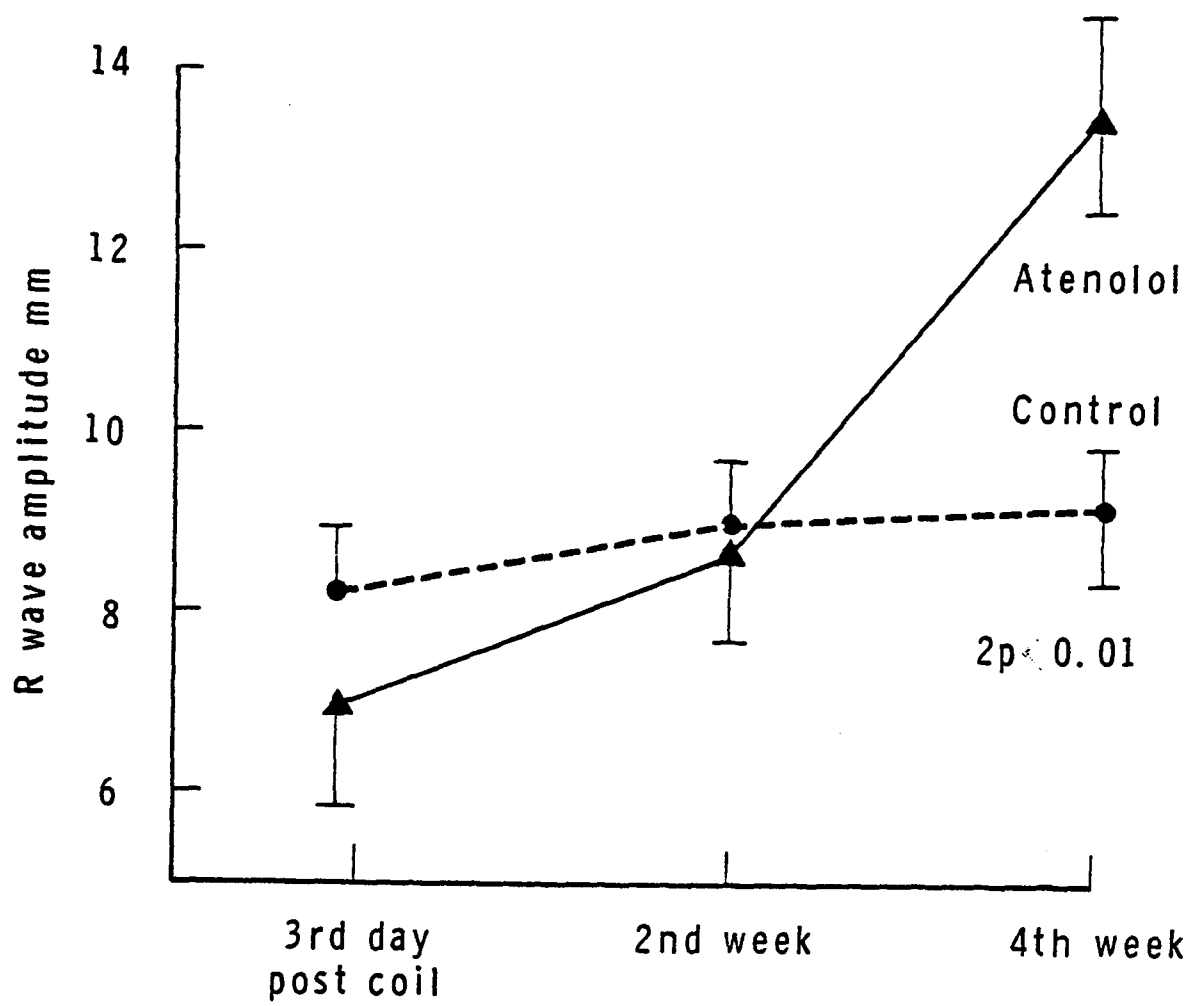


Figure 34: Increase in R wave amplitude in atenolol treated and control dogs.

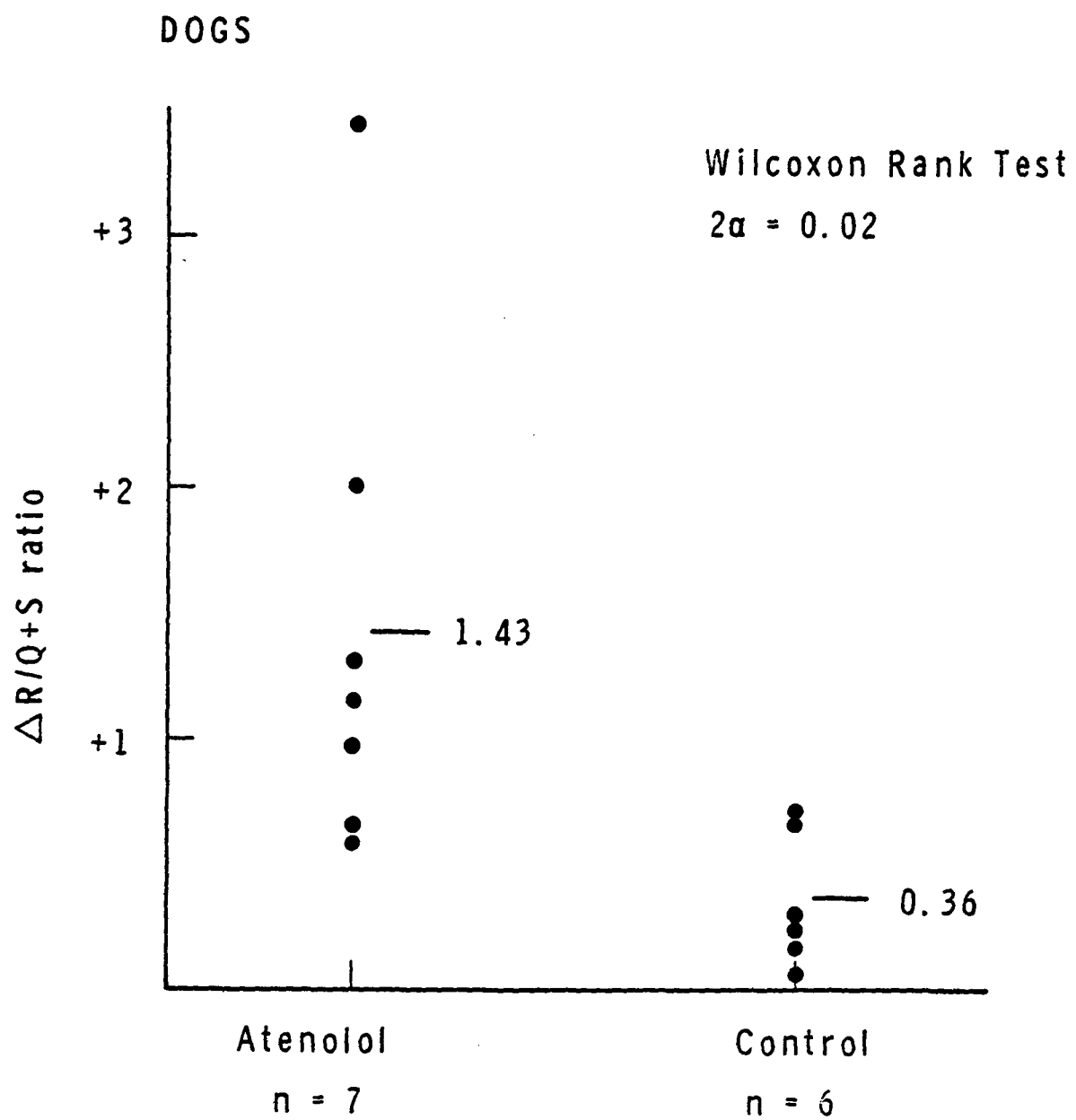


Figure 35: Change in R/Q+S ratio in treated and control dogs.

(ii) The scar area was significantly smaller in dogs treated with atenolol ($7.00 \pm 1.76\text{cm}^2$) as compared to control dogs ($10.20 \pm 2.93\text{cm}^2$) ($2p < 0.05$) (Fig. 36).

(iii) The thickness of the lower RV tended to be greater in the treated dogs ($3.17 \pm 1.25\text{mm}$) as compared to $1.96 \pm 0.31\text{mm}$ in the control dogs ($2p = 0.07$). (Fig. 37).

Comments on Experimental Work

In this section, I have reproduced the improved recovery of the R waves by long-term beta-adrenergic blockade in dogs. Gross pathological examination of their hearts revealed significantly smaller scars in treated dogs. This was inspite of the treated dogs having slightly larger infarcts prior to treatment (Fig. 33).

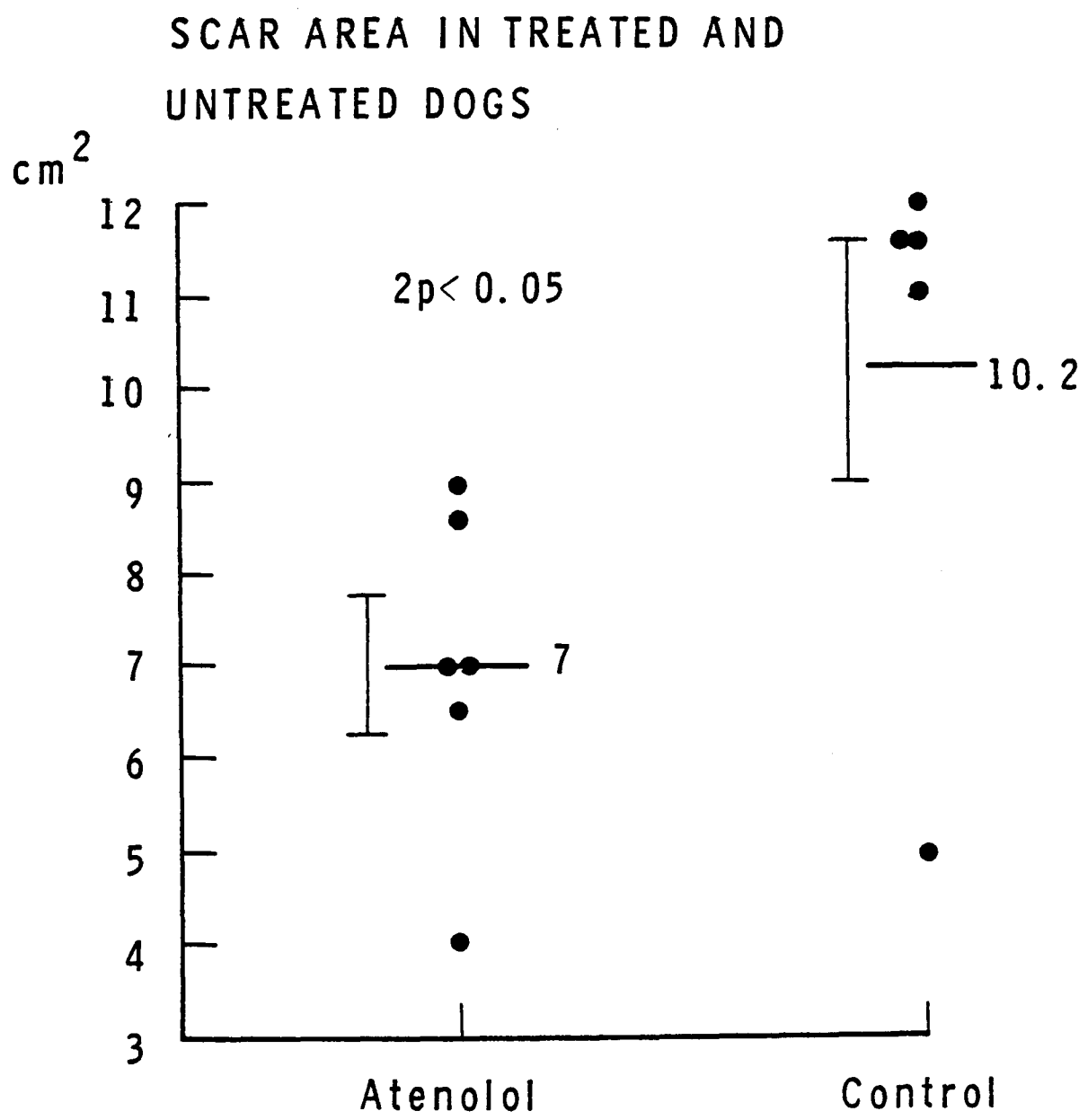


Figure 36: Scar area in atenolol treated and control dogs.

RIGHT VENTRICLE THICKNESS

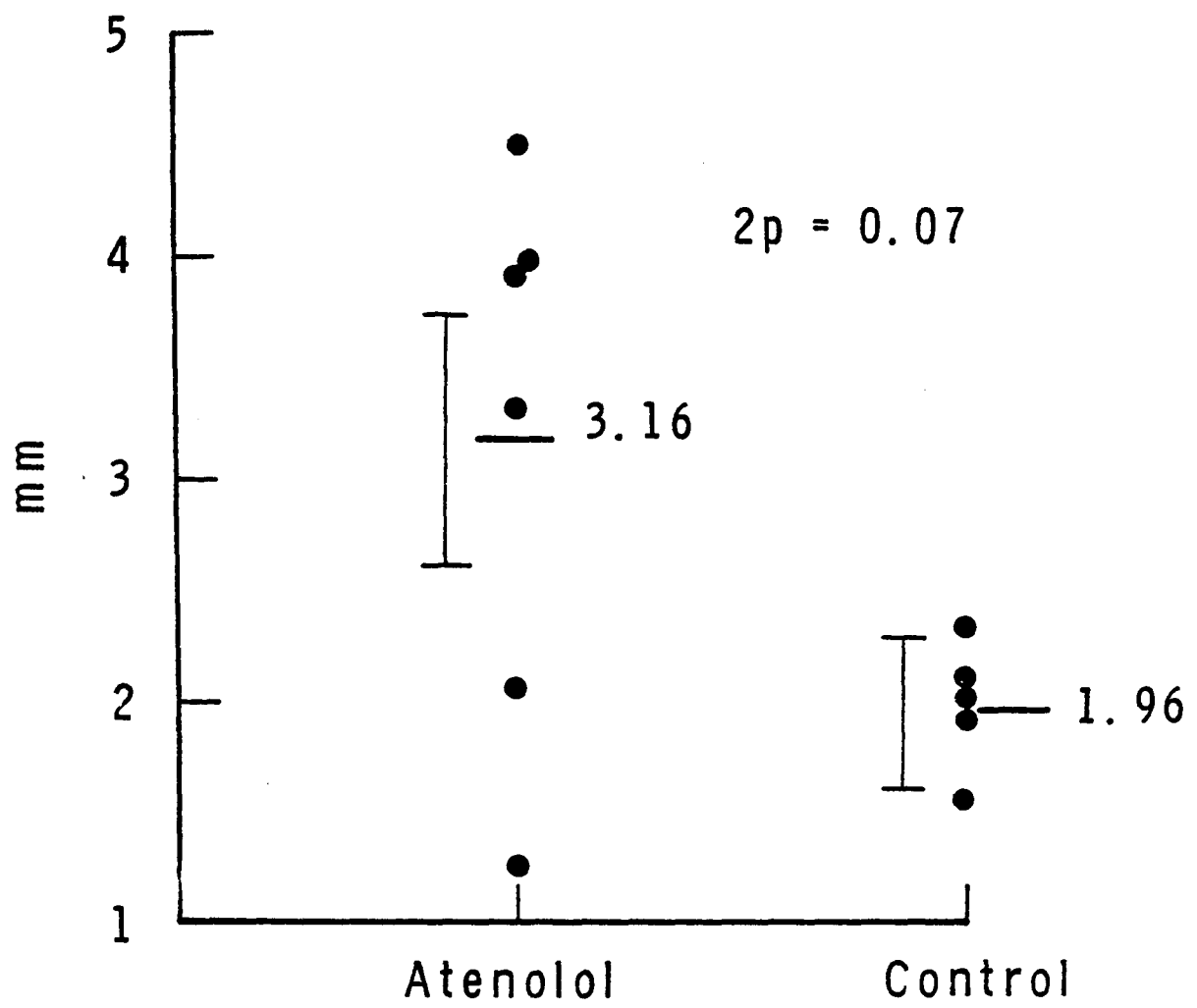


Figure 37: Thickness of the low right ventricle in atenolol treated and control dogs.

DISCUSSION

This chapter deals with a new phenomenon - i.e. the improved recovery of the ECG by long-term beta-blockade after myocardial infarction. Using the technique of praecordial mapping described earlier, I quantified the recovery of R waves and disappearance of Q waves in the chronic healing phase after myocardial infarction and showed that atenolol given in a dose of 100mg daily in man or 60mg daily in dogs significantly hastens this phenomenon. In the dog model of experimental infarction, care was taken to start the dosing of atenolol on the 3rd day at a time when infarct evolution was presumably complete (Jennings & Reimer, 1974; Singh et al., 1977). In the initial human study, it is unlikely that the oral administration of atenolol affected infarct size as it was found that maximum beta-blockade was achieved 12 hours after oral administration of oral atenolol by which time it may be too late to effect any myocardial salvage (Peter et al., 1978; and Chapter IV). Further the initial 'R' wave amplitudes in the control and treated groups were comparable (Fig. 23). Therefore, I believe that the recovery of the ECG is unrelated to myocardial salvage and occurs entirely in the healing phase.

Although in the initial atenolol study I suspected that this may be a heart rate related phenomenon, the number of subjects studied was too small to demonstrate this. In a larger group of patients studied with 12-lead ECG's, (although a less sensitive technique than 35-lead praecordial mapping), I have confirmed the quicker recovery of R waves in patients with slow heart rate. I have then shown that R wave recovery occurs in patients who have either a spontaneous low heart rate, or bradycardia induced by the administration of betablockers. Evidence that betablockers affect this process is clearly demonstrated by the atenolol study and is supported by data from the metoprolol study. Figure 28 demonstrates that 77% of the patients with low heart rate and the greatest R wave recovery were on betablockers as compared with 48% in the group with intermediate R wave recovery and only 27% of the patients in the groups with least R wave recovery. I have demonstrated that this is essentially a low heart rate related phenomenon as the trend of low heart rate and increased R wave recovery is observed when patients on placebo and betablockers are separately analysed.

Since low heart rates are known to be associated with smaller infarcts, (Lopez & Yusuf, 1978) it is possible that the improved R wave recovery was just an

accompanying phenomenon in patients who were intrinsically better and that later alterations in heart rate may be irrelevant. To test this hypothesis, we compared the peak LDH in the three subgroups divided based on heart rate (Figures 28-30) in the total group, placebo group and beta-blocker group. Except in one subgroup (Figure 28 - lowest heart rate group), peak LDH values were comparable in all other groups and differences in R wave recovery was observed in groups with comparable infarct sizes but with heart rates which were significantly different (Fig. 29).

We have observed that the scar area in dogs treated with atenolol is significantly smaller than in control dogs. Although we do not have direct anatomical measurements of initial infarct size in both groups, the ECG findings point towards a tendency ($2p = 0.20$) to larger initial infarcts in the treated group (the drop in ΣR was greater and the mean R per site was lower in AT treated dogs). In view of these observations, we believe there is good evidence to support improved scar shrinkage in the atenolol treated dogs.

However, as there was a suspicion that smaller infarcts were associated with a greater R wave increase (Fig. 29), I decided to investigate if initial infarct size was an independent variable affecting later R wave recovery. Patients were therefore divided into 2 groups

based on peak LDH levels and a significantly greater R wave recovery was observed in patients with an initial small infarct (Fig. 32).

Therefore, I have demonstrated at least two independent variables that affect the recovery of the ECG - an initial small infarct and low heart rate, either spontaneous or induced by beta-blockers.

The ECG data from the clinical and experimental studies support scar contraction as the underlying mechanism for this phenomenon. Scar contraction with apposition of the edges of the normal myocardium and a consequent decrease in the solid angle subtended at the recording site leads to a decrease in the electrical window (Holland & Arnsdorf, 1977). This, however, has never been actually demonstrated before. I have shown that the increase in R waves is confined to leads showing signs of infarction (Fig. 33). Similarly, Figures 25 and 26, show a contour map and ECG recording in a patient on atenolol and very clearly demonstrates that the area of Q wave abnormality shrinks. The mechanism by which atenolol could affect this process is not clear but may be related to diminished stretching of the scar as the heart beats a fewer number of times, thereby allowing greater scar shrinkage.

Another possibility worth considering is volume overload at low heart rates. This, however, seems unlikely as the increase in R wave amplitude was not seen in leads not showing evidence of infarction. In volume overload, one would expect the increase in R wave amplitude to be non-selective and seen in all leads. No difference in heart size on the chest X-ray was observed between beta-blocker treated and placebo groups. Compensatory left ventricular hypertrophy seems unlikely as one would expect the R wave increase to be in the non-infarcted leads, and not in the leads showing infarction as has been demonstrated. Further this was not seen at pathology in any atenolol treated dog.

I have not observed any significant widening of the QRS complex, which excludes the possibility of a gross intra ventricular conduction defect. However, smaller degrees of conduction abnormalities cannot be excluded. In two patients in whom the beta-blocker was stopped, no further change in the R wave amplitude was observed. Importantly, however, the increase in R wave amplitude that was already present, persisted in spite of a change in heart rate. This may indicate that this phenomenon is not related to conduction blocks occurring at slow heart rates.

Recently an increase in the vascularity of the myocardium has been demonstrated in young rabbits after chronic administration of beta adrenergic blockers (Vaughan Williams et al., 1977) or brady-pacing (Hudlicka & Wright, 1977). It is possible that the myocardium adjacent to the infarct may be partly hypoxic and this may stimulate improved vascularisation in the presence of a low heart rate.

Several epidemiological studies have used the ECG recorded several years after acute myocardial infarction and have reported a lower risk of sudden death in individuals reported to have fewer or smaller Minnesota Codable Q waves (Leren et al., 1970; Coronary Drug Project Research Group, 1971; Blackburn et al., 1970; Rose et al., 1978). Earlier in this thesis, I have demonstrated that the amplitude of the largest summed Q wave and smallest summed R waves obtained from the praecordial map is a good indicator of infarct size; infarct size in turn being related to prognosis (Bleifeld et al., 1977; Sobel et al., 1972). However, it is not evident if the reduction of these 'Q' wave abnormalities in patients with extensive initial infarction signifies a change in prognosis. If, indeed, this is related to a decrease in scar size due to better shrinkage, it may be associated with

fewer arrhythmias as the mass of tissue available for re-entrant circuits decreases (Surawicz et al., 1971). Further, better healing of the scar is likely to decrease left ventricular wall asynergy and can therefore lead to better cardiac function.

In conclusion, I have demonstrated a considerable improvement in the R wave amplitude and disappearance of Q waves in the chronic healing phase of clinical and experimental infarction. This process is favourably affected by low heart rate and therefore is facilitated by drugs like beta-blockers. An initial small infarct is also associated with a greater recovery of the ECG. These electrocardiographic changes correlate well with improved scar healing after experimental infarction.

CHAPTER VIII

DISCUSSION

DISCUSSION

The main theme of this thesis has been the evolution of myocardial infarct size and its modification by early and long-term betablockade. Individual observations have been discussed in earlier chapters; in this chapter I shall discuss further some of the main findings and shall try to relate them to our current knowledge and practice in managing patients with myocardial infarction.

The great variation in the time course of infarct size evolution raises several important points for discussion and speculation. Do the different patterns (i.e. rapid and gradual infarction) represent different mechanisms by which infarction may occur? Do patients with Type A infarct have a sudden coronary occlusion leading to rapid death of the distal myocardium? Do patients with Type B infarct represent those in whom increased oxygen demand occurs by factors like local catecholamine release in the presence of a critical fixed coronary stenosis? Is either type of infarct evolution related to the degree of collateral circulation? Do patients with rapid infarct evolution have poor collaterals and do patients with gradual infarction have better collaterals so that myocardial cells do not progress rapidly to occlusion? On the other hand, do patients

with rapid enzyme release represent those with relatively good flow to the "infarct zone" leading to quicker washout of enzymes and/or early end to the spread of ischaemic necrosis? Further experimental and invasive clinical studies are required to answer these questions. It is possible that different patterns of infarction may represent different mechanisms of infarction i.e. primary thrombosis, spasm of the coronary arteries, increased oxygen demand, local catecholamine release etc. (Baroldi et al., 1975; Fulton et al., 1977; Erhardt et al., 1977; Hellstrom, 1979).

Whatever the mechanism underlying the different patterns of infarct evolution, it is evident that infarction occurs over several hours with 40-50% being complete in less than 6 hours. The earlier one intervenes, the greater the possible benefit to individual patients. It is therefore important that future trials should focus on the prehospital period and aim at giving the drug in less than an hour or two of pain. This would mean that such therapy will have to be started by the general practitioners and possibly even by trained paramedical staff.

However, at the present moment, the general consensus of medical opinion (which I believe is not based on strong scientific evidence) is that early beta-blockade may be dangerous in patients with acute myocardial infarction. It is, therefore, important to confirm that

beta-blockers may not be as dangerous as generally believed, as is evident from our results. The next important question is whether acute intravenous beta-blockers can be given safely to unselected patients. It is generally believed that heart failure, heart block, hypotension, bradycardia and bronchial asthma constitute definite or relative contraindications to beta-blockade. The decision to use beta-blockers has to be based on the balance between possible benefit and possible harm to the patient.

Let us consider the dilemma of a general practitioner (G.P.) seeing the patient soon after the onset of symptoms in his home (and let us assume that most G.P.s do not have readily available an ECG machine but do have a stethoscope and sphygmomanometer). In our study, we assessed the suitability of the patient on clinical grounds, and in addition an ECG was available to us (to exclude heart block). The decision to include or exclude patients with possible heart failure was based entirely on the physical examination and not on the chest X-ray. Similarly heart rate, blood pressure and bronchospasm can be adequately assessed clinically. The only disadvantage a G.P. would be is the lack of an ECG to exclude heart block. Our data quite clearly suggests that giving beta-blockers to patients with 1st degree heart block is not dangerous. Although it is possible to suspect

the presence of 2nd degree or 3rd degree heart block on clinical grounds, an ECG is required to confirm this. However, in general, the number of patients who present with 2^o or 3^o heart block is likely to be small (and anyway, there is little objective evidence that such patients do worse when a beta-blocker is given). It is likely that the slow intravenous administration of a beta-blocker, coupled with the use of atropine if pulse rate or blood pressure drops may be adequate in most instances. Problems with bronchospasm can be reduced by the use of a B₁ selective blocker. Further, if bronchospasm occurs, a bronchodilator like salbutamol is usually all that is required (we have had 3 patients who had minor bronchoconstriction after betablockers. In all salbutamol inhaler was used and the betablocker was continued).

There is however little objective data to demonstrate that beta-blocker may be beneficial or dangerous in the first hour or two of myocardial infarction. The only data that are available comes from the practolol trial in which there was no excess mortality in patients who reinfarcted while on practolol. It is therefore possible that the early administration of beta-blockers by G.P.s is likely to be safe and beneficial. This, however, must be assessed in prospective randomised trials.

Patients with heart failure (usually due to large infarcts) are those most likely to have severe complications like late arrhythmias, secondary ventricular fibrillation and are also at greatest risk of death. It is this group that requires measures to reduce infarct size most urgently and it is unlikely that beta-blockers will be used, at present in these patients by most clinicians. There are two approaches to this problem. The first and more important suggestion is to use the drug as early as possible before failure actually develops. For instance, in the Tower Hamlet study, the incidence of heart failure when seen by the GP was 2-3% compared to 27% at discharge from hospital. In our own study the incidence of failure increased from 10% at entry to 30% at discharge in the control group (Table XI). This is, therefore, another strong argument to support the use of betablockers by general practitioners very soon after symptoms.

The alternative (and probably less widely acceptable) approach would be to give betablockers to patients with "moderate" heart failure seen within 12 hours of pain under haemodynamic monitoring. Mueller et al. (1977) have shown a drop in the left ventricular filling pressure after intravenous propranolol in patients with initial high pressures. This work, if confirmed, would be of great significance as patients who are likely to have large

infarcts may benefit the most.

Implicit in the entire discussion on the salvage of ischaemic myocardium is the belief that reducing infarct size in man can lead to a reduction in morbidity and mortality. It is likely that heart failure, late ventricular arrhythmias, late sudden death and mortality in general will be reduced.

However, we know little about the "salvaged myocardium". Are we preserving useless "arrhythmogenic" ischaemic myocardium? Will such salvaged myocardium demonstrate normal contractility? Will such myocardium remain ischaemic leading to a higher incidence of angina in such patients? These questions need to be answered satisfactorily before reduction of infarct size in man can be accepted as standard therapy. Our preliminary data on morbidity shows a lower incidence of subsequent heart failure, atrial fibrillation and secondary cardiac arrests in treated patients and it is essential that we confirm this in the second half of this study.

To assess if deaths can be prevented by reduction of infarct size, a large study of several thousand patients is required, and it is unlikely that any of the present studies will enroll sufficiently large number of patients (MILIS* or the Goteborg* study) to provide convincing results on mortality

* MILIS: Myocardial Infarction Limitation study coordinated by the NHLBI.

* Metoprolol Study coordinated by Å Hjalmarson - see Chapter I

If the reduction of subsequent heart failure is confirmed (this indicates better left ventricular performance), this is of great economic importance as well and is likely to lead to better work return (work return is influenced by factors like heart failure and angina; Pohjola et al., 1979), earlier mobilisation, discharge from hospital and the use of less supportive drugs like diuretics, digoxin, anti-arrhythmic drugs and anticoagulants.

Another logical extension of the concept of myocardial salvage is the use of beta-blockers to prevent the development of infarction in those with threatened infarction. Our results demonstrate this convincingly and confirm the earlier report by Norris et al. (1978). It is possible that beta-blockers reduce the O_2 demand in such patients who may have critical narrowing of the coronary arteries. We need to know other important facts. Do these patients have increased angina? Do they need and will they benefit from longer term beta-blockade? Is there a greater incidence of reinfarction in these patients? We are therefore following these patient after discharge.

The other main message of this thesis concerns the improved recovery of the ECG signs of myocardial infarction by long-term beta-blockade. This was an unexpected observation. Little earlier work has been

done on the healing process after infarction either in man or experimental animals and this may lead to new possibilities in affecting healing by various interventions. Preliminary experimental work suggests that this is related to improved scar shrinkage. This is likely to be of benefit as this could result in improved ventricular contraction as a result of a stronger scar. It could also decrease the frequency of ventricular arrhythmias by reducing the area for re-entrant rhythms (Surawicz et al., 1971).

On the other hand, we have seen a tendency (and at present not statistically significant) towards thicker right ventricles in treated dogs. This may be due to a mild long-term elevation in left ventricular filling pressure or a direct effect on the myocardium. Both are unconfirmed and more experimental work is required to fully understand this new observation.

The disappearance of the ECG signs of infarction in patients on long-term beta-blockers reduces the value of the ECG as an epidemiological survey tool especially as this is a commonly used drug in patients with Ischaemic Heart Disease. It is therefore possible that the ECG may underestimate the prevalence of infarction in patients on beta-blockers.

I have, therefore, demonstrated two separate mechanisms by which beta-blockers can be of benefit to

patients with infarction. Although it is likely that beta-blockers are of benefit in patients with acute myocardial infarction, routine use of this drug must await the results of large mortality studies.

APPENDIX A. COVER OF RANDOMISATION ENVELOPE

CCU TRIAL NO.

IF ELIGIBLE (PROBABLE INFARCT, NOT ALREADY ON BETA-BLOCKER, ONSET \angle 12 H. AGO) TRIAL DUTY DOCTOR (T.D.D.) MAY BE CALLED. FOR ANTERIOR OR UNCERTAIN INFARCTS T.D.D. SHOULD IF POSSIBLE DO A 35-LEAD ECG.

ENTRY: IF T.D.D. THINKS BETA-BLOCKERS ARE NOT CONTRA-INDICATED (E.G. BY SYSTOLIC \angle 100, HEART-BLOCK WORSE THAN GRADE 1, SEVERE CARDIAC FAILURE, ETC.)

- (a) RECORD EXACT TIME OF ONSET (OF SIGNS OR MAJOR PAIN THAT LED TO CCU ADMISSION) am/pm
- (b) RECORD EXACT TIME NOW am/pm
- (c) OPEN ENVELOPE, AND TREAT ACCORDINGLY
- (d) T.D.D. REQUESTS CONSENT FOR BLOOD SAMPLES

ALSO RECORD TIME(S) OF ANY PREVIOUS BLOOD SAMPLES THAT HAVE BEEN SPUN DOWN FOR ENZYMES: ALL MAY BE USEFUL.

APPENDIX B.

REVERSE OF RANDOMISATION ENVELOPE

COMPLETE BEFORE OPENING

SURNAME
DYSPTNOEA (Enter yes or no)
BASAL CREPITATIONS (approx.) LEFT cms.
area each lung) } RIGHT cms.
JUGULAR VENOUS PRESSURE cms.
B.P. / mm Hg.
HEART RATE /min.

DOCTOR'S NAME
AND SIGNATURE

APPENDIX C.

OPCS MORTALITY FOLLOW-UP FORM

OXFORD-WYTHENSHAW INFARCT LIMITATION STUDY

- 1 NHS Number _____
- 2 SURNAME _____
- 2a Previous name (if applicable) _____
- 3 Forename(s) _____
- 4 Date of birth _____ 5 Born in U.K.(Yes/No) _____
- 6 Town and County of birth, if in U.K. _____
- 7 Address _____
- _____ 8 Date Address current _____
- 9 Date of death _____ 10 FPC _____
- 11 Place of death _____

APPENDIX D.

CLINICAL DATA FORM

HOSPITAL PATIENT
IDENTIFICATION
STICKER

PLEASE COMPLETE BEFORE DISCHARGE:-

DATE OF E.C.G.: 12 LEAD / 35 LEAD

CXR:- i. CARDIAC ENLARGEMENT NO/YES
IF YES, C:T RATIO:
ii. EVIDENCE OF FAILURE NO/YES
IF YES, PROVIDE DETAILS
.....

PAST HISTORY:- (CIRCLE) PREVIOUS INFARCT (NUMBER)
HYPERTENSION
DIABETES

OTHER DRUGS:- PREVIOUS: 1. 2.
3. 4.
IN HOSPITAL: 1. 2.
3. 4.

BETA BLOCKER:- ANY DIVERGENCE FROM PROTOCOL NO/YES
IF YES, REASON, DATE AND DOSE ACTUALLY GIVEN
.....

ANY MAJOR RHYTHM ABNORMALITY WITH DATE:-
VENTRICULAR FIBRILLATION
VENTRICULAR TACHYCARDIA
IDIOVENTRICULAR RHYTHM
HEART BLOCK 1° / 2° / 3°
SVT/ATRIAL FLUTTER/
FIBRILLATION

ANY HEART FAILURE DURING HOSPITAL STAY
ANY OTHER RELEVANT HISTORY/OBSERVATION
.....
.....

DISCHARGE:- i. B.P. ii. H.R.
iii. CXR iv. DRUGS
if available

DATE OF NEXT APPT

DOCTOR'S NAME
AND SIGNATURE

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