THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION: AN ELECTROCARDIOGRAPHIC STUDY

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BY

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DECLARATION

This thesis describes research undertaken during my appointment as Research Fellow, and latterly as Registrar in the University Department of Materia Medica, Stobhill General Hospital, Glasgow. I have been fortunate in having the co-operation and collaboration of a number of colleagues who are formally acknowledged. Except where stated, the work of this thesis has been personally carried out by me, and the writing of it is entirely my own work. A list of publications and papers presented to learned societies arising from work contained in this thesis is given in appendix VIII.

ACKNOWLEDGEMENTS

During the period of research leading to the submission of this thesis, I have been fortunate in having the advice and collaboration of a number of colleagues. I am indebted to them all.

Firstly, I would like to thank Dr. W.S. Hillis for initially stimulating my interest in thrombolysis, for providing resources enabling this research to be performed, and whose enthusiasm and many helpful discussions have sustained the work of this thesis over the six years since its inception.

I am grateful to Professor J.L. Reid for his advice and encouragement, and to Dr. F.G. Dunn for his valuable comments concerning the writing of this thesis. I would like to thank Dr. A. Kelman for his expertise in helping to set up the digitized database and the automated QRS scoring system, and Kate Howie for providing expert statistical advice which has been invaluable. I would also like to thank Alison McKenzie who skilfully digitized a large proportion of the 12 lead ECG's. The help of Dr. I. Hutton who provided an independent score for the coronary arteriograms arising from the anistreplase/ streptokinase comparison trial is gratefully acknowledged. I/

I am indebted to Mrs. J. Clark for her skill and patience shown in the typing of this thesis.

Although the major part of this thesis concerns the sequential ECG changes taking place during thrombolysis and has been carried out by me personally except where stated above, the database used arises from a large patient pool, all of whom have been part of the active thrombolysis research programme conducted in Stobhill. This patient group represents an enormous amount of clinical and nursing care, and so, lastly I wish to formally acknowledge the co-operation of the coronary care nursing staff and my medical colleagues, Dr. W.S. Hillis, Dr. F.G. Dunn, Dr. A.P. Rae, Dr. R.S. Hornung, Dr. J.D. Gemmill and Dr. J.M.A. Burns with whom I have enjoyed sharing the clinical management of these patients.

SUMMARY

SUMMARY

The value of thrombolytic therapy in the treatment of acute myocardial infarction is now unchallenged following the publication of large scale clinical trials showing an impressive reduction in mortality. Intravenous administration of a thrombolytic agent in the early hours of myocardial infarction is established practice in all hospitals, from district generals to specialized cardiac centres. The aim is to obtain a patent artery, improve left ventricular function and decrease mortality. The effectiveness of intravenous therapy obviates the need for acute angiography and intracoronary administration, but a definitive statement concerning whether reperfusion has occurred cannot be made.

The 12 lead ECG undergoes well recognised dynamic changes in the early phase of myocardial infarction. Successful lysis, either induced or spontaneous, will modify these changes. Whether these modifications can be quantified and used as simple non invasive tests of reperfusion, myocardial salvage and infarct size has caused much speculation. To have such a simple, widely available, reproducible and inexpensive tool would be highly desirable in a clinical setting. This thesis has addressed these questions.

The first study demonstrated the rapid fall in ST segment elevation occurring in response to thrombolysis, and

introduced a measurement which expresses this fall as a proportion of the admission value. This is termed the Fractional Change and can be applied to either 24 hour tape recordings or to the 12 lead ECG. A Fractional Change Value $\geq$ 0.5 occurring by 2-3 hours following therapy is highly specific and sensitive for reperfusion. The next study examined whether an electrocardiographic marker of infarct size, the QRS score, was attenuated in patients achieving successful reperfusion compared with a historical cohort of patients with infarctions given no therapy other than simple analgesia. Only patients with anterior infarcts were studied, and although both groups had similar areas of myocardium at jeopardy on admission, the group of patients achieving successful reperfusion had a significant reduction in the QRS score at 48 hours compared to the control group.

These initial studies showed that dynamic changes in the ECG can reflect both reperfusion and myocardial salvage, but are limited in that they were performed in relatively small numbers, and the ECG measurements were made and tabulated manually. A method for digitizing 12 lead ECG's with subsequent computer storage of data for comparative analysis has been developed, and incorporates an automatic QRS scoring system. The developmental work involved in

setting this system up and its subsequent validation with inter- and intra-observer variation studies is presented in Chapter 5.

This system was then used to follow the sequential ECG changes in a prospective angiographically controlled, double blind randomised trial of 128 patients comparing anistreplase with streptokinase. The 90 minute patency rates for both drugs were found to be the same (anistreplase 55%, streptokinase 53%). Coronary angiography performed at 90 minutes post therapy allowed a detailed correlation between ECG changes on admission and acute coronary anatomy. The findings of this particular study showed that the height of ST segment elevation does not bear any relation to the age of the infarct, that there is a high incidence of reciprocal change early in the course of infarction, and that this is not related to coexisting disease or remote ischaemia, but is likely to be an electrocardiographic mirror phenomenon.

Examining the resolution of ST segment elevation and depression showed that it was the rate of fall which discriminates patent from non patent arteries, and that using a Fractional Change Value of ≥ 0.5 to detect reperfusion, calculated at 2 hours post treatment from a single lead showing maximal ST segment elevation, gave the best sensitivity (81%) and specificity (60%), when compared with a number of different parameters. In

addition, it appears that the presence of collaterals supplying the infarct area could result in a high Fractional Change Value despite no antegrade perfusion. This study also confirmed that achievement of a patent artery early (i.e. before 90 minutes) significantly attenuated Q wave development, R wave loss and the QRS score in anterior infarction, but did not affect electrocardiographic markers of infarct size when applied to inferior infarcts.

In summary, this thesis provides a detailed study of the electrocardiographic changes taking place in acute myocardial infarction, especially as a consequence of treating with thrombolysis, quantitates these changes and shows where they may be used in a clinical setting as non-invasive tests to aid patient management.

CHAPTER 1 - INTRODUCTION

SECTION A. THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

SECTION B. ELECTROCARDIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

A. THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

1.1 PATHOPHYSIOLOGY OF THROMBOSIS IN ACUTE MYOCARDIAL INFARCTION

The rationale of giving thrombolytic therapy to patients with acute myocardial infarction requires the presumption that the coronary occlusion has been caused by thrombus formation. Medical opinion appears to have turned full circle regarding this subject. Herrick first described thrombotic coronary occlusion in patients with acute myocardial infarction in 1912. Over the following decades the belief that thrombotic occlusion occurred as a result and not the cause of the infarction, was popularised by the work of Branwood and Montgomery, (1956) and Roberts and Buja (1972). Radiolabelled I^{125} fibrinogen was administered to patients with acute infarction 47 hours after the onset of symptoms, and subsequent post mortem examination revealed the intracoronary thrombus to be radioactive in all but 1 patient, providing further evidence for coronary thrombosis being a secondary phenomenon (Erhardt et al., 1973).

This work however was refuted by De Wood et al. (1980) in his classical paper where coronary angiography was performed in a total of 322 patients within 24 hours of the onset of acute myocardial infarction. This group showed a decreasing percentage of total coronary occlusion from onset of symptoms, being 87.3% between 0 and 4 hours,

85.3% between 4 and 6 hours, 68.4% between 6 and 12 hours and 64.9% between 12 and 24 hours. The main acute arteriographic finding indicating thrombus was identified as persistent staining of intraluminal material by the contrast agent. In addition, a subgroup of patients underwent surgical revascularization and thrombus was recovered in 88% of patients by an intraoperative Fogarty catheter, confirming in an in vivo model the importance of thrombus in acute myocardial infarction. In addition, this study suggested the existence of a spontaneous reperfusion rate by showing a decreasing incidence of thrombotic occlusion as the time from onset of symptoms to angiography increased. This is of particular importance when assessing reperfusion rates of different thrombolytic agents. Since this work, many patients have undergone emergency angiography within a few hours of onset of myocardial infarction for confirmation of diagnosis, and in some cases for administration of therapy. The findings confirm the high percentage of thrombotic total coronary occlusions early in the process of infarction (Table 1).

Trial	No. of Pts.	Time from onset	Percentage Total Occlusion
Rentrop et al. (1981)	29	(not given - R waves and pain still present)	76%
Anderson et al. (1983)	24	<4 hrs	83%
Kennedy et al. (1983)	250	<12 hrs	86%
TIMI Phase I (1985)	316	<7 hrs	74%
Simoons et al. (1985)	136	<4 hrs	82%
Blanke et al. (1985)	130	<12 hrs	69%
Williams et al. (1986)	47	<7 hrs	78%

TABLE 1: PERCENTAGE TOTAL THROMBOTIC OCCLUSION AT ANGIOGRAPHY IN EARLY STAGES OF ACUTE MYOCARDIAL INFARCTION

1.2. POTENTIAL FOR MYOCARDIAL SALVAGE

Over the same period as described above, several other groups were working to devise means of limiting the extent of myocardial damage. In Herrick's original paper (1912) he hypothesised that the "hope for damaged myocardium lies in the direction of securing the supply of blood, so as to restore as far as possible its functional integrity". The first evidence for reversibility of myocardial damage was presented by Tennant and Wiggers (1935). They showed in a dog model that reperfusion following temporary occlusion resulted in restoration of myocardial function. Later, work by Reimer et al. (1977) established the wavefront phenomenon of ischaemic cell death, again in a dog model. By varying the time of total circumflex occlusion from 40 minutes to 3, 6, 24 and 96 hours, they showed a time dependent increase in degree of myocardial necrosis. Subendocardial tissue showed necrosis very quickly, but a subepicardial zone of tissue remained viable, and therefore available for salvage for at least 3, and up to 6 hours. Salvage of jeopardised myocardium with betablockers (Maroko et al., 1971; Rasmussen et al., 1977) and hyaluronidase (Maroko et al., 1972) was subsequently shown.

One of the difficulties in dealing with animal models is whether the model will translate adequately for application to man. Nevertheless, following on from the conclusions derived from the above studies, various reports were published in the late 70's showing beneficial effects in man from hyaluronidase (Maroko et al., 1977), intra-aortic balloon pumping (Leinbach et al., 1978) and betablockers (Yusuf et al., 1980; The International Collaborative Study Group 1984).

These interventions attack the problem from 2 angles - firstly trying to reperfuse the occluded artery, and secondly, by reducing myocardial oxygen consumption. These two different mechanisms of action have led to combination therapy being tried, with apparent synergy in the dog model (Lo et al., 1985). Nevertheless, the most attractive form of treatment is to remove the initial insult by lysing the thrombotic coronary occlusion, and it is to this end that much research has focused over the last two decades.

The first report of intravenous thrombolytic therapy being administered in acute myocardial infarction was by Fletcher et al. in 1959, using streptokinase. Reperfusion data for the 22 patients treated in this way is not available, but a low mortality and morbidity rate suggested that intravenous streptokinase was safe and beneficial in this situation. Nevertheless, it took a

further 17 years before reports appeared showing successful lysis of coronary thrombi in acute myocardial infarction using the intracoronary route of administration (Chazov et al., 1976; Rentrop et al., 1979). Since then, many studies have been performed using both intravenous and intracoronary routes of administration, showing both efficacy and reduction in mortality, confirming the place of thrombolytic therapy given early in acute myocardial infarction.

1.3. THROMBOLYTIC AGENTS

A further area of intense research over the past decade has been the search for an ideal thrombolytic agent. The requirements for this drug would be, clot specificity with a high fibrin affinity and little fibrinogenolytic activity, ease of administration with a rapid onset of action with sustained local activity, and it should be non-allergenic. The three main drugs, streptokinase, anisoylated plasminogen streptokinase activator complex (anistreplase) and tissue Plasminogen Activator (tPA), will be described with particular reference to the above qualities. Published patient studies utilizing these drugs will be compared with respect to reperfusion, mortality and left ventricular function. No mention is made of urokinase or pro-urokinase, as this thesis does not contain work relating to these agents.

1.3.1. Streptokinase

As the first thrombolytic agent available, most clinical experience has been with streptokinase. It is a single chain protein (molecular weight 47,000 daltons) which is produced by Group C beta-haemolytic streptococci. Its action is to combine with the circulating proenzyme plasminogen and the resulting complex is capable of converting more plasminogen molecules to active plasmin with subsequent clot lysis. Due to previous streptococcal infections, patients may have a variable amount of circulating antibody to streptokinase. This needs to be neutralised before streptokinase has a therapeutic lytic effect, especially if given intravenously, as opposed to the more direct intracoronary route. In practice however, standard dosage regimens are used following the work of Verstraete et al. (1966) which showed that a dose of 1.25 million I.U. streptokinase intravenously will neutralise circulating antibodies and cause systemic fibrinolysis in more than 97% of the population. Administering streptokinase locally via a coronary catheter reduces the total dose which needs to be given (about 250,000 I.U.), but even this reduced dose has been shown to have significant effects on circulating fibrinogen levels, resulting in a systemic lytic state. Cowley et al. (1983) showed a 70% reduction in fibrinogen levels in 88% of patients receiving a mean of 201,000$\pm$24,000 I.U. streptokinase via the intracoronary route. Although bleeding complications are reported, they tend to be

associated with femoral puncture sites for angiography or venepuncture sites (Simoons et al., 1985).

As streptokinase is a foreign protein which can stimulate an antibody response, there is a theoretical risk of an allergic reaction following intravenous administration. Typically this is covered prophylactically by giving hydrocortisone and chlorpheniramine. However, the multicentre GISSI study (1986) did not require the administration of prophylactic steroid and recorded the incidence of anaphylactic shock at only 0.1%.

1.3.2. Anistreplase

Anistreplase is an anisoylated plasminogen streptokinase complex in which the active serine site on plasminogen is acylated with P-anisoic acid conferring chemical protection from the normal plasma inhibitors, alpha$_2$ antiplasmin and alpha$_2$ macroglobulin. The streptokinase plasminogen complex is still able to bind to fibrin through its lysine binding site. Once bound, hydrolysis causes deacylation and semi-selectively activates anistreplase at the clot surface. However, in doses of more than 10 units not all plasmin generated is neutralized by circulating alpha$_2$ antiplasmin, and a systemic fibrinogenolytic state ensues (Ferres, 1987). The deacylation half-life is 40 minutes (Smith et al., 1981) with a plasma clearance half-life of 70 minutes (Matsuo et

al., 1981). Compared with the shorter half-life of streptokinase of 18 minutes (Martin, 1982) these pharmacokinetic properties allow for a single bolus dose rather than a prolonged infusion regimen. An overview of the early patient studies with anistreplase is presented by Hillis and Hornung (1985) and illustrates the difficulties in achieving a balance between an acceptable reperfusion rate and limited systemic fibrinogenolysis. Dosing up to 15 units resulted in initial successful reperfusion, but a high early reocclusion rate (Hillis et al, 1983). The standard intravenous dose of alteplase is now accepted as 30 units which is inevitably associated with a degree of systemic fibrinogenolysis. Been et al. (1986) showed that at this dose the mean fibrinogen level fell to a third of the predosing level at 1 hour with few patients having a fibrinogen level below 0.5 g/L. Thus, initial trials have shown anistreplase to be effective in obtaining reperfusion, and to be advantageous in that it is given as a single bolus dose. The theoretical risk of anaphylaxis remains with anistreplase but similar to the GISSI findings with streptokinase, the recent AIMS study (Aims Trial Study Group, 1988) reported anaphylaxis in 2 of 502 patients (0.4%). Prophylactic steroids were not used routinely.

1.3.3. Tissue Plasminogen Activator

Although these serine proteases, called tissue plasminogen activators were known to exist as far back as 1947 (Astrup

and Permin), the low yield of these substances from human tissues delayed progress, until in 1982 Collen et al. reported the isolation and purification of human tissue type plasminogen activator (t-PA) from a melanoma cell line. A year later Pennica et al. (1983) cloned the gene responsible for the synthesis of recombinant t-PA (rt-PA) and expressed it using E.Coli. Thus, sufficient quantities were produced to evaluate its lytic activity and to provide treatment for patients with acute coronary occlusion. The attraction in developing this agent for widespread use was that it has several properties considered advantageous to a thrombolytic drug. As it is a naturally occurring compound, it lacks antigenicity, and it has been termed clot selective, thus supposedly avoiding the induction of a systemic lytic state. The half-life is short, in the order of 5 minutes (Garabedian et al., 1986), allowing manipulation to achieve haemostatic control if required for invasive procedures. Tissue plasminogen activator owes its clot selectivity to its binding properties. In circulation it does not bind avidly to plasminogen, but has a high affinity for fibrin, to which it binds at specific sites in the kringle structures. Plasminogen binds avidly to this t-PA fibrin complex, and is thus activated at the clot surface. Any plasmin which escapes will be inactivated by alpha $_2$ antiplasmin.

The ability of t-PA to lyse thrombi without producing a systemic lytic state was shown first in animals (Van de Werf et al., 1984a) and then in humans, where 6 out of 7 patients with evolving myocardial infarction were shown to reperfuse without depleting levels of fibrinogen, plasminogen and alpha$_2$ antiplasmin (Van de Werf et al., 1984b). Despite encouragingly high levels of reperfusion obtained initially with intravenous infusions of rt-PA, the problem has been that a high percentage of patients reocclude or suffer further infarction. Collen et al. (1984) reported an initial reperfusion rate of 75% after intravenous infusion of 0.5-0.75 mg/Kg rt-PA. Patients in this study who had been randomised to placebo were then given intracoronary rt-PA, 9 out of 13 patients achieving reperfusion. There was very little change in fibrinogen levels, but there were 5 early reocclusions. Gold et al. (1986) reported a reocclusion rate of 45% in patients with persistent high grade (>80%) stenoses. Prolonging the infusion of rt-PA over 4 hours maintained patency. In contrast, work from the European Co-operative Group for t-PA (Verstraete et al., 1987) reported a reocclusion rate of 8% within 24 hours, and there was no difference between patients receiving a maintenance intravenous infusion of 30 mg rt-PA over 6 hours and those who did not. Work arising from the TIMI study (Rao et al., 1988) compared the degree of systemic fibrinogenolysis induced by 1.5 million I.U. streptokinase to that caused by 80 mg of rt-PA. Fibrinogen fell by a mean of 33% 5 hours following

rt-PA compared to 58% after streptokinase. Similarly, plasminogen fell by 57% after rt-PA and 82% after streptokinase, suggesting less systemic effect. Verstraete et al. (1985b) showed a fall in fibrinogen levels to 52% of pre infusion levels folowing a dose of 0.75 mg/Kg. It is now thought that this systemic lytic activity may in fact be desirable to reduce the reocclusion rate.

One of the disadvantages of rt-PA is that it remains very much more expensive than either streptokinase or anistreplase. Of its claimed advantages, clot specificity is now thought to be less important for reasons outlined above. It is non allergenic, and it has been suggested that it is the drug of choice when administering a second dose of thrombolytic therapy to a patient who has previously received streptokinase especially if within the past year.

1.4 AIMS OF TREATMENT

1.4.1. Reperfusion

Restoring blood supply to the myocardium by lysing coronary thrombus is the rationale behind giving thrombolytic therapy. Reperfusion is assessed angiographically and various scoring systems (TIMI Trial 1985; Verstraete et al., 1985a) have been employed to quantify the degree of reperfusion. Unfortunately these

two scoring systems are not directly comparable, and the doses of agents used varies between studies. Similarly, reperfusion rates will vary depending on the time delay following the onset of symptoms to the initiation of treatment, the drug given and the method of administration. In addition, it is important to ascertain whether a study is reporting a patency rate or a true reperfusion rate. The latter requires that a pre-treatment angiogram is performed to document occlusion prior to treatment. Performing angiography only after thrombolytic therapy has been started will give a slightly higher incidence of open arteries as it does not take into account the incidence of spontaneous reperfusion reported by De Wood et al. (1980). These are termed patency rates, and are higher than reperfusion rates by about 15-20%. Figure 1 summarises reperfusion and/or patency rates from the major trials which have used different agents. Some of the smaller clinical trials are included to illustrate the problem of assessing drug efficacy when interpreting results for different series with differing protocols and small numbers.

As the length of time increases between onset of pain and administration of thrombolytic therapy, the reperfusion rate decreases (Smalling et al., 1982). Anistreplase was initially assessed in small patient numbers and an excellent reperfusion rate reported (Been et al., 1985; Kasper et al., 1986). Timmis et al. (1987) studied the

same number of patients using the same dose, but by extending the time window from 3 hrs to 6 hrs, the reperfusion rate dropped to 56%. When assessed in a much larger multicentre trial (Anderson et al., 1988) the reperfusion rate using anistreplase seems to have settled at 51% within a 6 hour time window.

An overall mean intracoronary reperfusion rate of 75% with streptokinase has remained the "gold standard" against which all of the agents and routes of administration are compared. Against this is the time saved if intravenous therapy can be administered soon after admission, rather than wait for the cardiac catheterisation laboratory to be set up. With the advent of effective intravenous administration, coronary angiography is no longer required to administer treatment, and is a non realistic means of determining if reperfusion has occurred in large patient groups outwith cardiac centres to whom thrombolysis will now be available. Non invasive methods of detecting reperfusion are required, and research has focused on utilizing the so-called "reperfusion arrhythmias", creatine kinase release curves and changes in the ST segment to determine reperfusion non invasively. The latter topic is discussed fully in chapter 3.

The value of arrhythmias in identifying reperfusion remains controversial, as, in the setting of acute

myocardial infarction, the incidence of ischaemia-induced arrhythmias is increased. Reperfusion associated arrhythmias have been described in both animal models and clinical practice (Penkoske et al., 1978; Goldberg et al., 1983a). Pre-treatment with lignocaine and atropine confuses the issue and has been given routinely in many studies.

Nevertheless, two arrhythmias are thought to be fairly indicative of reperfusion. Firstly, accelerated idioventricular rhythm has been shown to be significantly more common in patients achieving reperfusion with streptokinase than in a control group (Cercek and Horvat, 1985). Secondly, the development of bradycardia and hypotension, the Bezold-Jarisch reflex, is associated with reperfusion of the infero-posterior myocardium (Koren et al., 1986). The sensitivity and specificity of these arrhythmias for predicting reperfusion is not yet known, but it is generally accepted that they are benign arrhythmias which rarely require treatment. Of interest is the observation that life-threatening arrhythmias such as ventricular fibrillation show a lower incidence if thrombolytic therapy is given (Simoons et al., 1985).

Restoration of anterograde coronary arterial flow is associated with an early peak of creatine kinase. This "wash-out" phenomenon is seen irrespective of whether flow

has been re-established by thrombolysis (Blanke et al., 1984a) or by spontaneous reperfusion (Ong et al., 1983) and is therefore not specific for drug induced reperfusion (Gore et al., 1987). It is however a useful non-invasive marker, and the specificity and sensitivity of this technique has been addressed recently by Garabedian et al. (1988). This group compared a conventional radioimmunometric assay of plasma CK-MB with a rapid endpoint CK-MB immunofunctional assay (<15 minutes analysis time). Plasma CK-MB was estimated at the end of a 90 minute t-PA infusion and an increase from pre-treatment values of >2.5 fold for an LAD lesion and >2.2 fold for an RCA lesion was taken as evidence of reperfusion. The rapid analysis using the immunofunctional assay performed well with a sensitivity of 83%, and a specificity of 100% when compared to angiographic findings. The performance of this method has yet to be confirmed prospectively in a larger patient group.

CK-MB, although thought to be relatively specific for myocardium, only comprises about 15% of the total myocardial CK. CK-MM makes up the remaining 85% and its release into blood exhibits three bands on electrophoresis known as isoenzyme isoforms MM_1, MM_2 and MM_3 (Roberts, 1987). The isoform MM_3 is released during reperfusion, and is converted to MM_2 and then to MM_1. Morelli et al. (1987) showed that the MM_3:MM_1 activity ratio is a

sensitive measure of reperfusion with peak levels occurring much earlier in patients achieving reperfusion. Certainly the isoform MM_3 shows more dynamic temporal changes, and may be of future use in documenting early reocclusion.

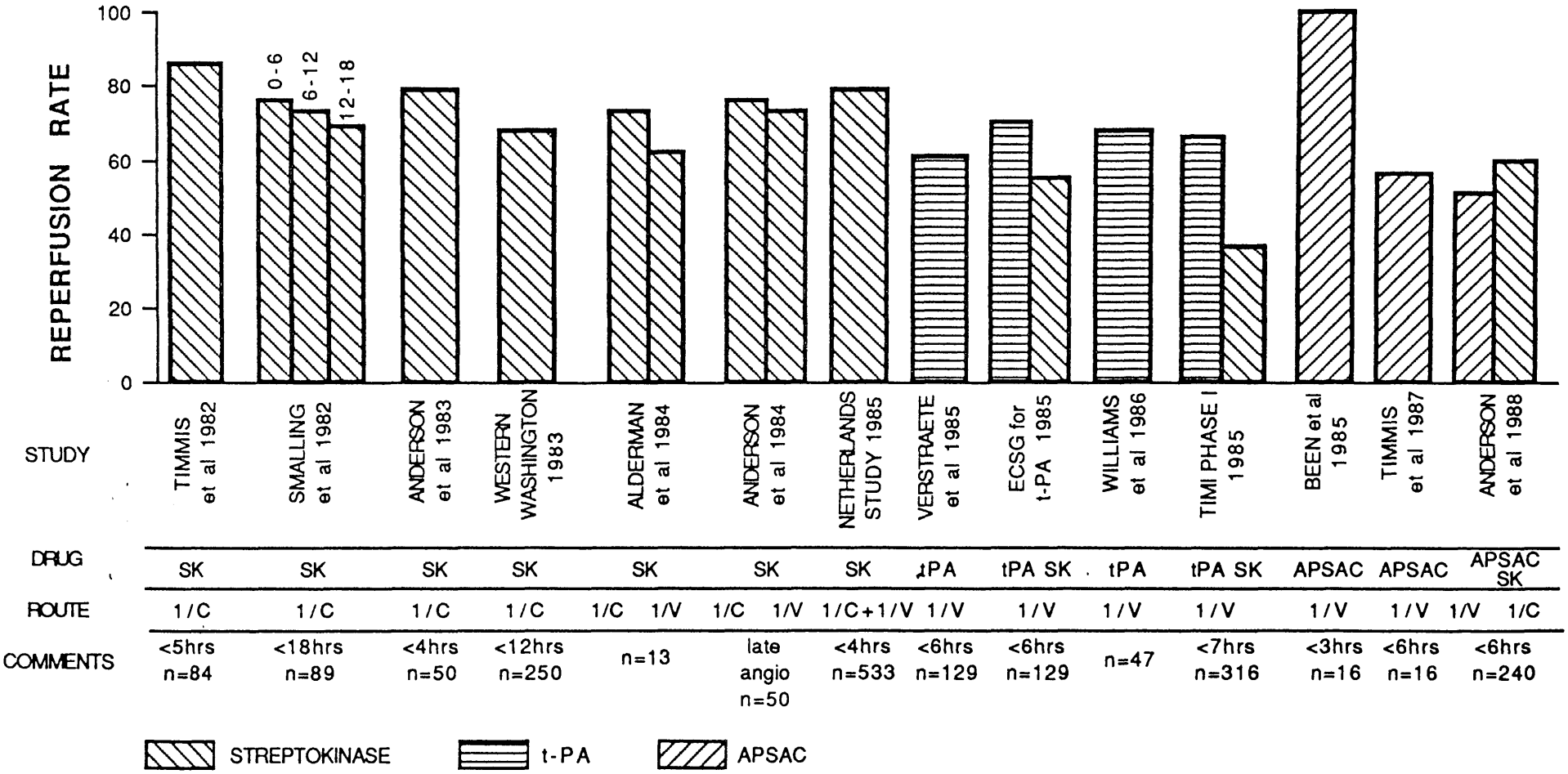


FIGURE 1 : REPERFUSION AND PATENCY RATES FOR MAJOR CLINICAL TRIALS USING STREPTOKINASE, ANISTREPLASE AND TISSUE PLASMINOGEN ACTIVATOR

1.4.2 Left Ventricular Function

A further objective end-point in assessing efficacy of thrombolytic treatment is to measure left ventricular function which can be done in several ways. Left ventricular angiography is invasive, and although patients have usually undergone cardiac catheterisation in the acute phase, it is more difficult to obtain serial recordings. Radionuclide angiography is non invasive and reproducible, allowing several measurements over a given time period. Echocardiography has also been used with the advantage that it is non invasive and easily repeatable (Anderson et al., 1983). Its disadvantages are that not all patients can be studied with the accuracy required to measure ejection fraction. Infarct sizing can also be carried out by Thallium 201 scintigraphy, which will show changes in perfusion following thrombolysis (Smalling et al., 1982).

There are several confounding variables to bear in mind when interpreting left ventricular ejection fraction in patients with acute myocardial infarction treated with thrombolytic therapy. Firstly, Schwarz et al. (1985) showed that there is spontaneous improvement in left ventricular ejection fraction in patients with acute myocardial infarction **not** treated with thrombolytic therapy. This change took place between admission and two weeks, and correlated with a degree of residual flow (either anterograde or via collaterals) to the infarct

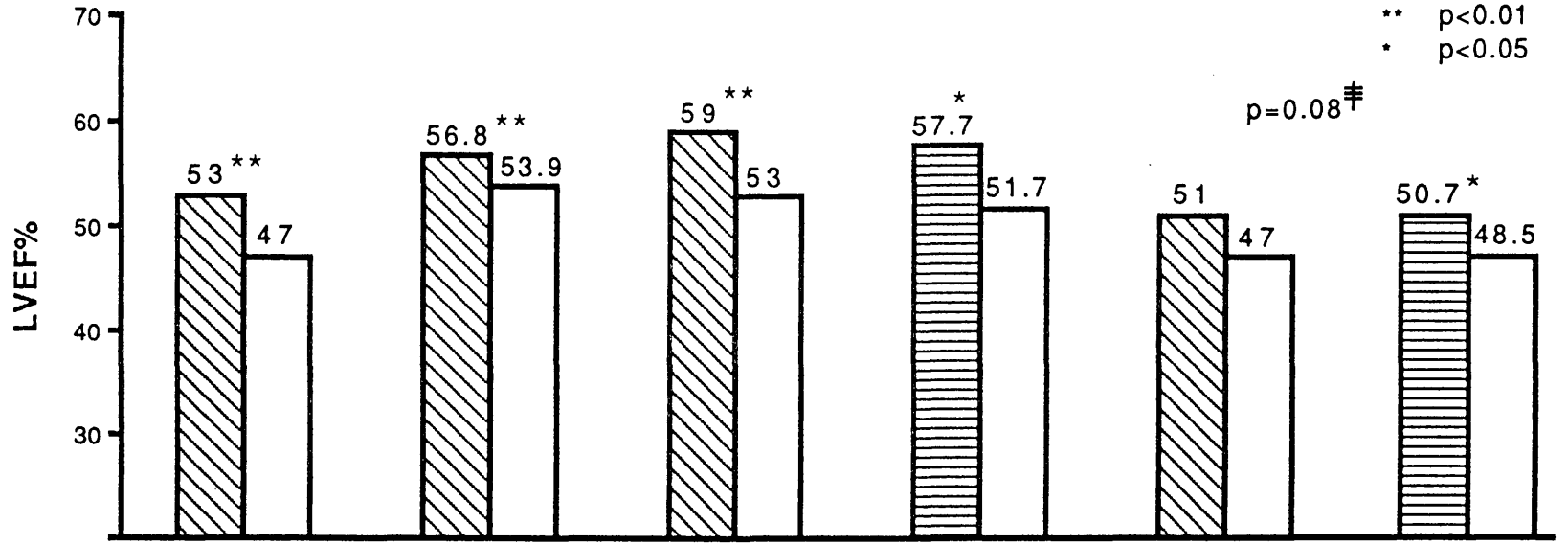
related segment. The mean change in ejection fraction for patients with residual flow was 6.9±2.3% vs -2.2±1.7% for patients without ($p<0.01$). This illustrates the problem if trials are not controlled. The improvement seen over a two week period suggests the phenomenon of stunning and Braunwald and Kloner (1982) suggested that the assessment of efficacy of any intervention designed to limit myocardial damage should be delayed for at least two weeks. They also purported that the basic mechanism behind stunning is thought to be ATP depletion. Reperfusion wash-out of ATP metabolites, which would otherwise be recycled for ATP manufacture, means that there is a prolonged resynthesis for nucleotide precursors.

Secondly, it is not enough to look at global ejection fraction, but to relate this to changes in regional wall motion , Rogers et al. (1984) showed that in patients with "no flow" to the infarct zone and an unsuccessful reperfusion, the fall in global ejection fraction seen over a two week period was due to a reduction in movement of the non infarct zone. This is thought to be due to an initial hyperkinesis of the non infarct area which is not sustained.

Despite theoretical work suggesting that a significant improvement in left ventricular function could be expected only if thrombolytic therapy was administered within 3 hours, early reports (Reduto et al., 1981; Smalling et al., 1982) did show improvement in global ejection fraction despite delays before treatment of 9 hours and 18 hours respectively. Although both trials provided control groups, they were not randomised. The randomised trials of Anderson et al. (1983) and Khaja et al. (1983) published conflicting results. The Western Washington Group were not able to show an improvement in left ventricular function in their intracoronary streptokinase trial (Ritchie et al., 1984), but showed a reduction in infarct size and increase in left ventricular ejection fraction in patients randomised to intravenous streptokinase (Ritchie et al., 1988). This improvement was limited to patients with anterior infarction treated within 3 hours of symptom onset. They attributed the difference in their results to the fact that the patients receiving intravenous therapy were treated on average about 1 hour earlier, 52% being randomised within 3 hours of symptom onset, compared with only 22% randomised in the same interval in the intracoronary group (Ritchie et al., 1988). A summary of the larger randomised trials is shown in Figure 2. These results confirm that administration of thrombolytic therapy early in the course of myocardial

infarction results in an improvement in left ventricular ejection fraction, and that this improvement may be more marked in specific subset of anterior infarction.

There appears to be a dichotomy between improvement in left ventricular function and mortality results. The ISAM Study Group (1986) showed an improvement in ejection fraction, but in this large group of 1,741 patients, they were unable to show an improvement in mortality, either in the short or long term (Shroder et al., 1987). Large scale multicentre studies such as ISIS 2 (1988) have shown benefit in mortality if treatment is commenced within a 24 hour time window. It would be unlikely looking at the results of Ritchie et al. (1988) that this benefit could be attributed to an increase in ejection fraction. There may be as yet some unidentified factor which contributes to improvement in mortality rates, but has no relation to left ventricular function per se. This may be due to a reduction in the propensity to arrhythmias, the accompanying systemic lytic state, a decrease in plasma viscosity, or reperfusion itself which may have a beneficial effect in preventing infarct expansion.



STUDY	NETHERLANDS STUDY 1986	ISAM STUDY GROUP 1986	WHITE+ et al 1987	NATIONAL HEART FOUNDATION OF AUSTRALIA 1988 †	WESTERN WASHINGTON TRIAL 1988	EUROPEAN COOPERATIVE STUDY GROUP 1988
SAMPLE SIZE	332	1741	219	144	368*	721
DRUG	1/C+1/V SK vs C	1/V SK vs P	1/V SK vs P	1/V t-PA vs P	1/V SK vs P	1/V t-PA vs P

\+ - benefits to patients with either anterior or inferior infarctions
† - more benefit to patients with anterior myocardial infarction
* - LVEF performed on 207 patients only
‡ - Authors concluded benefit to anterior infarction < 3hrs old.

PLACEBO/CONTROL
STREPTOKINASE
t-PA

FIGURE 2: LEFT VENTRICULAR FUNCTION FOLLOWING THROMBOLYSIS IN LARGE RANDOMISED CLINICAL TRIALS

1.4.3. Mortality Data

In the early 70's and 80's many small trials were conducted using streptokinase in acute myocardial infarction. Although these trials were randomised and placebo controlled, most of them did not show statistically significant changes in mortality (May et al., 1983). In order to assess the net benefit of this treatment Stampfer et al. (1982) reported on pooled results from randomised trials in which intravenous streptokinase had been used. They showed that intravenous streptokinase therapy reduced mortality over the subsequent few weeks by about 20%. In a similar manner Yusuf et al. (1985) pooled data from 33 randomised trials using both intracoronary and intravenous routes of administration, for both streptokinase and urokinase. An overview from this data indicated that intravenous treatment produces a highly significant reduction in the odds of death (22%$\pm$5%, $p<0.001$).

With improvement in treatment for cardiac failure and arrhythmias, the mortality rate for acute myocardial infarction dropped even before the introduction of thrombolytic therapy. Norris reported a fall in hospital mortality rates from 17% in 1968 (Norris et al., 1969) to 13% in 1977-79 (Norris and Sammel, 1980) and to 10% in 1982-84 (Norris et al., 1984). Thus, to show a significant reduction in mortality attributable to thrombolytic therapy, large scale trials are required.

The results of GISSI published in 1986 showed an 18% reduction in mortality comparing intravenous streptokinase to controls in over 11,000 patients. Other trials followed, and are shown in Figure 3. The mortality rates shown are overall rates for all age groups and all time windows before initiation of therapy. Once these are subdivided and analysed, it becomes clear that the hospital mortality rate for patients <70 years receiving intravenous thrombolytic therapy within 3-4 hours after the onset of myocardial infarction is about 5% (Norris and White, 1988). Comparing this with the placebo mortality rates shown, raises the question as to whether placebo controlled trials are ethical. Following publication of ISIS 2 (1988), most large thrombolytic trials now use 1.5 million I.U. streptokinase and aspirin as standard therapy, against which all other agents are compared.

The 47% reduction in mortality seen in the AIMS study group (1988) prompted termination of the trial early, recruiting 1,000 rather than the planned 2,000 patients. Criticism was levelled at this practice in a Lancet editorial which suggested that stopping early may have exaggerated the benefit (Anonymous, 1988). However, it does not negate a substantial reduction in mortality, and the recent publication of longterm mortality shows continued benefit at 1 year (AIMS Trial Study Group, 1990).

Streptokinase and anistreplase have both been shown to substantially reduce mortality. It was only recently that the results of the ASSET trial (Anglo-Scandinavian Study of Early Thrombolysis) confirmed that t-PA also reduces mortality by 26% (Wilcox et al., 1988). As yet it would appear that none of the agents is any better at reducing mortality than the others. The somewhat impressive 47% reduction with anistreplase seen in the AIMS study probably reflects the more stringent entry criteria required in this trial. If the subset of ISIS 2 patients fulfilling the AIMS criteria are examined, the reduction in mortality using streptokinase is 43%.

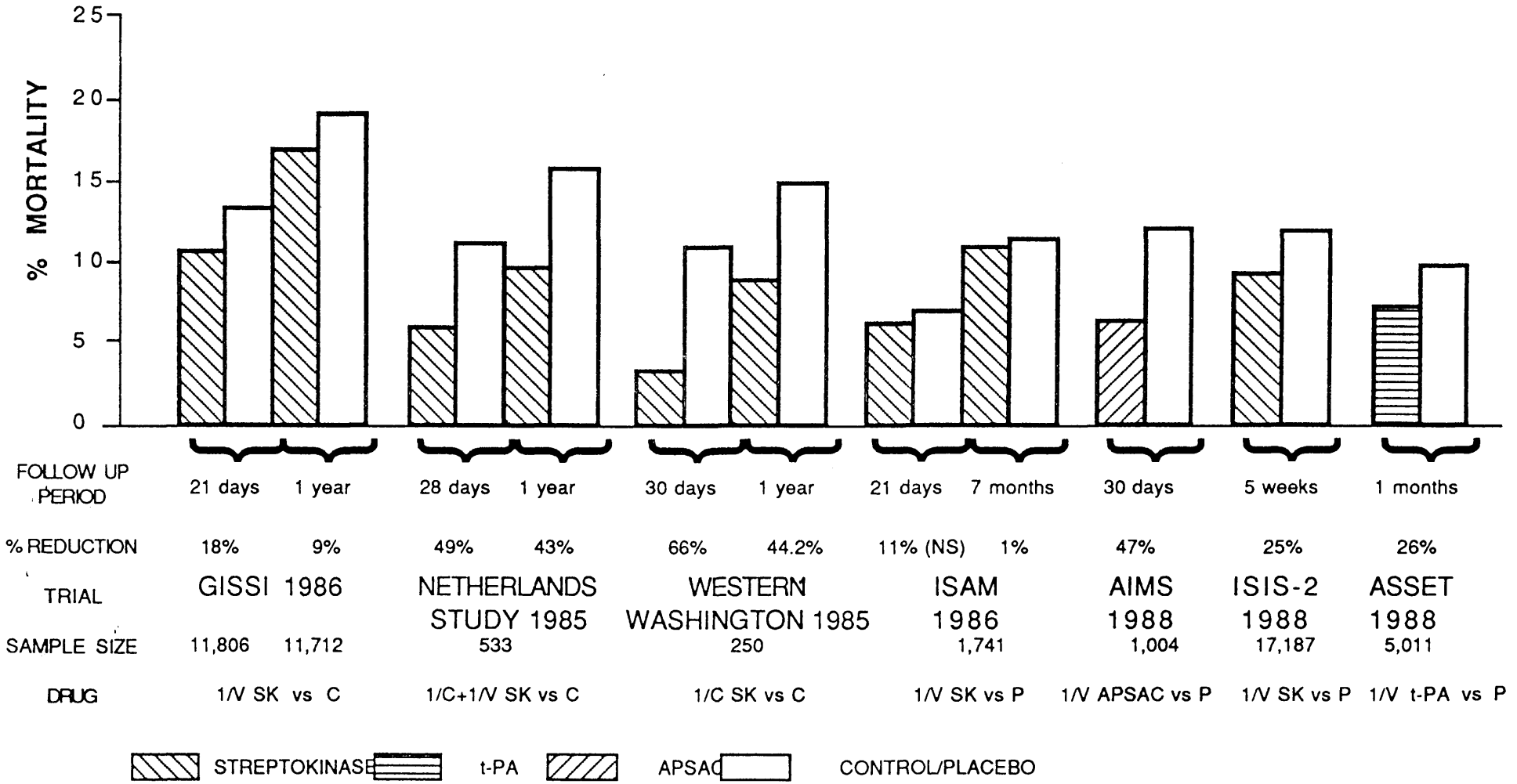


FIGURE 3: SHORT AND LONG TERM MORTALITY DATA FROM MAJOR CLINICAL RANDOMISED TRIALS ASSESSING THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

B. ELECTROCARDIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

1.5 HISTORICAL REVIEW AND CURRENT OF INJURY THEORY

The decision to treat a patient with thrombolytic therapy requires that an accurate diagnosis of acute myocardial infarction is made based on the clinical history and an admission ECG. Myocardial infarction is diagnosed by the electrocardiographic parameters of ischaemia, injury and necrosis, thought to be represented by T wave changes, ST segment elevation and Q wave formation respectively. The T wave changes are non specific and may be transient and therefore missed in man unless the ECG is recorded at the time of occlusion (Fisch, 1988). Q waves reflect necrotic tissue, and therefore it is the manifestation of injured, but potentially salvageable myocardium demonstrated by ST segment elevation that highlights patients suitable for thrombolytic therapy.

It was Pardee who first described ST segment elevation as a clinical electrocardiographic feature of coronary occlusion as far back as 1920 in an observational study describing a 38 year old chauffeur with an acute inferior infarction. The first experimental work dealing with ST segment change was published in 1928 by Otto. Since then it has been the subject of intensive investigation used both as a tool for the diagnosis of acute myocardial infarction, and for following the effect of interventions intended to limit infarct size.

There are two main theories to explain deviation of the ST segment from the isoelectric line. Both depend on a flow of current between healthy myocardium and the ischaemic area; the so called "current of injury". In the "diastolic current of injury" theory, the injured myocardial surface becomes electrically negative and surrounding healthy muscle has a positive surface charge. A continuous current flows even during electrical diastole from healthy tissue to injured tissue, and is recorded as a depressed TQ segment, automatically corrected in ECG machines back to the isoelectric line. During systole when the whole heart is depolarised no current of injury flows and the ST segment returns to baseline, but is interpreted as ST segment elevation.

In the "systolic current of injury" theory, true elevation of the ST segment is proposed in that the injured myocardium has a positive surface charge relative to healthy depolarised tissue, either due to early repolarisation (Samson and Sher, 1960) or an inability to depolarise initially (Eyster et al., 1938). This will result in a flow of current from injured tissue to healthy, but still depolarised tissue, creating true ST segment elevation.

Support for the "diastolic current of injury" has been provided by Prinzmetal et al. (1961) who documented partial depolarisation of ischaemic cells during diastole

associated with ST segment elevation in epicardial leads. Also Vincent et al. (1977) demonstrated depressed TQ segments in epicardial leads following coronary occlusion and Cohen and Kaufman (1975) used the magnetocardiogram to pick up the injury current in closed chest dogs with coronary occlusions, demonstrating a depressed baseline, providing further evidence for the "diastolic current of injury" theory.

1.6 SENSITIVITY AND SPECIFICITY OF THE 12 LEAD ECG IN THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

Not all patients presenting at casualty with acute myocardial infarction demonstrate electrocardiographic changes, and as many as 20% may have a normal tracing (Behar et al., 1977). Other studies have shown overall sensitivity rates using the admission ECG in patients subsequently proven to have acute myocardial infarction of 66% (Gunraj and Rajapakse, 1974) and 51% (McGuinness et al., 1976). These two studies showed much higher sensitivity rates when serial ECG's were used - 93% and 83% respectively. Decision making about administration of thrombolytic therapy however cannot wait for serial ECG's to be performed. Rude et al. (1983) addressed this problem in screening 3,697 patients with greater than 30 minutes of chest pain for eligibility for entry to the MILIS trial (Multicenter Investigation of the Limitation

of Infarct Size). The diagnosis of acute myocardial infarction was made if one or more of the following criteria were met:

1. New or presumably new, Q waves ⩾30 m.sec and 0.2 m.v deep in at least 2 contiguous leads (i.e. II, III, AVF, or V_1-V_6 or I and AVL).
2. New or presumably new ST segment elevation or depression of ⩾0.1 m.V. in at least one of the above lead combinations, or
3. Complete left bundle branch block.

Using these criteria the diagnostic sensitivity was 81% and the specificity 69% resulting in a predictive value of 72%. When combined with the MILIS exclusion criteria (i.e. age >75, symptoms >18hrs duration, cardiogenic shock etc.) the overall rate of confirmed myocardial infarction was 86%. Bren et al. (1987) in a later review further subdivided these ECG criteria showing a 75% sensitivity and 77% specificity for ST segment elevation or depression and a diagnostic sensitivity of only 46% and specificity of 91% when using ST segment elevation alone. He commented that when applied to inclusion or exclusion criteria for thrombolytic trials, many patients may be excluded from entry because of the lack of sensitivity of ST segment elevation.

1.7 THE 12 LEAD ECG, INFARCT LOCATION AND ARTERIOGRAPHIC FINDINGS

Initially ECG accuracy in localising acute myocardial infarction was assessed by comparing ECG findings with post mortem results. Myers et al. in a series of post mortem examinations published between 1948 and 1949 correlated the 12 lead ECG with evidence of myocardial necrosis. Their findings remain the basis of infarct localisation today, but various modifications and additions are now included to deal with both right and left bundle branch block (Besoain-Santander and Gomez-Ebensperguer, 1960; Dressler et al., 1950a&b). An accepted nomenclature for site of infarction according to electrocardiographic leads showing sequential changes is shown in Table 2. These studies by their very nature pre-select the study group. They may therefore not represent adequately, all patients sustaining an acute myocardial infarction. A similar post mortem study from Canada (McQueen et al., 1983) suggested that the ECG was frequently unhelpful in diagnosisng acute transmural myocardial infarction due to the incidence of bundle branch block or paced rhythm. Again only patients succumbing to the disease were studied and by implication have a higher rate of complications which would include conduction changes and heart block. Using radionuclide techniques by technetium pyrophosphate imaging of the myocardium in acute infarction addressed the problem in a more typical group of patients (Yasuda et al., 1982). The

sensitivity and specificity of 12 lead ECG's localising the acute infarct to one of five left ventricular wall segments were determined. This study screened 34 patients and gave an overall accuracy of localisation of 86% which was further increased when 4 patients with left bundle branch block were excluded. The sensitivities and specificities for 12 lead ECG localization for each of the five ventricular segments and the ECG lead criteria used are shown in Table 3.

The correlation of ECG findings with obstructive coronary lesions demonstrated angiographically in acute myocardial infarction has been studied by Blanke et al. (1984b). The sensitivity, specificity and predictive value for different sites of infarct were reported and are shown in Table 4.

With the introduction of thrombolytic therapy many trials have performed coronary angiography to document the obstructed coronary artery early in the course of myocardial infarction prior to treatment, irrespective of whether the intracoronary or intravenous routes of administration are used (Timi Study Group, 1985; Simoons et al ., 1985). This has allowed further correlation between the admission ECG and arteriographic findings. These studies have confirmed the earlier work of de Wood et al. (1980), in that patients studied up to 6 hours after the onset of pain, as many as 14% may have

incomplete coronary artery occlusion. The ability to identify this subgroup using the admission ECG may have implications regarding whether to administer thrombolytic therapy or not, as it is already known that this group do better than their counterparts with complete occlusion (Schwarz et al., 1985). Conflicting evidence exists in the literature regarding the ability of the ECG to highlight this good prognostic group. Rentrop et al. (1981) could find no difference in the degree of ST segment elevation between patients with complete and incomplete occlusions, but von Essen et al. (1985) reported that if the sum of ST segment deviation in leads I, II and III was < 0.2 mV, this was useful in highlighting a small group of patients (3/56) with incomplete occlusion. Ross, (1985) on behalf of the TIMI Study Group found that he could not differentiate between these groups based on the degree of ST segment change.

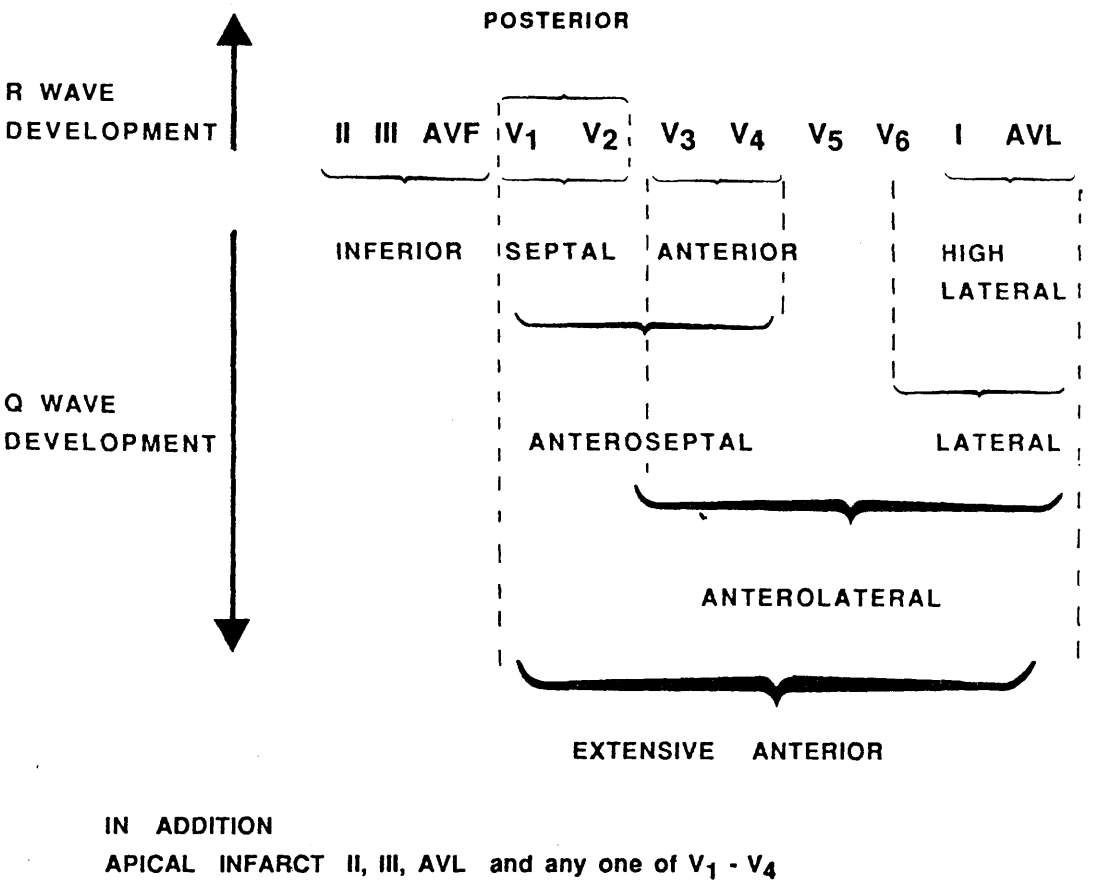


TABLE 2: NOMENCLATURE FOR SITE OF INFARCTION ACCORDING TO ELECTROCARDIOGRAPHIC LEADS SHOWING SEQUENTIAL CHANGE

LV wall segment	Leads designating infarct site*	Sens-itivity	Spec-ificity
Anterior wall	V1-V4	86%	89.5%
Lateral wall	V5-V6	73.7%	80%
High lateral wall	I, AVL	80%	87.5%
Inferior wall	II, III, AVF	87.5%	100%
True posterior wall	V1, V2	83.3%	86.4%

* Leads required to show sequential change of infarction - i.e. development of Q waves, loss of R wave voltage, ST-T changes or development of R waves in V1 V2 in true posterior infarctions.
(Yasuda et al., 1982).

TABLE 3: THE SENSITIVITY AND SPECIFICITY OF THE 12 LEAD ECG IN LOCALIZING ACUTE INFARCTION TO 5 LEFT VENTRICULAR SEGMENTS

ECG Site of Infarction	Obstructed Coronary Artery	Sens-itivity	Spec-ificity	Pre-dictive Value
ANTERIOR (I, V1-V4)	LAD	90%	95%	96%
INFERIOR (II, III, AVF)	RCA or Cx	53%	98%	94%
POSTERIOR/LATERAL R>S V1/AVL V4-V6	RCA or Cx	20%	100%	100%
INFERIOR (II, III, AVF)	RCA	56%	97%	88%
POSTERIOR/LATERAL R>S V1/AVL V4-V6	Cx	24%	98%	75%

ECG diagnosis of infarction required Q waves or ST segment elevation in at least 2 of the lead groupings shown. (Blanke et al., 1984b).

TABLE 4: SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES OF ECG CLASSIFICATION OF INFARCT SITE CORRELATED WITH ANATOMICAL SITE OF CORONARY OCCLUSION.

1.8 EVOLUTION OF INFARCT PATTERN

Before the electrocardiographic changes occurring in response to reperfusion following thrombolysis can be assessed, it is mandatory to know what changes evolve in patients with acute infarction not receiving interventional therapy. The typical pattern of evolving myocardial infarction is for the ST-T and T wave changes to occur (discussed in section 1.5) and to be followed by development of Q waves and symmetrical T wave inversion. There is considerable inter-patient variability in the time course of these sequential changes as demonstrated by Thygesen et al. (1979). There is remarkably little literature giving absolute quantification in timing of these evolving ECG changes, and in the most recent edition of "Heart Disease" (Braunwald, 1988) a textbook of cardiovascular medicine, QRS evolution is discussed only in reference to hand drawn diagrams originally published by Lepeschkin, (1951). This diagram suggests that acute QRS changes are limited to the first day after the onset of myocardial infarction.

In serial 72 point mapping studies, Selwyn et al. (1977 & 1978) characterised the natural history of both Q waves and ST segments. In 47 patients with uncomplicated acute myocardial infarction the sum of ST segment elevation ($\sum$ ST elevation) was shown to slowly decrease over a period of 1 week. A progressive fall in mean $\sum$ST segment elevation expressed in percentages of 17%, 12% and 15%

occurred between the time points 4-8, 8-12 and 12-24 hours respectively. The largest fall of 34% occurred between 1 and 4 hours. However, this fall depended on only 8 patients being admitted within the 1 hour time bracket, compared with 28 in the 1-4 hour bracket. Despite small numbers, it does suggest that this may reflect hyperacute changes occurring early in the phase of infarction which then resolve quickly. A later study (Selwyn et al., 1978) which looked at 45 uncomplicated anterior myocardial infarctions demonstrated Q wave formation within 2 hours of onset of chest pain, the sum of all Q waves, $\sum Q$, on the precordial map increased significantly at 6 and at 12 hours, but thereafter $\sum Q$ plateaued and did not change over 4 days. $\sum$ST elevation steadily dropped with the biggest fall occurring over 12 hours - 18 patients were recruited within 2 hours of onset of symptoms in this group and the large fall of 34% reduction in ST segment height between 1 and 4 hours seen in the first study was not repeated here. The number of positions on the 72 lead map showing ST segment elevation correlated well with the number of positions showing Q waves at 24 hours, but only the precordial sum of ST elevation at 45 minutes (n=8) correlated with $\sum Q$ at 24 hours. Thus, ST segment elevation would appear to be a qualitative, rather than quantitative marker for subsequent Q wave development.

Certainly Q wave formation appears to be complete within 12 hours of onset of pain, and to remain static over at least 4 days.

Zmyslinski et al. (1979) described a biphasic pattern to the natural evolution of ST segment changes following anterior myocardial infarction. The changes he describes were comparable whether using either the six precordial leads from a 12 lead ECG or 35 leads from an electrocardiographic map. There was a significant decrease in $\sum$ST at 7-12 hours following onset of chest pain (-1.13$\pm$0.38 mV) but this then increased at 25-48 hours. These patients did not have pericarditis. Values were shown to return to base line within 8 days.

Long-term recovery of the ECG has been described by Montague et al. (1986), using 120 lead body surface maps over a period from day 5 to 6 months post myocardial infarction in 23 patients (12 anterior, 11 inferior). The ECG parameters measured were different from work already described as they represent computed time intervals acquired from a signal averaged lead. The Q zone (QZ) integral represents the area under the first half of the QRS curve. The Q wave (QW) integral represents the area under the QRS curve from the initial negative deflection until it returns to baseline. The units are expressed in uV.s. In anterior infarctions, the Q zone integral improved from -34$\pm$20 to -24$\pm$13 uV.s at 6 months and the $\sum$Q

wave from $-160\pm122 \times 10^2$ to -120 ± 90 uV.s $\times 10^2$ over the same time period. In the inferior infarction group there was a significant improvement over the same time period in the $\sum Q$ wave from -91 ± 40 uV.s $\times 10^2$ to -68 ± 24 uV.s $\times 10^2$. There was no such change in QZ. This work suggests that there is continued gradual recovery in the ECG following infarction over a period of at least 6 months, and would appear to be heterogenous in different clinical groups, although the small numbers in either group here may not be totally representative of the normal infarct population.

In a small percentage of patients, the Q wave may disappear completely, leaving a normal ECG. Pappas (1957) found that out of 742 cases of myocardial infarction, 14 cases normalised their ECG's. This change took between 2 and 18 months except for one patient who developed a normal ECG within one month. Nine patients had anteroseptal infarction, 4 had posterior infarction and 1 had both.

An extension to the 6 month follow up by Montague et al. (1986) is provided by Richter et al. (1987) with data arising from the Goteberg Metoprolol Trial (Hjalmarson et al., 1981). Sixty patients with proven anterior myocardial infarction had 24 lead precordial maps performed at day 4, 3 months, 6 months and 1 year. R and

Q wave amplitudes were measured for each lead, and then summed to give $\sum R$ and $\sum Q$. The $\sum R$ increased from a mean value of 95 mm on day 4 to 114 mm at 3 months, 122 at 6 months and a small, but further increase to 128 mm at 1 year. The sum of Q waves decreased from a mean value of 102 mm on day 4 to 75 mm at 3 months, 68 mm at 6 months and 57 mm at 1 year. Half of this group were receiving metoprolol up to the 3 month period, thereafter the study was stopped and most patients were given open metoprolol. The results between the two groups for $\sum R$ and $\sum Q$ up to 3 months were not different. In conclusion, it would appear that the ECG has the facility to show continued improvement up to 1 year following myocardial infarction. The reason for this is not clear, but may reflect shrinkage of the necrotic area so that the overlying electrode only picks up the depolarization wave forms due to healthy tissue (Holland & Arnsdorf, 1977).

1.9 DEVELOPMENT OF SCORING SYSTEMS

The above techniques depend on sophisticated precordial mapping systems which are not available to every physician. The standard 12 lead ECG remains the cornerstone for clinical detection and location of infarction as it is universally available, reproducible, non invasive and inexpensive. Following the hypothesis that electrocardiographic changes occurring during myocardial infarction reflect the degree of necrosis, various scoring systems have been developed for estimation

of infarct size using the 12 lead ECG. A summary of the development and description of these scoring systems is given below:

1.9.1. The Selvester Score

Studies examining the depolarisation pathways in both dogs (Scher & Young, 1956) and the isolated human heart (Durrer et al., 1970) provided Selvester and his associates with the necessary knowledge to devise computer simulations which produced vectorcardiographic loops resembling those seen in normal individuals (Selvester et al., 1965). This group simulated the human heart in a mathematical model using computer analog techniques which divided the heart into 20 segments, 4 for right ventricle, 7 for septum and 9 for left ventricle. By removing segments corresponding to necrotic areas seen in pathological studies in humans, revealed similar simulated vectocardiographic loops as seen in these patients. Later, the same group (Selvester et al., 1967) devised a digital computer model using 20 dipoles - each representing an area of the heart, and simulated vectorcardiograms of myocardial infarctions were produced. This model showed good correlation between not only the vectorcardiographic data, but also electrocardiographic data; both from the 12 lead ECG and the the total body surface map. Surface maps derived from

this model simulated those seen in normal subjects (Taccardi, 1963) even when torso and lung simulations were added (Selvester et al., 1968).

From these computer simulations, both quantititative and qualitative criteria were produced to form a 32 point scoring system to determine infarct size based on 57 criteria. Each point was designed to represent 3% of the left ventricle, and depends on Q and R wave durations, R and S wave amplitudes and ratios, the presence of late R waves and early R notches. This scoring system was devised using ECG's in a group of caucasian men aged 40-49 years. When applied to a bigger, more disparate group of normal subjects (Hindman et al., 1985) it was felt that the scoring system had to be at least 95% specific for the identification of myocardial infarction. Fifty-one out of the 57 criteria met this required standard, of the 6 that failed, 3 were modified and 3 were eliminated, leaving a 54 criteria/32 point complete system. This allowed normal subjects over the age range 20-69 to score 3 points before diagnosing myocardial infarction with 95% specificity. This low scoring in normals requires that screening criteria for diagnosis of myocardial infarction be used prior to performing a score, so that false positives are excluded. Anderson et al. (1982) have proposed such a system.

Wagner then developed and evaluated a simplified version of the above, known as the Simplified Selvester Score (Wagner et al., 1982). Qualitative data such as slurs and notches were not evaluated due to difficulties encountered in defining rules for these wave forms which could be universally applied by doctors to large numbers of ECG's. Also ignored were absolute amplitudes of wave forms due to variation in the normal population. Thirty-seven criteria taken from 10 leads (I, II, AVL, AVF, V_1 -V_6) give rise to a 29 point system and when applied to a group of 349 normal subjects, 93% scored 0 or 1 point, 5% scored 2 points, 2% scored more than 2 points and only 1 subject scored 4 points. This gives 98% specificity for diagnosing an infarct when a score of more than 2 is obtained. Of the 37 criteria, only 2 did not reach individual specificities of $\geq$95%, R/S $\leq$1.5 in V_4 achieved 92% specificity, and R/S $\leq$3 in V_5 achieved 92% specificity. These criteria were than modified to R/S $\leq$1 in V_4 and R/S $\leq$2.0 in V_5 yielding specificities of 98% and 97% respectively. This then forms the basis of the simplified scoring system which has been used in subsequent studies, and is shown in Table 5. Each criteria achieved at least 91% intra and inter observer agreement.

The above scoring system has been evaluated in various ways. Post mortem studies in patients succumbing to a first myocardial infarction with no other complicating

features such as right or left ventricular hypertrophy, right or left bundle branch block, or anterior or posterior fascicular block showed highly significant correlations between the QRS score and percentage infarction of the left ventricle r=0.8, r=0.74 and r=0.72 for anterior, inferior and posterolateral infarcts respectively (Ideker et al., 1982; Roark et al., 1983; Ward et al., 1984). The evolution of QRS scores over 3 days following the admission of 82 patients with acute inferior myocardial infarction was demonstrated by Anderson et al. 1983. This shows that 53% of the study group had a score of 0 on admission, but increased their scores over the next two days. These workers interpreted their results as meaning that Q waves evolve over 2-3 days, and suggest that interventional therapy designed to salvage myocardium may still be effective if administered after the first few hours. In this paper however there is no information made available regarding over what time scale from onset of pain the patients were admitted, and further comment regarding evolution of Q waves and QRS scores is unjustified.

Testing the hypothesis that left ventricular function depends on the extent of necrosis which in turn is dependent on the QRS score has led several groups to attempt to predict left ventricular ejection fraction using the QRS score. A summary of regression lines and

correlation coefficients for each group of workers is shown in Table 6. With the exception of de Pace et al. (1982) the regression lines are all fairly similar - this is surprising when the different methodologies, different patient groups and time scales in each study are taken into account. In particular, Seino et al. (1983) performed radionuclide ventriculography within 48 hours of admission, and related this ejection fraction to 12 lead electrocardiographs taken at 3 and 7 days, and found no correlation at 3 days, but a significant r value of -0.72 at 7 days. Left ventriculography so early in the course of myocardial infarction although previously shown to be a reasonable prognostic indicator (Shah et al., 1980) may be complicated by hypercontractility of non injured segments up until at least 5 days post infarct (Montague et al., 1986). The phenomenon of stunned myocardium may cloud the issue further. De Pace et al. (1982) performed radionuclide ventriculography at 2 weeks and correlated his result with a 12 lead ECG performed at the same time. This gave a weaker, but still significant correlation in acute infarcts (r=-0.61), but this group was unable to repeat this when studying a group of old infarcts retrospectively. Palmeri et al. (1982) in contrast followed their group of patients for at least 1 year and found better correlations which were reproducible (r=-0.88).

Unfortunately this QRS scoring system did not perform well when applied to a much bigger group of patients (n=285) two weeks following myocardial infarction (Fioretti et al., 1985). A similar correlation to that of de Pace et al. (1982) of -0.61 was determined between QRS score and radionuclide ejection fraction, but the spread of data either side of this line was large (standard error of estimate = 11%). It was concluded that the QRS score is less accurate than ejection fraction in predicting late survival following infarction.

SIMPLIFIED SELVESTER SCORE

Lead	Duration	Amplitude Ratio	Max. Points
I	Q ≥ 30 msec (1)	R/Q ≤ 1 (1)	2
II	Q ≥ 40 msec (2) Q ≥ 30 msec (1)		2
AVL	Q ≥ 30 msec (1)	R/Q ≤ 1 (1)	2
AVF	Q ≥ 50 msec (3) Q ≥ 40 msec (2) Q ≥ 30 msec (1)	R/Q ≤ 1 (2) R/Q ≤ 2 (1)	5
V1	Any Q (1) R ≥ 40 msec (2) R ≥ 40 msec (1)	R/S ≥ 1 (1)	4
V2	Any Q or R ≤ 20 msec (1) R ≥ 60 msec (2) R ≥ 50 msec (1)	 R/S ≥ 1.5 (1)	4
V3	Any Q or R ≤ 30 msec (1)		1
V4	Q ≥ 20 msec (1)	R/Q or R/S ≤ 0.5 (2) R/Q or R/S ≤ 1 (1)	3
V5	Q ≥ 30 msec (1)	R/Q or R/S ≤ 1 (2) R/Q or R/S ≤ 2 (1)	3
V6	Q ≥ 30 msec (1)	R/Q or R/S ≤ 1 (2) R/Q or R/S ≤ 3 (1)	3
			29

TABLE 5: THE 37 CRITERIA AND 29 POINT SYSTEM FOR THE SIMPLIFIED SELVESTER SCORE

Study	Correlation Coefficient	Regression Analysis Prediction of E.F. using QRS Score
Palmeri et al.	-0.88	EF = 60-3.0 x QRS Score
De Pace et al.	-0.61	EF = 45-2.0 x QRS score
Young et al.	-0.60	EF = 61-2.5 x QRS score
Roubin et al.	-0.81	EF = 66-3.3 x QRS score
Seino et al.	-0.72	EF = 60-2.2 x QRS score

TABLE 6: SUMMARY OF PUBLISHED WORK CORRELATING QRS SCORE WITH LEFT VENTRICULAR EJECTION FRACTION

1.9.2. Cardiac Infarction Injury Score (CIIS)

This score designed by Rautaharju et al. (1981) was based on 707 subjects, 387 with myocardial infarction, and 320 without evidence of infarction. A training and test group were selected and various ECG parameters examined to detect the best classifiers of infarction against non infarction. This group showed by statistical modelling that the classical criteria used in decision making from the Minnesota Code (Blackburn et al., 1960) were suboptimal and were rejected. The resulting CIIS expresses the likelihood of an infarction on a continuous scale using eight binary (single threshold), three ternary (two threshold) and four non thresholded features, each individually weighted to produce the CIIS scores. For practical visual coding of ECG's, 12 observations are made in check list fashion using 9 standard leads, II, III, AVR, AVF, V1-V5 and 2 inverted leads -AVR, -AVL which were found to improve the diagnostic accuracy of the score. The CIIS detected myocardial infarction with a sensitivity of 85%, and a specificity of 95%. It appears to perform best on infarcts that are 1 week to 1 month old, but in the group of patients who have had an infarct more than 1 year old, for a specificity of 98%, sensitivity dropped to only 80%. The authors felt that the place of the CIIS would be in large epidemiological studies to pinpoint a deterioration in the ECG due to new ischaemic events, and did not address whether it would be an accurate predictor of infarct size. Young et al. (1983) found that not only

did the CIIS not predict reliably the presence of infarction, but that there was a poor correlation coefficient between the score and the ejection fraction (r=-0.49).

1.9.3. Askenazi

In an attempt to relate changes in the 12 lead ECG with ejection fraction, this group studied 73 patients with ischaemic heart disease, all of whom underwent left ventriculography (Askenazi et al., 1978). The patients were separated into four groups (normal, anterior, inferior, and a combined anterior and inferior group) depending on the presence or absence of abnormal Q waves ($\geq$40 m.secs duration and $\geq$0.2 mV amplitude). The sum of R waves, $\sum$R was calculated from leads I, AVL and V1-V6 and the number of abnormal Q waves, nQ, determined. Separating the patients into the four groups described and calculating nQ for each ECG showed no correlation with either the basal or augmented ejection fraction. There was however a positive correlation between $\sum$R and both the basal (r=0.61) and augmented (r=0.77) ejection fraction. The highest correlation coefficient (r=0.82) was between R and the augmented ejection fraction in patients with an anterior myocardial infarction.

1.9.4. Arditti

As the 12 lead ECG has fewer leads representing the inferior aspect of the heart compared to the anterior surface, it is not surprising that Palmeri et al. (1982) found a lower degree of correlation between the simplified Selvester QRS score and ejection fraction when dividing his patients into groups according to site of infarct ($r=-0.69$, -0.87 and -0.8 for inferior, anterior and combined infarcts respectively). Arditti et al. (1985) devised a very simplified scoring system for use in inferior infarcts using only the R/Q ratio in lead II. Previous work by Schamroth (1975) had shown that the terminal R wave in lead II accurately reflects the potential of non infarcted myocardium. The patients were arbitrarily divided into those with R/Q >2 (Group 1), R/Q >1 (Group 2), R/Q $\leqslant 1$ (Group 3). The relation of these groupings to left ventricular ejection fraction was assessed both by radionuclide ventriculography and echocardiography. The mean lead II R/Q ratio for each of the groups is as follows: Group 1, 7.22 ± 4.81, Group 2, 1.27 ± 0.26, and Group 3, 0.12 ± 0.17. This difference between groups significant at the 0.1% level. Patients in Group 1 had a low wall motion score of 1.5 ± 1.4, and a normal left ventricular ejection fraction (LVEF) ($60.2 \pm 8.9\%$). Group 2 had a higher wall motion score of 5.25 ± 2.44 ($P<0.001$ vs Group 1) and a lower LVEF ($51.2 \pm 16.5\%$ NS vs Group 1) and Group 3 had the highest wall motion score of 6.16 ± 2.54 ($P<0.001$ vs Group 1 and

P<0.05 vs Group 2) and a low LVEF of 51.5 ±9.4% (NS vs Group 2, but P<0.005 vs Group 1).

Although extremely simplistic in approach and quick to perform, the scoring system would appear to be really only useful in placing patients into relatively wide groupings which may have prognostic implications, but does not allow a definite estimate of an individuals ejection fraction or infarct size.

1.9.5. Frank Lead Orthogonal Electrocardiograms

Various groups have used the Frank lead system of XYZ to develop scores which would relate to left ventricular function. Howard et al. (1976) concluded that the vectorcardiogram is superior to the electrocardiogram in the diagnosis of obstructive coronary artery disease and left ventricular contraction abnormality. Gottwik et al. (1978) showed that Q and R voltages from leads XY and Z provided information leading to an accurate estimation of ejection fraction, but this work was later refuted (Luwaert et al., 1983; Young et al., 1983). As vectorcardiography is not performed routinely in patients being admitted to Stobhill, the advantages and disadvantages of such a technique are not further discussed here.

1.9.6. Conclusion

Of all the scoring systems discussed, that of Selvester modified by Wagner seems to have been most intensively studied and validated, both with respect to pathologic infarct size, left ventricular function following myocardial infarction and most recently has been shown to be of prognostic value in patients with coronary artery disease (Bounous et al., 1988).

CHAPTER 2 - GENERAL METHODOLOGY

2.1 INTRODUCTION

This chapter describes the Coronary Care Unit at Stobhill General Hospital, and the facilities which have been developed to enable thrombolytic therapy to be administered and angiography to be performed early in the course of acute myocardial infarction. Protocol design is discussed with special reference to inclusion and exclusion criteria, and the various studies which have provided the patient and electrocardiographic data which form the work of this thesis are described. Details concerning the collection of electrocardiographic data are given.

2.2. CORONARY CARE UNIT AND DIRECT ADMISSION POLICY

Stobhill General Hospital provides the cardiological services for the North-East portion of Glasgow and serves a population of 220,000. The Coronary Care Unit has six beds and is situated geographically in the middle of the Medical block. Between 800 and 900 patients are admitted annually. The Coronary Care Unit operates a direct admission policy for General Practitioners which facilitates the early admission of patients with suspected acute myocardial infarction. The admission of patients via a "back-door" leading directly to the Coronary Care Unit, and therefore bypassing Casualty, reduces the intra-hospital delay. Patients admitted this way have a

clinical history, examination and ECG performed in an adjacent assessment area, and are then admitted to the Coronary Care Unit or to a General Medical ward, as considered appropriate by the Coronary Care Registrar.

To further reduce the delay between onset of symptoms and admission to Coronary Care, a direct telephone link which bypasses the hospital switchboard was established at the beginning of 1987. The General Practitioners in the area had previously identified getting through to the hospital switchboard, with subsequent referral calls, both to Casualty and the medical receiving team, as time consuming. Letters with the direct telephone number prominently displayed were circulated to practices within the Stobhill catchment area. A General Practitioner using the direct line calls through to the Coronary Care Unit, a nurse on duty takes the details and accepts the referral, letting the medical staff know of the imminent admission. The impact this method has had on the suitability of patients for thrombolysis has been reported by Burns et al. (1989). The direct telephone link with a back-door admission policy reduced the delay by a mean of 55 minutes, doubling the number of patients admitted within a 3 hour time window.

2.3. ACUTE ANGIOGRAPHY

The admission assessment area is also used as a procedures room, allowing coronary angiography to be performed within the Coronary Care Unit. There are no other catheterisation facilities at Stobhill, routine investigational work is performed at Glasgow Royal Infirmary. The methodology used at Stobhill to enable acute angiography to be performed could be translated to every District General Hospital at very little extra cost. The Stobhill system and one year's experience with it's use has been previously published (Hillis et al., 1986).

A mobile x-ray image intensifier with a television display (Siremobil 2N/2H) was already used for the insertion of temporary pacemakers. It has a circular arm, allowing rotation about the horizontal axis, enabling the standard angiographic views to be performed. To visualize the right coronary artery a 60^{o} LAO and 30^{o} RAO are performed, and for the left anterior descending and circumflex arteries, a 10^{o} RAO, 30^{o} RAO and 60^{o} LAO are routinely taken. Linking this unit to a heavy duty video cassette recording system (JVC CR-8200E) allows permanent recording of coronary arteriograms and left ventriculograms.

Each angiogram is performed by a consultant aided by a registrar. The Coronary Care nursing staff assist with the procedure, usually one nurse at staffing level or above being present. Screening with the image intensifier

is provided by a radiographer, and an ECG technician is present to record pressure tracings.

A conventional Seldinger technique is used, and a no.7 sheath (Hemaquet, USCI International) inserted. Following acute angiography, this sheath is flushed with heparin and left in situ for 24 hours, allowing, in some instances a second arteriogram to be performed 24 hours after therapy. The sheath is removed once the coagulation has returned to normal. Antibiotics (cephalexin 500 mg tid) are given as prophylaxis over the time of the sheath being in situ.

2.4. CLINICAL TRIALS

Stobhill Coronary Care Unit has been active in administering thrombolytic therapy under the direction of Dr. W.S. Hillis since 1982. Up until November 1988, none of the lytic agents were licensed for treatment in acute myocardial infarction, and their use prior to this time necessitated administration according to the guidelines of approved clinical trials. All trials conducted in Stobhill Coronary Care Unit and referred to in this thesis were approved by the local research and ethical committee.

Thrombolytic therapy is administered under the responsibility of the Consultant Cardiologist on duty for Coronary Care. Two or three Registrars/Research Fellows are on call to assess patients, obtain informed consent,

and administer treatment, as well as to participate in acute angiography and the taking of blood for research purposes. I have personally been involved in such a rota since August 1984. This system provides 24 hour cover, 7 days a week. A previous report by Hillis et al. (1986) showed that 40% of acute infarcts were admitted outwith the normal working hours of 9 am to 5 pm. Patient recruitment is thus maximised. Radiography, ECG and audiovisual services also provide an on call system, facilitating emergency out-of-hours angiography.

2.4.1.Patient Selection

All patients presenting to the Coronary Care Unit with a suspected diagnosis of acute myocardial infarction are considered for thrombolytic therapy if they have the following criteria:-

1) onset of cardiac pain of $\geq$30 minutes duration and $\leq$6 hours by time of admission to the Coronary Care Unit.
2) confirmatory electrocardiographic evidence of myocardial infarction (ST elevation $\geq$1 mm in at least 2 standard limb leads or 2 mm ST elevation in at least 2 precordial leads).

Exclusion criteria are chosen to avoid the known potential side-effects of lytic agents. Thus, although details may vary from protocol to protocol, exclusion criteria precluding entry to thrombolytic trials are as follows:

1) cerebrovascular disease
2) documented or suspected active peptic ulceration within the past 6 months
3) history of bleeding diathesis
4) extreme hypertension (i.e. >200/120 mmHg)
5) severe renal or hepatic disease
6) menstruating or potentially pregnant females
7) prolonged cardio-pulmonary resuscitation or insertion of central venous lines via the subclavian route prior to treatment
8) proliferative diabetic retinopathy

In trials requiring emergency angiography, a further exclusion criteria would be if the patient had severe peripheral vascular disease, although this does not per se constitute an absolute contraindication to thrombolytic therapy.

Informed consent was obtained in all patients, and the procedure explained to accompanying relatives where possible. An example of the patient information sheet and accompanying consent form are shown at the end of appendix I. Description of individual trials providing the database for this thesis are attached below..

2.4.2. Intracoronary Streptokinase Trial

Patients were recruited for this trial conducted in an open fashion between December 1981 and March 1983. Patient selection was according to criteria already outlined. Acute angiography was performed and the obstructed artery visualized. Isosorbide dinitrate (2 mg) was administered into the coronary artery to relieve spasm. Prior to the intracoronary infusion of streptokinase, 100 mg hydrocortisone and 10 mg chlorpheniramine were administered intravenously. Streptokinase was then infused selectively or sub-selectively in a dose of 250-500,000 units over 30-45 minutes. The presence or absence of reperfusion was determined visually at the end of the procedure. In some cases mechanical perforation of the thrombus was performed. Patients were returned to the Coronary Care Unit following this procedure, and subsequently heparinized.

2.4.3. Intravenous Anistreplase Trial

The aim of this study, performed in an open fashion, was to determine a patency rate following a dose of anisoylated plasminogen streptokinase activator complex (30 U anistreplase). Patients were recruited according to the criteria already defined. After informed consent was obtained from each patient, 30 U anistreplase was infused through a peripheral line over 5 minutes. Hydrocortisone 100 mg, and 10 mg chlorpheniramine were given

prophylactically in each case. Coronary angiography was carried out at 90 minutes following therapy, although was postponed if the patient's haemodynamic status or cardiac rhythm was unstable. Pre-treatment angiography was not performed, and therefore it is a patency rate and not a reperfusion rate which is derived. Following successful thrombolysis, the patients were anticoagulated using heparin and warfarin. The results for 94 patients have previously been reported (Hillis et al., 1987).

2.4.4.Streptokinase/Anistreplase Comparison

This is a double-blind randomised protocol, designed to assess any differences in patency rates between 30 U intravenous anistreplase and 1.5 million I.U. intravenous streptokinase in patients ⩽70 years old with an acute myocardial infarction of less than 6 hours duration. One hundred and twenty eight patients were recruited, and the study ran between April 1987 and December 1988. Coronary angiography was performed at 90 minutes and again at 24 hours utilising the femoral sheath which had been left in situ. A full protocol description is listed in appendix I.

2.5. ELECTROCARDIOGRAPHIC DATA COLLECTION

12 lead ECG's are performed in the Coronary Care unit by nursing staff trained in electrocardiography. The tracings are performed during quiet respiration in the semi-supine position with the back rest at 20^{o} from the horizontal. The standard chest positions are marked on admission to Coronary Care with an indelible marker to ensure reproducibility (Table 7). All ECG's are performed using a Hewlett Packard Page Writer Cardiograph (Model 4700A) which provides a one-page recording. Each ECG is marked with a calibration signal (10 mm = 1 mV), lead annotation, lead switching marks and the recording speed. Diagnostic 12 lead ECG's are always recorded at 25 mm/sec. Multiple leads are acquired simultaneously from the patient in standard lead groups (i.e. I, II and III, AVR, AVL and AVF, V_1, V_2, V_3 and V_4, V_5, V_6). These lead groups are smoothly switched, providing continuous rhythm across the 10 second record. A continuous lead II is recorded along the bottom of the tracing. The machine has a memory function which provides exact duplicates of the recording, allowing copies to be stored in nursing proformata, case record forms, and to be used for research purposes.

Bipolar leads

I	Derived from electrodes on the right arm and left arm
II	Derived from electrodes on the right arm and left leg
III	Derived from electrodes on the left arm and the left leg

Unipolar leads

AVR	Augmented unipolar right arm lead
AVL	Augmented unipolar left arm lead
AVF	Augmented unipolar left leg lead
V_1	Fourth intercostal space to right of sternum
V_2	Fourth intercostal space to left of sternum
V_3	Midway between V_2 and V_4
V_4	Mid clavicular line over 5th intercostal space
V_5	Anterior axillary line at same level as lead V_4
V_6	Mid axillary line at same level as leads V_4 and V_5

TABLE 7: STANDARD LEAD PLACEMENTS FOR 12 LEAD ELECTROCARDIOGRAPHY

CHAPTER 3

USE OF THE ST SEGMENT AS A NON INVASIVE MARKER OF REPERFUSION

3.1. LITERATURE REVIEW

Since Pardee (1920) described ST segment elevation as a feature of acute coronary occlusion, many experimental and clinical studies have attempted to use this functional electrocardiographic marker as an index of ischaemic injury, and to assess the efficacy of pharmacological interventions to reduce myocardial infarct size such as the administration of beta-adrenoceptor blocking compounds (Gold et al., 1976) and hyaluronidase (Maroko et al., 1977). With the first reports of intracoronary thrombolysis came the observation that reperfusion was accompanied by rapid resolution of ST segment elevation (Rentrop et al., 1981; Mathey et al., 1981). Ganz et al. (1981) showed resolution of ST segment elevation back to baseline occurring over a 2 hour period from time of reperfusion. However, these trials were all uncontrolled and were descriptive rather than quantitative. Interpretation of subsequent papers is made somewhat difficult due to variation in methodology. The rapid sequential change in ST segments occurring with reperfusion has been demonstrated by either standard electrocardiography or multilead precordial mapping systems in an angioplasty setting (von Essen et al., 1985). Differing conditions between trials leaves the area somewhat confused.

The first two controlled trials to be reported in 1983 were in agreement. Anderson et al. (1983) in his randomised study of intracoronary streptokinase showed that by summing the ST segment elevation in all infarct leads, or by using a single lead (maximal ST segment deflection), that these measurements were similar in both groups prior to treatment, but there was a significant fall in the streptokinase treated group over a period of 3 to 6 hours ($p<0.01$). Blanke et al. (1983) confined his study to anterior infarctions and measured $\sum$ST elevation in leads V1-V6. Twelve lead electrocardiograms were performed prior to coronary angiography and at a mean of 3, 12, 24 and 48 hours following angiography. $\sum$ST V1-V6 was not different between the groups prior to treatment, but after intracoronary streptokinase the treated group showed a mean fall of some 60% at 3 hours, compared with only 13% in the control group. There remained a difference in $\sum$ST V1-V6 between the two groups even at follow up. However, their results show very wide standard deviations, suggesting wide inter-patient variability.

These results were in contrast to the work of Timmis et al. (1982) who described ST segment changes in their group of patients given intracoronary streptokinase. Using a single lead with maximal ST segment elevation they showed an almost identical change post infusion (from approximately 0.29 mv to 0.2 mv) irrespective of whether the patient had reperfused (n=27) or not (n=8). The

values for the control group were not given, and measurements were made immediately following streptokinase infusion. Similarly Ross, (1985) reporting on behalf of the TIMI group stated that by monitoring ST segment elevation (mean of 2 contiguous leads showing injury) it was impossible to identify patients who had achieved succcesful clot lysis from those who had not.

A further method of looking at ST segment change is to use an on-line mapping system with several precordial leads (von Essen et al., 1985). Although this group reported on this technique to detect recurrent ischaemia in patients receiving thrombolytic therapy, and its use during angioplasty, its main use was to monitor R waves to determine myocardial salvage. This same group found that by measuring "ST shift", (the summation of ST elevation and depression in limb leads I, II and III), this gave a simple electrocardiographic index which helped identify reperfusion. In 43 out of 56 patients the infarct-related artery was recanalised, and the summated ST shift decreased from a mean of 0.68 ± 0.32 mV pre treatment to 0.09 ± 0.12 mV post treatment. In 13 patients who did not achieve reperfusion, the ST shift was 0.44 ± 0.29 mV pre treatment and 0.44 ± 0.36 mV post treatment. Again standard deviations are large and suggest prediction of reperfusion on an individual basis may be difficult.

The studies described above are primarily observational, and it was Krucoff et al. (1986) who first attempted to use the change in the ST segment on a predictive basis to identify reperfusion. The method they used was continuous ST segment monitoring by Holter tapes, and the measurement they made was the time to ST "steady state" which was defined as "the first 30 minutes when the ST level was equally or less deviated than the final steady state level". In 19 out of 36 patients who reperfused (after intracoronary streptokinase) the ST steady state was achieved at a mean of 55$\pm$32 minutes, and in patients who did not reperfuse, the mean time to steady state was 211$\pm$141 minutes. Achievement of steady state within 100 minutes after streptokinase indicated successful reperfusion with 89% sensitivity and 82% specificity.

Prediction of reperfusion on an individual non-invasive basis would seem desirable as the intravenous route for administration of thrombolytic therapy increases. Which of the different methodologies described above would be most accurate is not yet known. From previous work, the 12 lead ECG has been shown to be more useful than anterior precordial mapping in diagnosing and following serial changes in patients having sustained an inferior myocardial infarction (Madias et al., 1975). Leinbach et al. (1978) further confirmed that both the rate and degree of ST segment fall could be followed accurately by single leads reflecting the zone of maximum ECG injury. Using

conventional 12 lead electrocardiograms is attractive as they are widely available and easily applicable within the community and district hospital settings. Disadvantages with this technique is that the ST segment may be altered by factors other than coronary occlusion, such as pericarditis (Thadani et al., 1971), metabolic abnormalities including hyperkalaemia (Levine et al., 1956) and where repolarisation abnormalities due to development of bundle branch block may not reflect ischaemia (Sodi-Pollares et al., 1963). The use of a ventricular pacemaker will also invalidate ST segment analysis.

3.2. AIM OF STUDY

The aim of this study was to analyse ST segment changes using both the 12 lead electrocardiogram and Holter monitor in patients during thrombolysis, with a view to detecting a simple, sensitive, widely applicable technique to detect successful reperfusion non invasively.

3.3. PATIENTS AND METHODS

Forty-five patients were studied, age range, 39-75 years, mean age 58.5 years. Twenty-three anterior infarctions (18 M, 5 F) and 22 inferior infarctions (16 M, 6 F) were included with a mean time to admission following onset of

pain of 2.7±1.6 hours. All patients were treated within 6 hours of symptom onset. Individual patients details are shown in appendix II.

Thrombolytic therapy was given according to the current Coronary Care protocol. Seventeen patients received streptokinase by the intracoronary route, and 28 received intravenous anisoylated plasminogen streptokinase activator complex (anistreplase 30U). The division of patients into these groups was purely temporal, and not affected by clinical severity on admission. Inclusion and exclusion criteria and protocol design for both treatment groups are described in Chapter 2 and will not be further discussed here.

3.4. ECG ANALYSIS

3.4.1. HOLTER Monitoring

On admission to the Coronary Care Unit, 24 hour continuous ECG monitoring was commenced using an Oxford Medilog II system. The ECG electrodes were placed in a modified V5 position. The tapes were analysed using a Reynolds Medical Pathfinder with an ST segment trend analysis. ST segment elevation was measured as a pre treatment control value, M_1, and a second value, M_2, was made 2 hours following intracoronary and 3 hours following intravenous thrombolytic therapy. The post therapy value was calculated as a proportion of the control value and this index was expressed as the "Fractional Change". If

complete reversal of ST segment elevation occurs, then the Fractional Change value becomes 1 or a number near to 1 (Fig. 4a). If the ST segment remains elevated to the same degree, the Fractional Change value will be zero or a number near zero. If increased ST segment elevation occurs due to infarct extension, then the Fractional Change value will become negative (Fig. 4b).

3.4.2. 12 Lead Electrocardiograms

Conventional 12 lead electrocardiograms were performed on admission, and at a mean of 302±141 min following admission. The lead with most ST segment elevation was identified and taken for serial analysis. Measurements were made manually with calipers and ST segment elevation was measured at the J point taking the PR segment as the isoelectric line. The Fractional Change was calculated in the same way as detailed for the Holter Monitor. In both groups of ECG data, the calculation of Fractional Change was performed by one observer (the author) blindly, without knowledge of the angiogram results.

3.5 STATISTICAL ANALYSIS

Linear discrimination was performed on an ICL2980 main frame computer using the programme BMDP (P7M) (Brown, 1977). The patients were randomly subdivided using a random numbers generator into two groups, one a training group for devising a rule, and a second test group for checking the rule.

Sensitivity measures the ability to detect true cases which have reperfused, and is expressed by the number of reperfusions detected on non invasive grounds as a percentage of angiographically documented reperfusions. Specificity measures the ability to detect true cases which have not reperfused, and is defined by the number of true non reperfusions determined on non invasive grounds as a percentage of angiographically determined non reperfusions e.g.

$$\text{Sensitivity} = \frac{\text{Number of true reperfusions (by ECG criteria)}}{\text{Total No. of true reperfusons (by angiography)}} \times 100\%$$

$$\text{Specificity} = \frac{\text{Number of true non reperfusions (by ECG criteria)}}{\text{Total No.of non reperfusons (by angiography)}} \times 100\%$$

3.6 RESULTS

Analysis was performed on ECG recordings obtained in 39 subjects, 6 were excluded from analysis. In 4 patients there was incomplete collection of data due to technically inadequate Holter Monitor tapes, 1 subject had left bundle branch block precluding ST segment interpretation, and 1 patient had inadequate visualisation of the coronary arteriogram. The remaining 39 patients were randomly split into a training group (n = 22) and a test group (n = 17). Figure 5 shows scatter diagrams of Fractional Change results for these two groups, both for Holter tapes and 12 lead ECG's. The coronary arteriographic patency rate was high (79.5%). As ST segment elevation is not completely reversed following coronary artery reperfusion, several arbitrary values of ST segment reduction were examined including 0.25, 0.5 and 0.75. A Fractional Change value of ≥ 0.5 appeared most useful in separating those cases who had reperfused from those who had not. Table 8 gives the specificity and sensitivity for detecting reperfusion using this technique applied both to training and test groups. Using the Fractional Change derived from the Holter tape gave 100% specificity, both for the training group and for the test group. Sensitivity was also high at 88% and 93% respectively. Using the Fractional Change derived from the 12 lead ECG resulted in 100% specificity for the training group but only 67% specificity for the

test group. This fairly large drop actually reflects the small numbers of non reperfusions in the test group (n=3) and the fact that only one was misclassified. Sensitivity remained high at 94 and 93% respectively.

Linear discrimination was then employed using a BMDP programme to devise a rule which would lead to maximum separation of the two groups i.e. reperfusions and non reperfusions. This programme utilised the following electrocardiographic parameters as variables: FCH (Fractional Change with Holter monitoring), FC (Fractional Change with 12 lead ECG), M_1 (height of ST segment on admission) and M_2 (height of ST segment following therapy). From these the following classification functions were derived for the training group:-

1) Using FCH

$$\text{Reperfusion} = -3.31 = (2.42 \times \text{FCH}) + (1.45 \times M_1) - (1.36 \times M_2)$$

$$\text{Non reperfusion} = -8.48 - (4.74 \times \text{FCH}) - (1.03 \times M_1) + (3.72 \times M_2)$$

2) Using FC

$$\text{Reperfusion} = -2.80 + (1.21 \times \text{FCH}) + (1.28 \times M_1) - (0.87 \times M_2)$$

$$\text{Non reperfusion} = -7.01 + (-3.09 \times \text{FCH}) - (0.57 \times M_1) + (2.64 \times M_2)$$

To use these classification functions, the Fractional Change value (either from 24 hour tapes or 12 lead ECG's) and the height of the ST segment on admission and following therapy must be known. These values are inserted in the appropriate formula, both for reperfusion and for non reperfusion and whichever value is greater designates the group to which the patient belongs. Thus, for a patient with a FCH of 0.65, M_1 = 3.5 and M_2 = 1.7, the values of 1.03 and -8.84 are calculated for the reperfusion and non reperfusion classifications respectively. As 1.03 is greater than -8.84, these findings are consistent with reperfusion on non invasive grounds.

Using this form of discriminant analysis resulted in complete correct separation of the two groups in the training group (sensitivity 100%, specificity 100%) with sensitivity being maintained when applied to the test group, but the specificity dropping to 33% only. This dramatic fall in specificity is explained somewhat by the small numbers in the test non reperfusion group (n = 3) and the fact that only one of the non reperfusions was correctly identified.

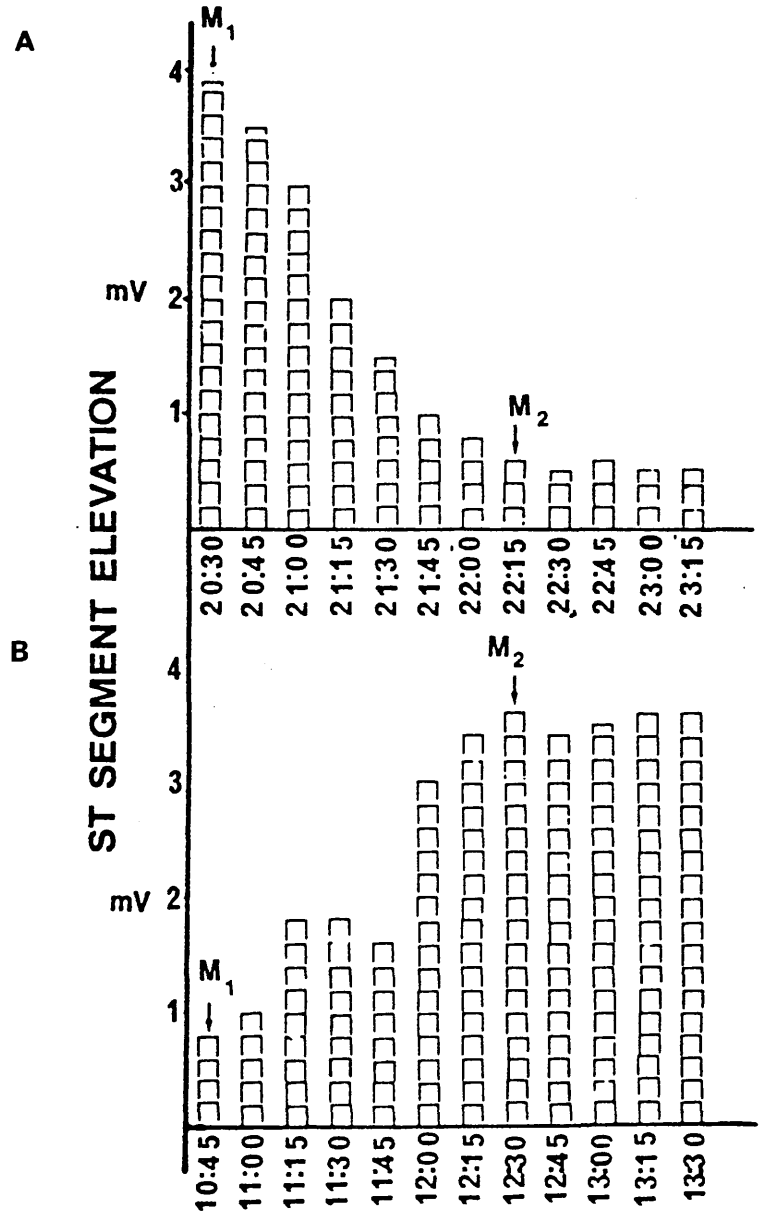


FIGURE 4: CALCULATION OF FRACTIONAL CHANGE FROM HOLTER MONITOR RECORDINGS. Typical examples of ST segment analysis from Holter Monitor recordings in patients receiving intracoronary thrombolysis, in a successful reperfusion A, and a non reperfusion B. Real time is represented on the X axis in 15 minute intervals. Measurement M1 is made on admission prior to treatment and M2, 2 hours post treatment. The Fractional Change value is calculated using the formula M1-M2 - M1 and therefore the Fractional Change value for A is (3.9-0.6) - 3.9 = 0.85 and the Fractional Change value for B is (0.8-3.6) - 0.8 = -3.5.

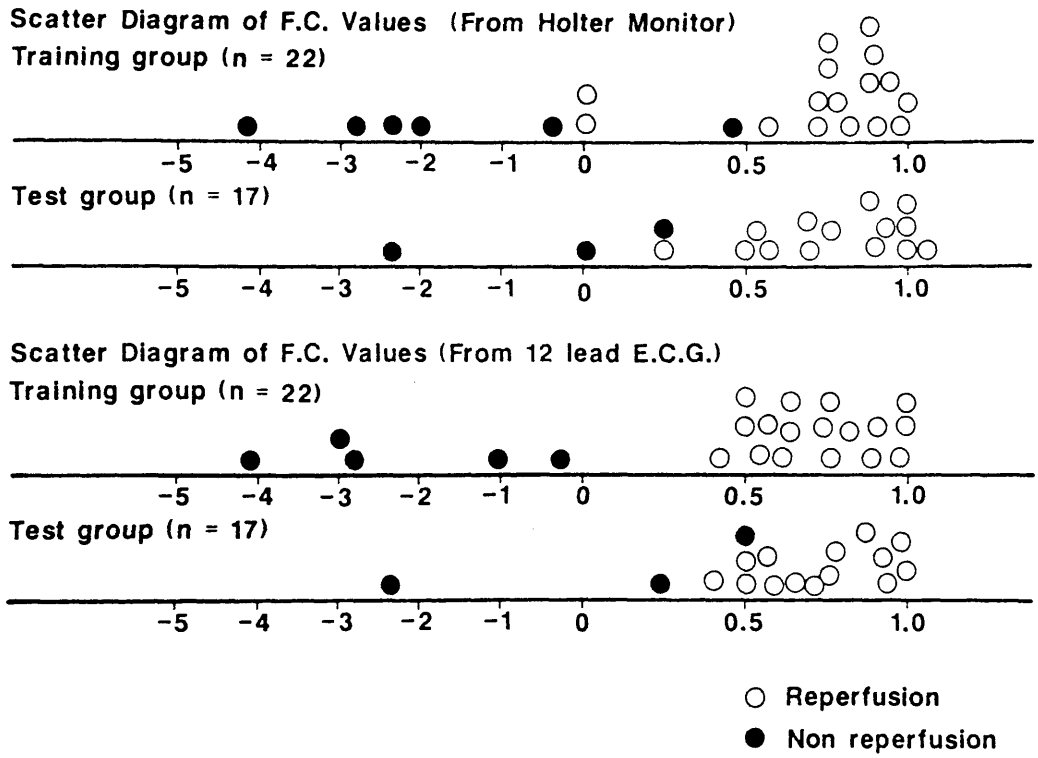


FIGURE 5: SCATTER DIAGRAMS OF FRACTIONAL CHANGE VALUES BOTH FOR HOLTER MONITOR AND FOR 12 LEAD ECG

ECG Parameter		Specificity %	Sensitivity %
FCH	Training Group (n = 22)	100	88
	Test Group (n = 17)	100	93
FC	Training Group (n = 22)	100	94
	Test Group (n = 17)	67	93

FCH - Fractional Change calculated from Holter Recording

FC - Fractional Change calculated from 12 lead ECG

TABLE 8: SPECIFICITY AND SENSITIVITY OF USING A FRACTIONAL CHANGE VALUE OF ≥ 0.5 TO DENOTE REPERFUSION

3.7 DISCUSSION

These results confirm the usefulness of ST segment analysis as a non invasive predictor of coronary artery patency following thrombolytic therapy in patients with acute myocardial infarction. This technique can identify patients who may require further pharmacological regimes to prevent coronary artery reocclusion, or who may require subsequent invasive investigation with a view to performing coronary angioplasty or bypass surgery for residual arterial stenoses. Of interest is the fact that a simple rule of a Fractional Change value of ≥ 0.5 denoting reperfusion is more specific, but not as sensitive as using the more complex classification functions derived from linear discrimination. This Fractional Change Value of 0.5 (or 50%) compares well with the percentage change in ST segments of >55% reported by von Essen et al. (1985) occurring over the first hour in all patients achieving reperfusion following intracoronary streptokinase. Blanke et al. (1983) reported a mean fall of 60% in ST segment levels in his treatment group over the same time period as we studied. The work presented in this chapter confirms that a change in the ST segment measured in a single lead of $\geq$50% within 3 hours of thrombolytic therapy is associated with reperfusion.

The Fractional Change derived from the Holter monitor was more specific, but not quite as sensitive when compared to the Fractional Change calculated from the 12 lead ECG. The lack of sensitivity was due to 2 patients scoring a Fractional Change Value of zero while angiography had shown them to have reperfused. These 2 patients had inferior myocardial infarction, and it may be that the standard lead positions used may have been inadequate to show myocardial injury in the inferior wall of the heart.

The results of this study suggest that the simple calculation of the Fractional Change derived from ST analysis of a single lead showing injury either by continuous ECG monitoring or the 12 lead ECG gives a value which is of predictive use to determine whether reperfusion has occurred or not.

Continuous electrocardiographic monitoring has the advantage of incorporating a computerised assessment of the ST segment change with less subjective variability, although it is more complex and time consuming to analyse. The 12 lead ECG can be used quickly for bed-side assessment which becomes important when clincal decisions regarding further management and drug regimes are being decided.

The method of choice for clinical application depends on acceptable values of sensitivity and specificity. These levels may change depending on the purpose for which they are being used. Following successful coronary artery reperfusion, reocclusion has been reported in up to 40% of cases. Pharmacological regimes have recently been developed to prevent reocclusion. A test with a high sensitivity of detecting reperfusion will be of value in deciding which patients require specific follow on therapy. Comparison of reperfusion rates following administration of different thrombolytic agents would require a high specificity. While an attempt has been made to validate the rule by using a training and test group, the small sample sizes that this technique generates leads to wide errors in estimation of confidence intervals for sensitivity and specficity, and the application of these results to large population groups is required.

Coronary artery reperfusion can ony be definitively shown by coronary angiography, and in those patients treated by intracoronary infusion, the time of reperfusion was confirmed during the invasive procedure. In those cases treated by the intravenous route, no pre-treatment angiogram was performed, but the patency was confirmed angiographically within the time-scale during which the ECG's were performed. Although some of these patients may not have a total occlusion at the time of their

presentation (de Wood et al., 1980), all patients had the same clinical and electrocardiographic entry criteria, and presumably had critical reductions in coronary artery flow at time of presentation.

The methodology has shown no difference between the results obtained with different thrombolytic compounds, being similar with both conventional streptokinase and anistreplase. This suggests that this functional marker reflects the consequences of obtaining adequate coronary artery perfusion rather than a specific action of an individual compound, and is therefore applicable to the assessment of other pharmacological agents such as tissue plasminogen activator and urokinase.

The high percentage of patients in the non reperfusion group who showed an increase in ST segment elevation resulting in a negative Fractional Change raises the question of whether this may reflect reocclusion rather than just non-reperfusion. By definition, reocclusion requires that the vessel initially reperfused, and this would be represented by a biphasic curve in the ST segment printout. Over the time window examined no patient demonstrated this phenomenon, and in addtion, no patient had recurrence of chest pain to suggest reocclusion. Application of this technique may however be useful if studied over a longer time period.

In summary, Fractional Change can be obtained from a single lead using Holter Monitoring techniques or from 12 lead ECG's utilising the lead most indicative of myocardial injury. It appears to be a useful non invasive marker of treatment outcome, and a value of ≥ 0.5 predicts a patent artery within the time-scale of this study. Using a more sophisticated classification function, will increase sensitivity at the expense of specificity. Future work may derive classification functions with better discriminatory power by adding additional variables such as creatine phosphokinase release or the presence or absence of reperfusion arrhythmias.

Criticism of this study arises from the relatively small numbers involved, especially those who do not reperfuse. The usefulness of a Fractional Change measurement to detect reperfusion non invasively needs to be tested prospectively in a larger patient group.

CHAPTER 4

ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL SALVAGE FOLLOWING THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

4.1. LITERATURE REVIEW

Having shown the ST segment to be a dynamic functional marker reflecting change in ischaemia or reperfusion, the next step was to investigate if Q and R wave amplitude changes, considered to be the electrocardiographic markers of necrosis, would reflect the degree of myocardial damage following thrombolysis. Work by Blumenthal et al. (1975) and Beller et al. (1977) looking at experimental occlusions with subsequent reperfusion, suggested that the development of these electrocardiographic markers may lag behind the anatomical evidence of necrosis. Ganz et al. (1981) suggested that the evolution of Q wave formation and R wave loss was "perfusion-dependent". This classic paper shows accelerated development of Q waves associated with diminution of the R wave, 20 minutes following reperfusion in a dog model and 2 hours following reperfusion in a patient study. These workers suggested that had reperfusion not occurred, then these changes would have taken very much longer to evolve. This rapid evolution of ECG changes following reperfusion was confirmed by Goldberg et al. (1983b). Thus, somewhat paradoxically, reperfusion is thought to accelerate ECG changes of necrosis, the hypothesis being that the total amount of Q wave development and R wave diminution is reduced.

Several studies have sought to prove this hypothesis, and similar to the results with ST segment changes, not all are in agreement. Direct comparison between studies is complicated by differing methodologies and patient treatment groups. Blanke et al. (1983) looked only at anterior myocardial infarction, and measured the sum of R waves($\sum$R V1-V6), and the number of Q waves (nQ V1-V6) on the 12 lead ECG in patients receiving intracoronary streptokinase and in a control group. There did not appear to be an early accelerated change in $\sum$R V1-V6 or nQ V1-V6 in the treatment group, the changes seen parallelling those in the control group. However, after 12 hours $\sum$R V1-V6 increased in the streptokinase group along with a reduction in nQ V1-V6. The control group values did not change. This partial regrowth in R waves following reperfusion has also been described by Goldberg et al. (1983) and in patients with acute myocardial infarction not receiving interventional therapy by Montague et al. (1986). This latter paper emphasizes the need for controlled studies.

Anderson et al. (1983) showed a significant difference in relative R wave loss between controls and patients given intracoronary streptokinase 10 days after treatment. The streptokinase group also showed a significant reduction in nQ at day 1 and day 10. When this group reported their randomised trial of intravenous and intracoronary streptokinase a year later (Anderson et al., 1984) they

were able to confirm a significant attenuation in R wave loss following treatment (compared to historical controls) but were unable to show any difference in Q wave evolution.

Following the evolutionary changes in a single lead showing maximum ST segment shift, Timmis et al. (1982) were unable to show any significant difference in Q or R waves following intracoronary streptokinase regardless of whether or not the patient achieved successful recanalization. This assessment was made within 1 day. When the same group looked at "minimaps" (I, AVL, V1-V6 for anterior infarcts, II, III, AVF for inferior infarcts) prior to discharge, they were able to show a trend to a smaller $\sum Q$ and slightly greater $\sum R$ if recanalization was sustained in anterior infarcts in comparison to patients in whom streptokinase had failed or in controls. None of these changes were statistically significant, and indeed the control group of inferior infarcts appeared to show greater R wave preservation.

Von Essen et al. (1985) limited their study group to patients with anterior myocardial infarction and performed a 48 electrode map immediately following the administration of intracoronary streptokinase (patients treated within 8 hours) and again at 4-6 months. Vessel patency was assessed angiographically, and the patients

divided into 4 subgroups; Group A - incomplete occlusion at initial angiography, Group B - successful persistent reperfusion, Group C - successful reperfusion with subsequent reocclusion and Group D - non reperfusion. They were able to show a significant increase in $\sum R$ between early and late maps in Groups A and B, a decrease in $\sum R$ for Group C and no significant change for Group D (Table 9).

These studies suggest that achieving reperfusion (either spontaneous or following intervention) does result in accelerated evolution of the ECG which then undergoes a dynamic change, reflecting what is thought to be myocardial salvage. The time for this change to occur is not clear, and would seem to be temporally unrelated to any measured change in left ventricular function, or indeed mortality data. As with the ST segment literature, absolute changes in R and Q waves are small and standard deviations are large.

A single measurement encompassing all R and Q wave data from a 12 lead ECG would be of use in monitoring those changes occurring following treatment. The simplified QRS score designed by Wagner et al. (1982) and further assessed in post-infarction patients by Palmeri et al. (1982) is based on R and Q wave amplitudes and durations.

This scoring technique is fully discussed in Chapter 1. Published studies using this score in thrombolytic trials give conflicting results.

Koren et al. (1985) studied 53 patients given intravenous streptokinase, and showed that there was no difference in QRS score irrespective of whether the infarct-related artery was reperfused or not (7.5±5.6 vs 5.2±3.4 NS). It was only when this group examined the influence of time to treatment, and re-divided the patients into those receiving therapy within 1.5 hours and from 1.5-4 hours, were they able to show a significant attenuation of the QRS score in the group treated early (5.6±4.9 vs 8.6±5.5, $p<0.01$). Distinction was not made between site of infarct and 21% of the patients in the early group had non Q wave infarctions, compared to 9% in the late group. Pre-treatment angiography was not performed, and the incidence of incomplete occlusion is not known.

Comparison between QRS scores in patients with reperfusion, and those without were published a year later by Mikell et al. (1986). 131 patients were included, 100 of which reperfused. The QRS scores were not different between the two groups (6.0±3.2 vs 6.4±4.2) despite a significant higher ejection fraction being recorded in those that reperfused (53± 13% vs 46±15%, $p<0.05$). The ECG sampling time was not fixed in this study, occurring at a mean of 4.9±7 days post treatment.

Despite earlier work which suggests there is a reduction in Q wave formation, and an increase in R wave amplitude following successful treatment with thrombolytic therapy, there is no convincing evidence that these changes can be translated into significant reductions in the simplified QRS score, which in turn can relate to left ventricular function.

Gp	n	$\sum$R (mV) Post SK	4-6 months	P value
A	11	18.1	23.2	0.04
B	25	12.4	16.2	0.006
C	8	14.0	9.8	0.003
D	10	11.8	10.7	NS

Group A = incomplete occlusion

Group B = reperfusion

Group C = reperfusion followed by reocclusion

Group D = non reperfusion

From von Essen et al. (1985)

TABLE 9: RESULTS OF $\sum$R FROM 48 LEAD PRECORDIAL MAPS FOLLOWING STREPTOKINASE.

4.2. AIM OF STUDY

This study investigates the sequential changes occurring in conventional 12 lead electrocardiograms during acute anterior myocardial infarction. It compares the functional electrocardiographic changes occurring in control subjects with the changes in those who have obtained coronary artery reperfusion following thrombolytic therapy. The aim is to investigate by using the admission electrocardiogram as an index of myocardial injury, whether there is a predictable reduction in electrocardiographic indices of myocardial infarct size measured at 48 hours post treatment in patients obtaining successful reperfusion.

4.3 PATIENTS AND METHODS

Three patient groups were studied. All groups entered the study, within 6 hours of the onset of cardiac pain and had confirmatory electrocardiographic evidence of acute anterior myocardial infarction ($\geq$2 mm ST elevation in at least 2 precordial leads). Patients were excluded if they had sustained a previous myocardial infarction or had electrocardiographic changes which invalidated ST segment and Q wave analysis, including bundle branch block or pacemaker dependence.

Group 1 comprised historical controls who sustained an acute anterior myocardial infarction, but received no therapy other than conventional analgesia. They were

admitted prior to the introduction of routine thrombolytic therapy. All patients admitted to the Coronary Care Unit have prospective proformata filled out detailing patient identification, clinical features on presentation, examination findings, treatment administered and final diagnosis. These data are recorded on punch cards and stored in a mainframe computer. All electrocardiographic and haemodynamic tracings performed are stored separately as hard copy. This policy allows a review of coronary care admissions and facilitates division of patients into subsets for research purposes. The control group chosen for this study had no complications requiring specific cardio-active agents, nor received routine administration of any drugs which might influence myocardial infarct size, specifically betablockers, calcium channel blockers or nitrates. The ECG changes measured therefore represent those occurring in a patient group with acute anterior myocardial infarction without cardiogenic shock or haemodynamic decompensation.

Group 2 consisted of patients who received thrombolytic therapy using the agent of our then current thrombolysis protocol. Both groups are similar with respect to age, sex and time to presentation (Table 10). Group 2 received either intracoronary streptokinase (n=13) or an intravenous bolus dose of anistreplase (n=20) according to the protocols outlined in chapter 2. Coronary artery

patency was determined by selective coronary arteriography, performed during therapy in the intracoronary cases or 60-90 minutes following administration of the intravenous therapy. The coronary arteriograms were read independently by two of the cardiologists not involved in the individual patient study. The patency of the infarct-related vessel was decided according to the European classification (Verstraete et al., 1985a). A vessel was considered patent if the distal part of the infarct related artery filled within 3 cardiac cycles. It was considered unethical to perform emergency angiography in the Group 1 patients who received only opiate analgesia, and therefore the incidence of coronary artery occlusion at time of admission and of spontaneous reperfusion is unknown (De Wood et al., 1980).

Group 3 consisted of 22 patients (19 male, 3 female, age range 31-68, mean age 53.6 years) receiving either 1.5 M.U. streptokinase over 1 hour or 30 U anistreplase over 5 minutes. Reperfusion was assessed angiographically at 90 minutes after the start of treatment in all cases. Individual patient data for all three groups is listed in appendix III.

4.4 ECG ANALYSIS

Following admission to the Coronary Care unit, 12 lead electrocardiographs were performed using a Hewlett Packard

Cardiograph 4700A as discussed in Chapter 2. ECG's were measured manually using hand held calipers. The ST segment area was calculated for each lead showing ST elevation (1 mm in the limb leads or 2 mm in the precordial leads taken at the J point) and measured as the area above the isoelectric line from the J point to the end of the T wave. The scores for all leads were summed as an index of myocardial injury or ischaemia reflecting potential infarct size, $\sum$ST.

A second electrocardiograph was taken at 48 hours following the onset of symptoms and a measurement of the evolved infarct size was made using the QRS scoring system described by Wagner et al. (1982) which has been previously discussed.

4.5 STATISTICAL ANALYSIS

Results are expressed as mean values $\pm$SD. Statistical analysis was undertaken using the Students unpaired 't' test to compare groups. Linear regression was performed using the statistical package VASP on a Nodecrest computer, and an F test applied to test the regression lines. Prediction intervals of QRS scores for the test group patients (Group 3) were calculated based on the data from the known reperfusion data. This predicts the level of QRS score that would be expected if the patient reperfuses.

4.6 RESULTS

Figure 6 shows a representative electrocardiograph on admission a, and at 48 hours b, from which the $\sum$ST segment area and the QRS scores respectively were calculated. The degree of ischaemia on the electrocardiogram at presentation was similar in both groups, $\sum$ST area group 1 m = 115$\pm$60 mm^2, group 2 m = 126$\pm$77 mm^2 (N.S). This indicates that both groups had comparable myocardial ischaemia and potential infarct size. Of the patients in group 2 who received thrombolytic therapy, 11/13 receiving intracoronary streptokinase achieved successful reperfusion, and 19/20 receiving intravenous anistreplase were found at angiography to have a patent infarct-related vessel (LAD). At 48 hours the evolved infarct size as assessed by the QRS score was significantly lower in those patients obtaining reperfusion (mean QRS=4.1$\pm$2.5) compared with the control group (mean QRS=7.8$\pm$2.6) ($p<0.01$). The relationship between myocardial ischaemia at admission ($\sum$ ST area) and eventual infarct size is shown for both the control group and those patients achieving reperfusion in Figure 7. Only 3 subjects in group 2 failed to show reperfusion and therefore no formal statistical analysis has been performed to compare the ECG score of the reperfusion group with the non reperfusion group. The non- reperfused subjects however showed Q wave development, and a subsequent QRS score, similar to the control group (Table 11). The patients in group 2 were

further divided by the time elapsed between the onset of cardiac pain and the time to thrombolytic therapy: group 2a<3 hours (n=16), group 2b>3 hours but <6 hours (n=14). The presenting values for $\sum$ST segment area were 142$\pm$82 mm^2 and 107$\pm$70 mm^2 respectively (N.S.). The evolved infarct size scores were not significantly different for the two groups. Group 2a QRS=4.2$\pm$2.8, group 2b QRS=4.1$\pm$2.1.

Figure 8 shows a scatter diagram representing individual scores for Group 1 and Group 2 with respective linear regressions, QRS = 4.6+0.027.$\sum$ST area, and QRS = 1.6+0.020.$\sum$ST area. These regressions describing each group separately fit the data better than a single regression through all points ($p<0.05$).

Ninety-five percent prediction intervals for QRS scores were calculated using the group 2 reperfusion data. These intervals are shown in Figure 9 with group 1 control data superimposed. There is a substantial number of control patients (51%) whose QRS score falls within the 95% prediction intervals for reperfused cases.

To investigate whether these intervals could be used to accurately predict QRS scores in individual patients, Group 3 was used as a test group. The intervals were used to predict the QRS scores expected if new patients had

reperfused. Out of 22 patients given thrombolytic therapy, 11 obtained a patent artery at 90 minutes after treatment, and 11 were classed as non reperfusions. Both sub groups had similar degrees of myocardial injury on presentation, $\sum$ST area = 147$\pm$74 mm^2 (reperfusion group) and $\sum$ST area = 171$\pm$76 mm^2 (non reperfusion group) (NS). Patients obtaining reperfusion had lower QRS scores compared with the non reperfusion group, 4.5$\pm$3.1 v 9.3$\pm$3.4 ($p<0.01$). However, Figure 10 shows that 5 of 11 non reperfusions fall outwith the prediction intervals for reperfused cases, but that 6 of 11 cases fall within this band. All cases except 1 which achieved reperfusion fall within the prediction intervals shown. The wide inter-individual variability does not allow the prediction of a QRS score on an individual basis.

Gp	n	M	F	Mean Age	Treatment	Mean time to Presentation
1	35	29	6	55.5	Control (n=35)	3 hrs. 28 min. ±96 min.
2	33	22	11	57.3	i/c Streptokinase (n=13) / i/v Anistreplase (n=20)	2 hrs. 40 min. ±87 min.

TABLE 10: BASELINE CHARACTERISTICS FOR GROUP 1 AND GROUP 2

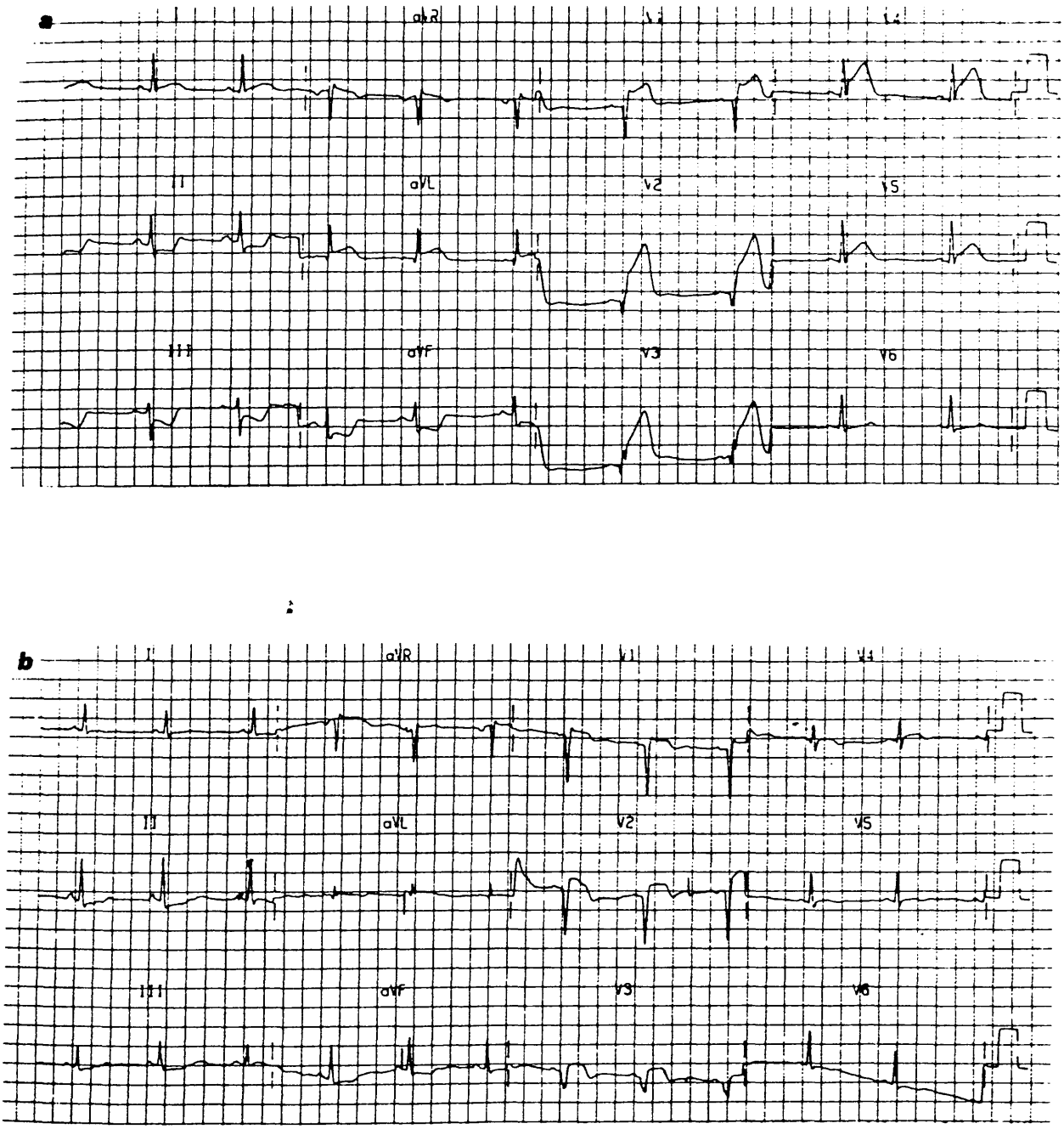


FIGURE 6: REPRESENTATIVE 12 LEAD ECG FROM PATIENT WITH ACUTE ANTERIOR MYOCARDIAL INFARCTION A, AND 48 HOURS FOLLOWING SUCCESSFUL REPERFUSION B.

The $\sum$ ST area on the admission ECG is 218 mm^2.
The QRS score 48 hours after treatment is 3.

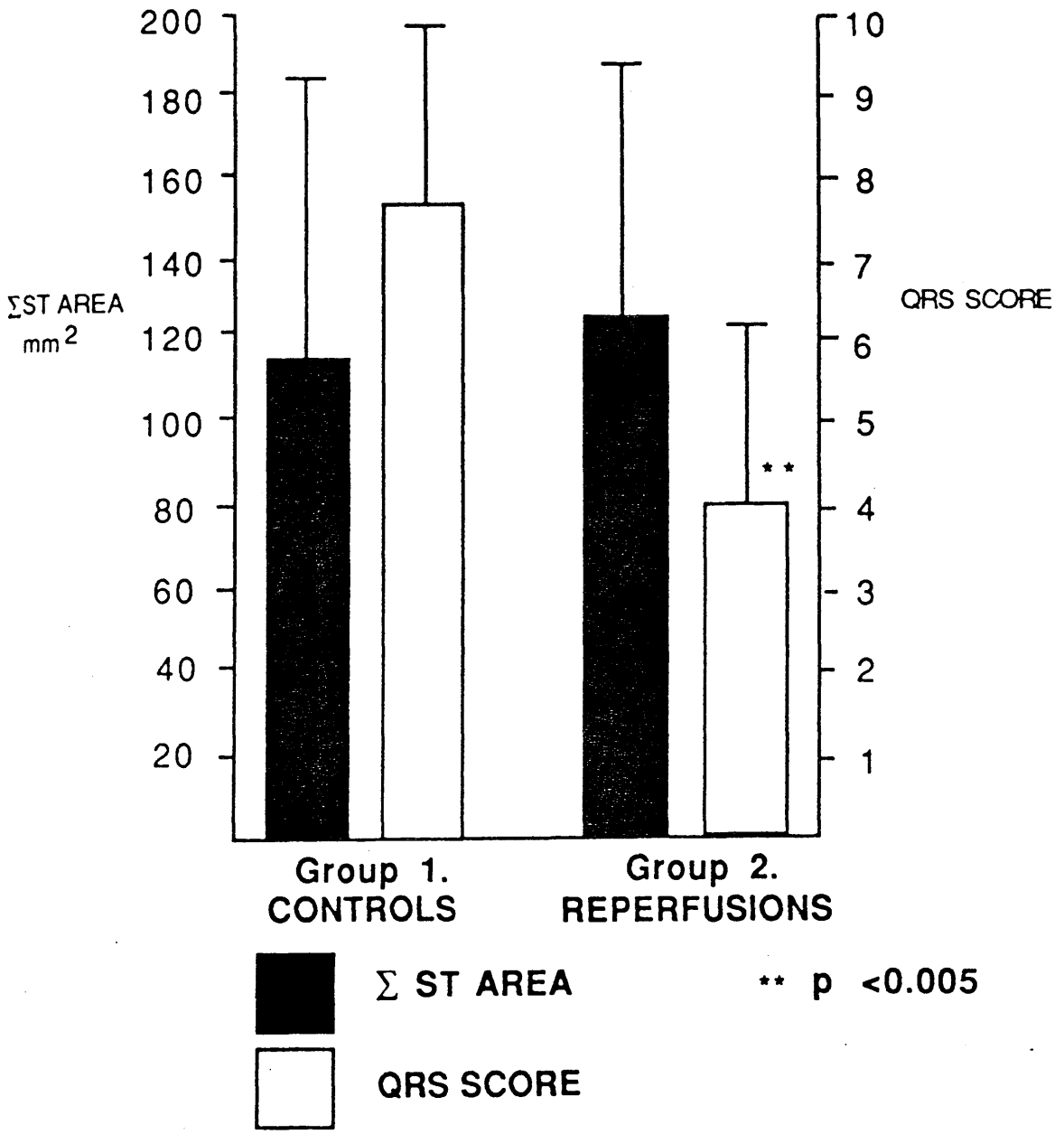


FIGURE 7: RELATIONSHIP BETWEEN $\sum$ST AREA ON PRESENTATION AND SUBSEQUENT QRS SCORE AT 48 HRS POST ADMISSION IN GROUP 1 AND GROUP 2

	Group 1	Group 2	
	Control n=35	Reperfusion n=30	Non Reperfusion n=3
$\sum$ ST Area (mm2)	115±60	126±77	279±44.7
QRS score	7.8±2.6	4.1±2.5	7.3±4.5

TABLE 11: MEAN VALUES AND STANDARD DEVIATIONS FOR $\sum$ ST AREA AND QRS SCORES FOR GROUPS 1 AND 2 DEPENDING ON CORONARY ARTERY PATENCY

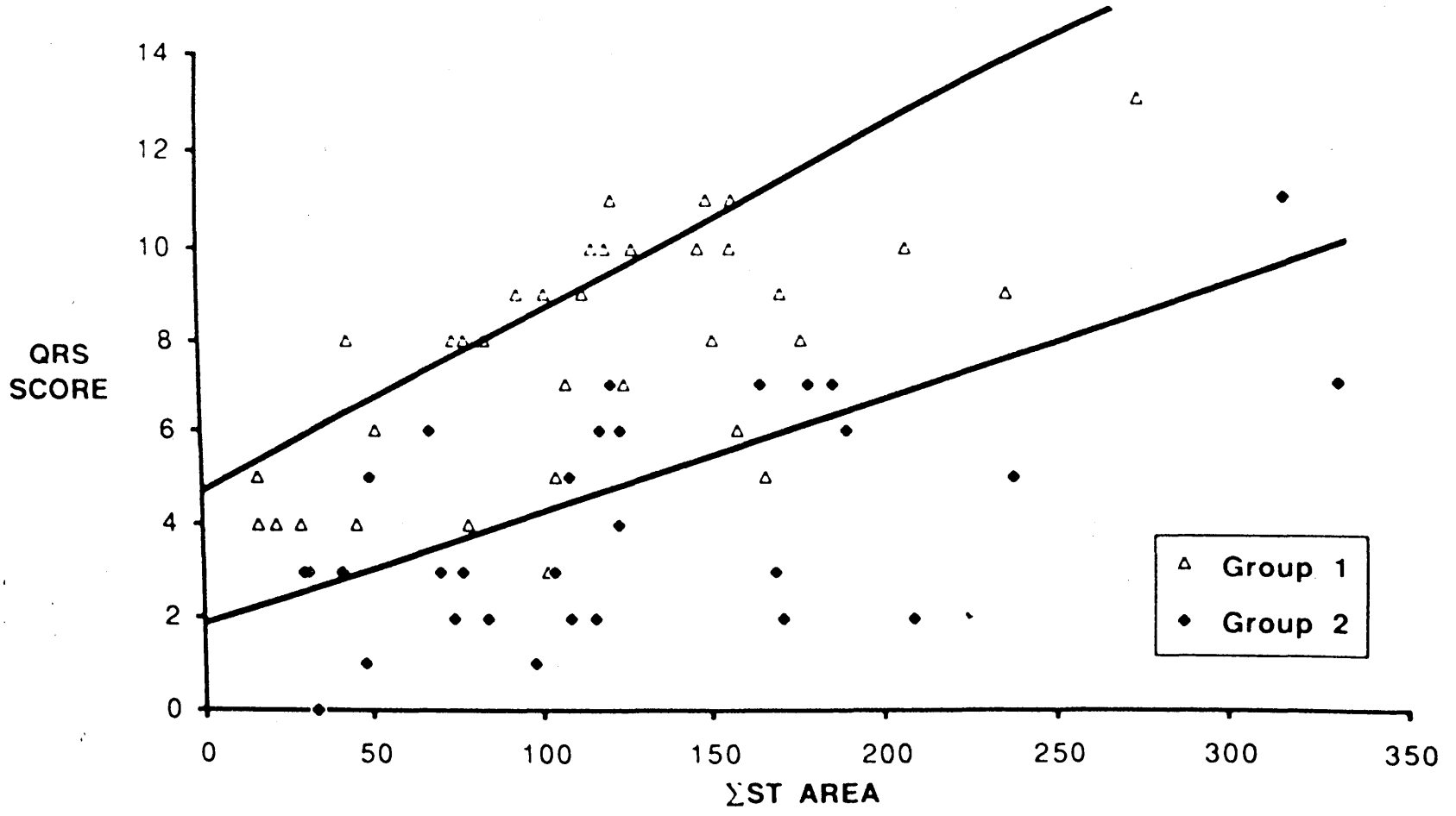


FIGURE 8: SCATTER DIAGRAM WITH INDIVIDUAL SCORES FOR GROUP 1 AND GROUP 2 SHOWING LINES OF LINEAR REGRESSION FOR EACH GROUP

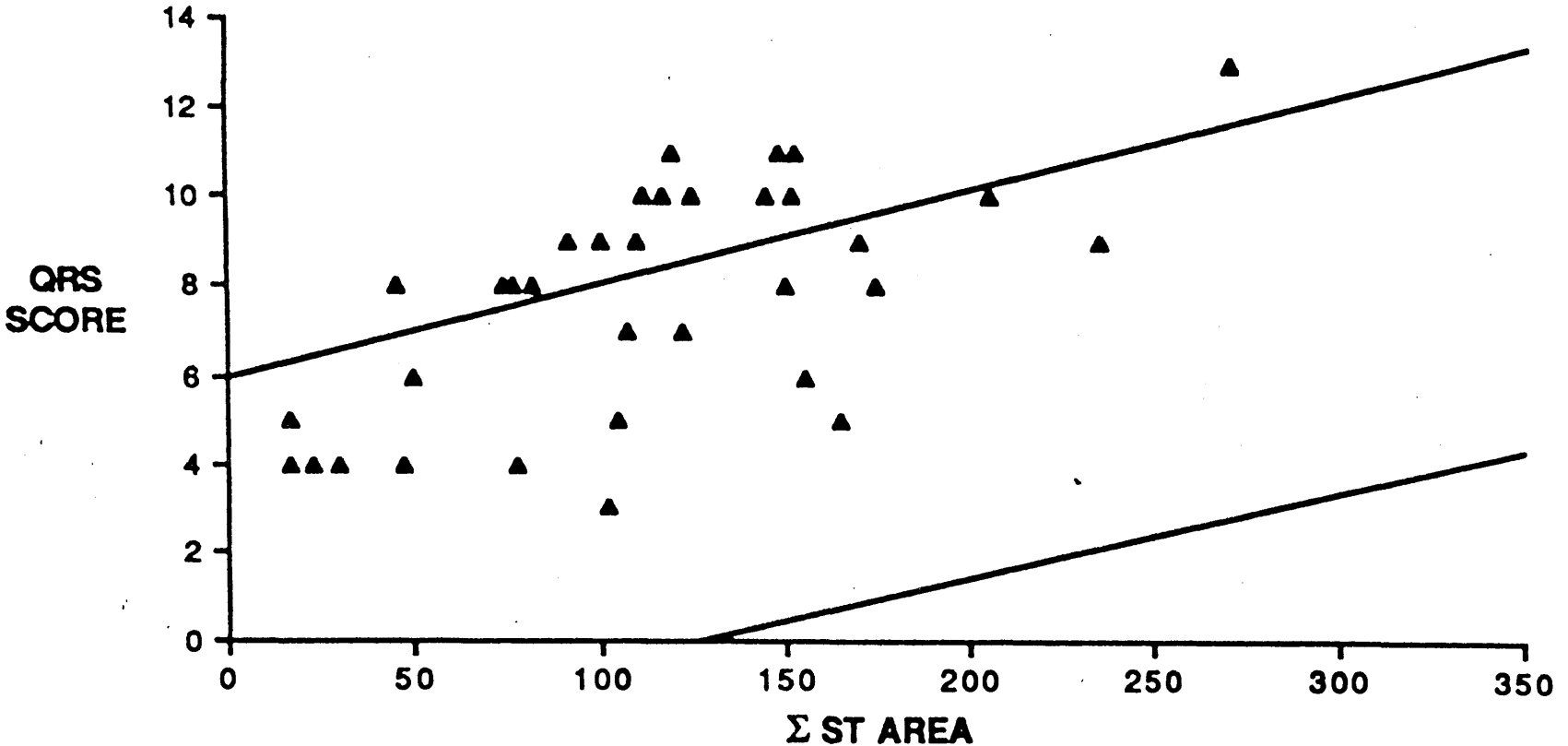


FIGURE 9: 95% PREDICTION INTERVALS FOR QRS SCORES FOR PATIENTS ACHIEVING SUCCESSFUL REPERFUSION.
The results for group 1 (control) are superimposed. ▲ Controls.

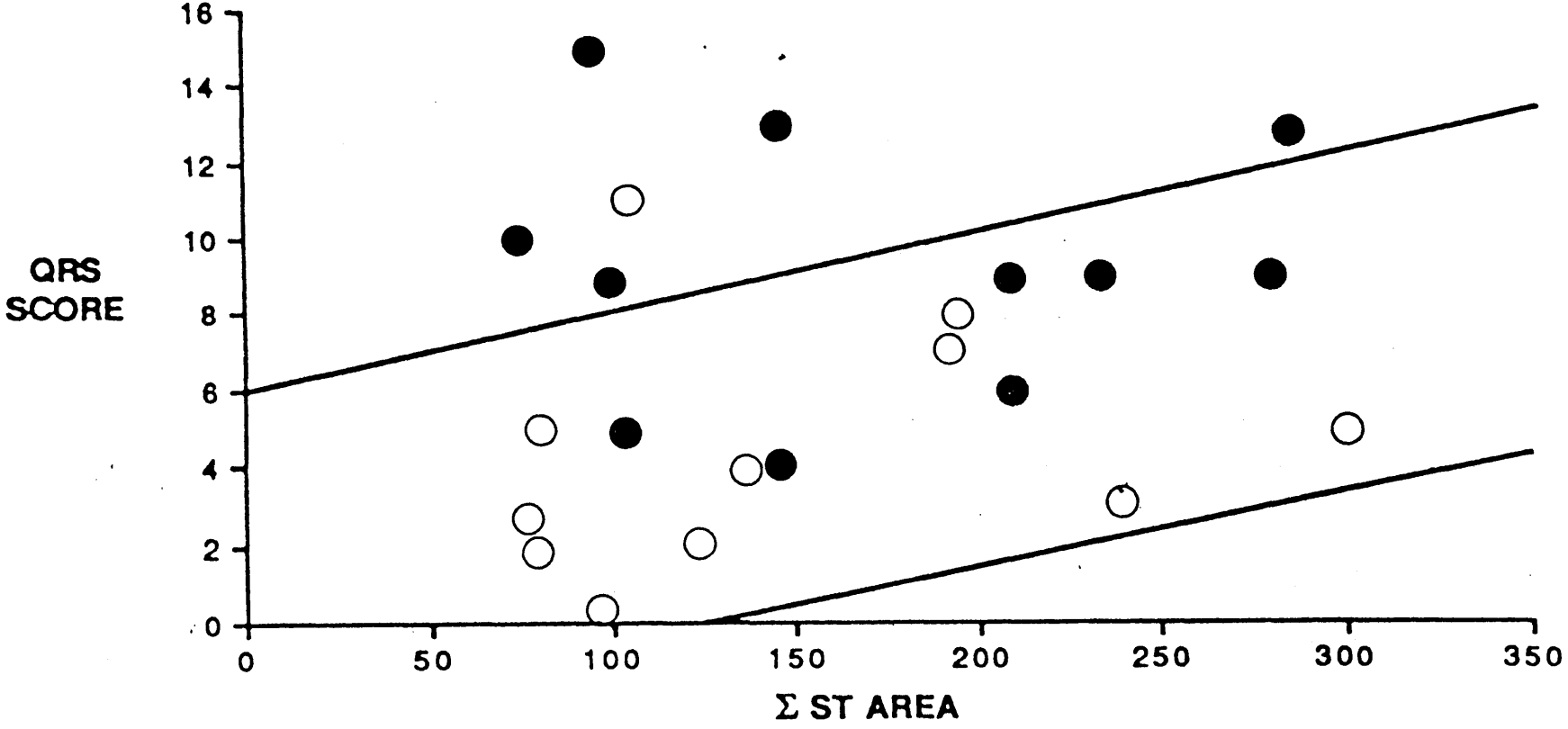


FIGURE 10: RESULTS FOR $\sum$ST AREA AND QRS SCORES FOR GROUP 3.

○ reperfusion n = 11 ● non reperfusion n = 11

4.7 DISCUSSION

This study shows that the sequential electrocardiographic changes are attenuated in patients with acute anterior myocardial infarction who achieve coronary artery reperfusion following thrombolytic therapy. The question of whether this attenuation in electrocardiographic infarct size could be used on an individual basis to predict QRS scores assuming reperfusion in patients with acute anterior infarction was then addressed.

Although this study was not randomised, the control and intervention groups show similar distribution of baseline characteristics including sex, age, time to presentation and similar levels of ST elevation on the admission ECG. Patients in the control group were on no drugs which could influence myocardial infarct size and patients with cardiogenic shock or cardiac failure were also excluded. Selection for this group was therefore biased against inclusion of clinical sub sets which may have had major myocardial damage, and hence high QRS scores. The electrocardiographic changes shown in this group therefore represent the true natural history occurring during acute anterior myocardial infarction. As it was considered unethical to perform angiography in patients not receiving thrombolytic therapy, the control group may include patients with a sub total coronary artery occlusion at the time of presentation or those who had spontaneous reperfusion (De Wood et al., 1980). Such coronary artery

morphology may be associated with less eventual myocardial damage, and the inclusion of such subjects would again tend to bias results against finding a difference in evolved QRS scores.

Selwyn et al. (1978) showed that in patients with acute anterior myocardial infarction, the precordial area of ST segment elevation at 2 hours was directly related to the extent of developed Q waves at 24 hours after the onset of pain. An arbitrary time interval of 48 hours from presentation was chosen for the measurement of evolved infarct size in this study as Q wave development is believed to be complete at this time. Animal studies using an epicardial mapping system have shown a convincing correlation between ST segment changes, subsequent Q wave development, myocardial creatine phosphokinase release and histological evidence of necrosis (Hillis et al., 1976). However, opinion is divided regarding the ability of ST segment elevation to predict either the severity or the extent of myocardial necrosis in humans. In man, using precordial mapping techniques, both Norris et al. (1976) and Thompson and Katavatis (1976) found little relationship between ST segment elevation and subsequent infarct size as assessed by creatine phosphokinase release. Problems can arise as coronary artery occlusion is not the only stimulus to affect the ST segment. Nevertheless, Askenazi et al. (1977) have reported that

there is a predictable distribution of leads with ST elevation which ultimately develop signs of necrosis, and have suggested that a reduction in Q wave development would be of value in monitoring therapy designed to preserve myocardium. This has been confirmed in similar work by Yusuf et al. (1979).

The present study confirms that a reduction in Q wave formation is associated with coronary artery reperfusion and that the reperfusion group score lower QRS values than the control group. This is in contrast to the findings of Mikell et al. (1986) who found that the QRS scores were the same irrespective of whether or not the patient had achieved successful reperfusion. This group did show an improvement in left ventricular ejection fraction if the patient had reperfused, and suggested that there was a lag between electrocardiographic changes and left ventricular recovery or function. The patients studied by this group had a preponderence of inferior infarctions, and this may explain why a difference in QRS scores was not seen. Previous studies have shown that both ST segment changes and QRS scores are more variable when applied to patients with inferior infarcts. This may reflect the small number of leads which show changes with inferior infarction, and therefore represent only a limited proportion of the underlying myocardium.

Despite being able to show a reduction in QRS scores for these patients who reperfused, when prediction intervals were calculated for this group, the limits were so wide and overlap between groups such that clinical predictions regarding infarct size on an individual basis were not helpful. This degree of interindividual variability may be accounted for by several reasons. Hackworthy et al. (1986) showed that collateral formation resulted in a smaller than expected infarct size using the same QRS scoring system. Only in patients with a totally occluded artery with no collaterals did the initial peak ST elevation correlate with electrocardiographic infarct size. Certainly the presence of collaterals may reduce the expected QRS score in patients with no anterograde flow, classed as non reperfusions. We know from de Wood et al. (1980) that 15% of patients presenting within a 6 hour time window will have a sub total occlusion, and that there is a spontaneous reperfusion rate. Huey et al. (1987) confirmed that patients with a natural high patency rate at 10-13 days post infarction had better left ventricular function and less development of Q waves. Similarly Hackworthy et al. (1986) showed a reduction in the expected QRS scores if related to a sub total occlusion.

It is of interest in the present study that beneficial changes in electrocardiographic indices of myocardial infarct size could be demonstrated even in those subjects given thrombolytic therapy within a 3 to 6 hour time window. This suggests that functional benefit measured electrocardiographically may still be obtained if therapy can be started within 6 hours of the onset of cardiac pain. The potential for benefit may be present in those patients in whom coronary collaterals have previously developed or in whom acute infarction is associated with a sub total coronary artery stenosis rather than a complete occlusion (Rogers et al., 1984).

In conclusion, using conventional 12 lead electrocardiograms this chapter demonstrates significant attenuation in the developed QRS score, in patients who achieved reperfusion following thrombolysis for acute anterior myocardial infarction. Beneficial change in this functional marker can be obtained following successful reperfusion up to 6 hours from onset of pain. There is a wide inter-individual variability in QRS scores making prediction regarding infarct size on an individual basis unhelpful. This variability may be accounted for in part by degree of collateral supply, time to reperfusion, or by the presence of a sub total occlusion at time of

presentation. However, the reduction in QRS scores seen in patients who achieve reperfusion following thrombolytic therapy may provide a non invasive index of myocardial salvage on a population basis.

CHAPTER 5

DEVELOPMENT OF DIGITIZED ECG DATA COLLECTION AND VALIDATION OF SYSTEM

5.1. INTRODUCTION

Chapters 3 and 4 have shown that the 12 lead ECG can be a dynamic functional marker of myocardial reperfusion and salvage. The ECG measurements performed in these studies were made manually using hand held calipers, and the studies were in relatively small patient numbers or specific subsets - i.e. anterior infarction. Verification of these initial results was required in a larger patient group. In addition, different groups of workers use different methods of measurement and different parameters, a variety of which are shown in Table 12. It is not clear which are the most sensitive and specific techniques to follow therapeutic interventions in myocardial infarction.

In order to attempt to answer these questions, at least in part, a computerized data base for collection of electrocardiographic data has been developed. Twelve lead electrocardiographs were digitized and individual parameters stored to examine which measurements, or combinations of measurements, would be most useful on a clinical basis to detect reperfusion and to give an index of myocardial infarct size. This system allows storage of data for a large number of patients, each with several sequential ECG's. It was intended that the system should be doctor or technician run. This chapter describes the system that was developed, the parameters measured, and the validation of the technique by presenting an inter and intra observer variation study.

STUDY	ECG	ST SEGMENT	R WAVES	Q WAVES
Selwyn et al (1977)*	72 lead map	$\sum$ST ↑ (if > 2mm)	Not addressed	not addressed
Zmyslinski et al (1979)*	35 lead map	$\sum$ST ↑ (35)	$\sum$R (35) area	$\sum$Q (35) area
	12 lead ECG	$\sum$ST ↑ (V_1-V_6)	$\sum$R (V_1-V_6) area	$\sum$Q (V_1-V_6) area
Timmis et al (1982)ϕ	12 lead ECG	single ST ↑ maximum	Single R (mV)	Single Q (mV)
Anderson et al (1983)	12 lead ECG	single ST ↑ maximum $\sum$ST in all infarct leads	Relative R wave loss (in leads showing ST ↑)	n $\sum Q^+$
Blanke et al (1983)*	12 lead ECG	$\sum$ST(V_1-V_6)	$\sum$R (V_1-V_6)	n $\sum$ Q(V_1-V_6)$^+$
Anderson et al (1984)	12 lead ECG	$\sum$ST↑	$\sum$R mm (infarct leads)	n $\sum$Q (infarct leads)$^+$
Ross et al (1985)	12 lead ECG	mean of 2 contiguous leads with max ST ↑	mean R(mV x 10^{-1})	mean Q(mV x 10^{-1})
Von Essen et al (1985)	12 lead ECG	$\sum$ST shift (↑+ ↓) (I, II, III)	not addressed	not addressed
	48 lead map*	–	$\sum$R	$\sum$Q
Krucoff et al (1986)	Holter Tape	single lead, time to steady state	not addressed	not addressed
Vermeer et al (1986)	12 lead ECG	$\sum$ ST↑ in pre-defined 'minimaps'	not addressed	not addressed

* Anterior infarcts only
ϕ All measurements made in single lead showing greatest ST segment elevation
\+ The number of leads showing pathological Q waves

TABLE 12 - HETEROGENEITY OF PUBLISHED ECG PARAMETERS TO FOLLOW CHANGES AFTER INTERVENTION IN ACUTE MYOCARDIAL INFARCTION.

5.2 GENERAL METHODOLOGY

The digitizer board (Summagraphics Corporation Supergrid) was linked to a Nodecrest computer. The individual thrombolytic studies undertaken in the Coronary Care Unit since 1984 were listed separately in data files. Each study has different timing of ECG sampling, and this allowed data to be listed in a logical and chronological fashion for subsequent analysis (Table 13.) This list can be, and has been expanded to accommodate further studies.

The 12 lead ECG to be analysed is fixed to the surface of the digitizer board. The operator then accesses the programme required, the appropriate study is selected, the patient identified and the timing of the ECG inserted. When the system was being developed, it was necessary to plan carefully which particular ECG parameters would be measured, and subsequently stored. Future analysis comparing scoring systems or methods of following intervention would depend on the initial data base, and therefore all potentially useful data must be keyed in at the start. While requiring a comprehensive analysis of each ECG, it must not be so detailed and complex to be excessively time consuming (from the initial study listing in Table 13. there is space for 2,643 12 lead ECG's). Measurements were made of ST segment elevation and depression (both area (mm^2) and height (mV)) , Q wave duration and amplitude, R wave duration and amplitude and S wave amplitude. All leads except AVR were screened for

the above features, and measured if present. An average heart rate was computed for each ECG, measured from a long lead II and each ECG was calibrated for m.sec and m.V by digitally recording 1 second and 1 mV before each separate 12 lead ECG analysis. The average of 2-3 beats were measured per lead, and the isoelectric baseline identified for each complex. This was to prevent inaccuracies arising from minor baseline shifts occurring over 2-3 beats. An example of the print-out obtained for each ECG is shown in Figure 11. This also provides R/Q and R/S ratios, allowing computation of the simplified Selvester QRS score (Wagner et al., 1982, and Table 5) which is displayed in the initial print-out. The program written to calculate the QRS score from the digitized ECG data is shown in Appendix IV.

Following an initial learning period of 2-3 weeks, the analysis time for each 12 lead ECG was in the order of 7-10 minutes, including the entry of demographic data into the computer.

Study	n	ECG times*
1. ICSK	80	Pre, post angio, 24, 48 hrs
2. Open APSAC	150	Pre, 2,4,6,8,10,12,24, 48 hrs
3. APSAC/SK comparison	128	Pre, 2,4,16,18,24 hrs
4. TPA Study 1	11	Pre, 3,12,24,48 hrs
5. TPA Study 2	30	Pre, 3,12,24,48 hrs

* Time in hours refers to time following administration of thrombolytic agent.

ICSK = intracoronary streptokinase

APSAC = anistreplase

TPA = tissue plasminogen activator

TABLE 13: THROMBOLYTIC STUDIES LISTED ON NODECREST COMPUTER FILE STORE. (List at end of October 1988)

SUBJECT - DAVID CONNOLLY NO.OF ECG - 1

LEAD	I	II	III	AVL	AVF	V1	V2	V3	V4	V5	V6
ST EL/DP... (MV)	.03	-.06	-.14	.08	-.14	.09	.35	.53	.61	.21	.05
ST AREA.... (SQ.MM.)	10.14	-9.24	-24.44	14.59	-24.50	10.47	64.86	86.61	84.26	29.70	8.33
Q AMPLIT... (MV)	0.00	0.00	.08	0.00	0.00	1.24	0.00	0.00	0.00	0.00	0.00
R AMPLIT... (MV)	.34	1.09	.82	.09	.89	0.00	.14	.22	1.29	1.39	.92
S AMPLIT... (MV)	.09	.18	.16	.33	.18	0.00	2.30	1.48	.18	.08	.08
R/S RATIO..	3.63	6.08	5.13	.29	5.06	0.00	.06	.15	7.22	17.44	10.82
R/Q RATIO..	0.00	0.00	10.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q-WAVE DUR. (MSEC)	0.00	0.00	15.94	0.00	0.00	55.78*	0.00	0.00	0.00	0.00	0.00
R-WAVE DUR. (MSEC)	41.83	43.82	41.83	27.89	43.82	0.00	15.94*	19.92*	43.82	45.82	43.82

MEAN HR.... 52.35 (B/MIN)

ECG SCORE.. 3.0

FIGURE 11: REPRODUCTION OF DIGITIZED ECG PRINTOUT. Eleven leads are analysed, AVR is not digitized. This patient demonstrates an acute myocardial infarction with inferior reciprocal changes. ST elevation is represented by a positive measurement and ST depression is represented by a negative measurement. The asterisks (*) show the 3 criteria which give rise to a QRS score of 3. Each criteria scores 1 point.

5.3. ELECTROCARDIOGRAPHIC ANALYSIS

A clearly defined set of rules had to be established for identification of electrocardiographic waveforms to ensure reproducible results. Due to the nature of thrombolytic trials, many of the ECG's analysed demonstrated hyperacute changes with marked shifts from baseline which require clear definitions concerning from which point to measure the degree of ST segment deviation. These guidelines have been drawn up paying attention to the recommendations for measurement standards by both the CSE Working Party (1985) and the report of the American Heart Association Committee on Electrocardiography (1975). Further recommendations were obtained from the methodological paper by Hindman et al. (1985). Where controversy exists concerning the measurement of a particular waveform, the method chosen was the one which would be most reproducible and introduce least variability when being digitized. Some specific points are discussed below.

5.3.1 Measurement of Baseline

The American Heart Association recommends that the reference level for Q, R and S amplitude measurements and the displacement of the J point is taken from the PR segment, but that the reference level for measurements of the ST segments, the T wave and the U wave is taken on the TP or UP interval. This may not be easily defined as the heart rate increases, and has led the European Working group to recommend the uniform use of a horizontal

baseline taken on the PR segment. The onset of the QRS is readily identified, more so than the end of the T wave, and so the isoelectric reference point for digitized data was on the PR segment prior to QRS onset.

5.3.2. Small and Inconsistent Waveforms

The CSE Working Party identified a minimum threshold which a wave form had to reach before being described as present (20 uV amplitude and 6 m.sec duration). The diagnostic implications of deflections smaller than this are not known, but identification of these waveforms may result in bizarre labelling of the complex, with subsequent changes in Q and R wave durations and the QRS score. Before identifying a small waveform its consistency should be examined in the same lead, and also across leads. For use with the digitizer if a wave form was inconsistently present and measured <0.05 mV, its presence was not recorded.

5.3.3. ST Segment Analysis

Previous work is controversial regarding the ideal position from which the displaced ST segment should be measured from the baseline. Varying distances from the J point have been used - examples of which are shown in Table 14. Many more papers do not specify at all where the ST measurement is taken from. It can be seen from Table 14 that most published studies have made use of an inappropriate baseline reference point, as well as using a heterogenous range of positions at which to measure ST segment displacement. The J point, defined as the point or shoulder which marks the end of the QRS complex where the steep slopes of QRS deflection are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave (AHA Committee report, 1975), was felt to be the most easily recognised and reproducible for digitized work. Using this point ensured that further variation would not be introduced by "estimating" 20 or 40 m.secs from the J point before digitizing this as ST segment displacement. The reference baseline point was the PR segment as discussed above.

Study	ST Measurement	Reference Point
Bar et al. (1987)	at the J point	not specified
Blanke et al. (1983)	0.02 secs after J point	TP
Muller et al. (1975)	0.02 secs after J point	TP
Zmyslinski et al. (1979)	0.04 secs after J point	TP
Selwyn et al. (1977a)	0.06 secs after nadir of S wave	TP or PQ

TABLE 14: PUBLISHED WORK SHOWING VARIATION IN POSITION AT WHICH ST SEGMENT DISPLACEMENT IS MEASURED

5.3.4. Duration Measurement

The points taken for duration of individual waveforms are covered fully in the set of rules which follows. However, in some instances slurring of waveforms resulted in thickened electrocardiographic upstrokes and downstrokes. From the work of Mazzoleni and de Maria (1983) a decision was made to measure duration from the middle of the tracing in all cases. This group showed that measuring from the leading or trailing edge could result in an under or over-estimation of the true wave duration.

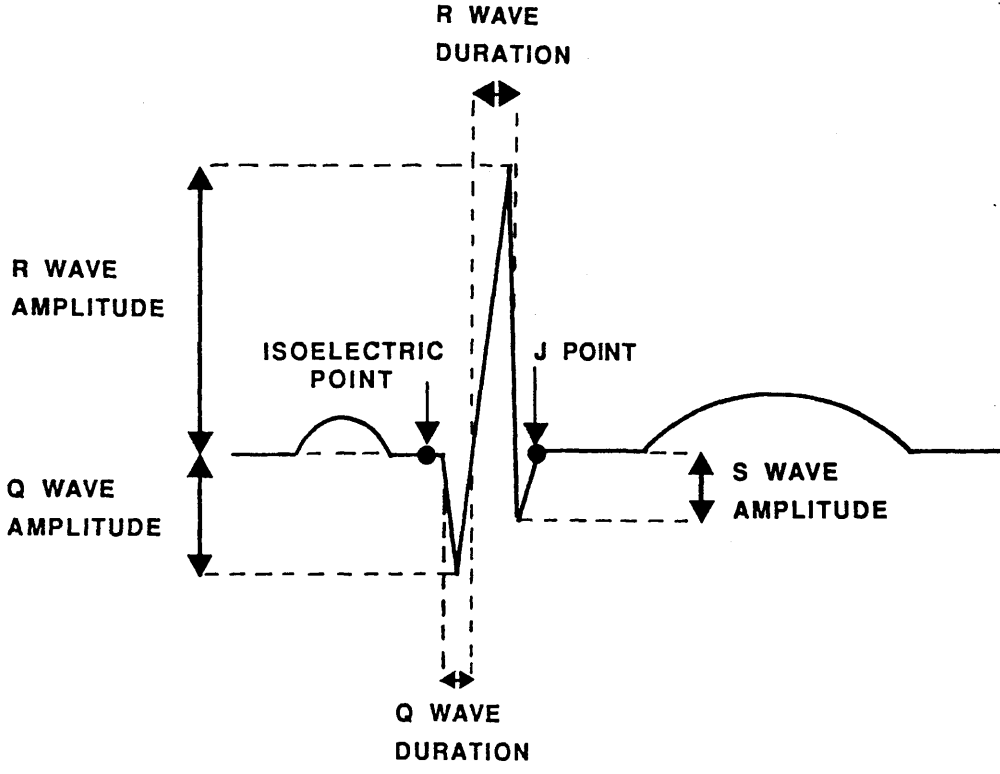
5.3.5. Exclusion from Analysis

Patients who developed left axis deviation, right or left bundle branch block, temporary pacemaker dependence or a sustained idioventricular rhythm were excluded from analysis. If however these effects were temporary, and normal sinus rhythm was restored, the subsequent ECG was analysed.

5.3.6. Set of Guidelines for digitized measurement of ECG data

The above decisions resulted in the writing of a set of rules for the digitized measurement of ECG data, which are illustrated in the next 6 pages. This allows the analysis of 12 lead ECG's to be approached in a logical and consistent manner. With over 24 months experience using the digitizer this set of rules has proved easy and practical to adhere to.

1. THE NORMAL ECG



Duration in milliseconds
Amplitude in millivolts.

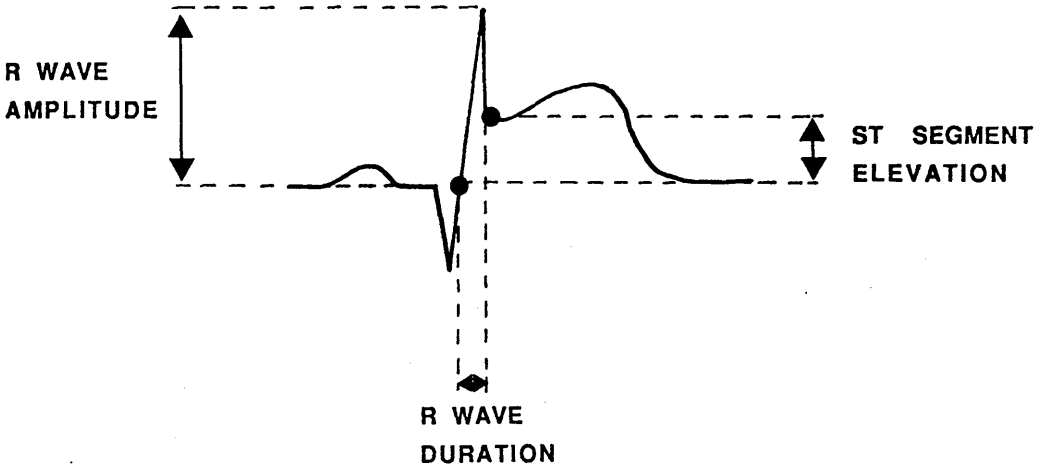
a. Isoelectric point taken in the interval before QRS onset for all QRS and ST-T measurements.

b. J POINT taken for measurement of ST Segment elevation or depression.

FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

2. Measurement of R and S waves - with Junctional Deviation i.e. ST Segment Elevation or Depression

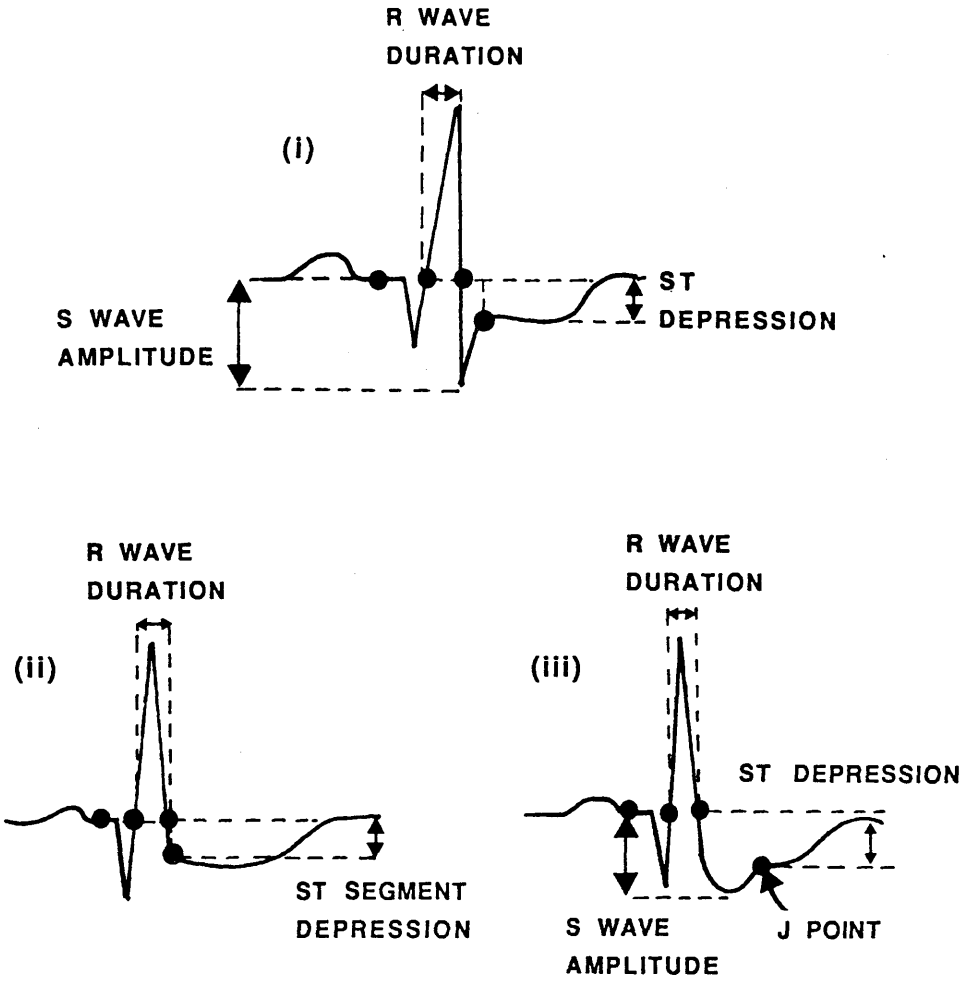
(i) ST Segment Elevation



a) End of R wave taken at J point
b) Isoelectric point taken on PQ Segment

FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

(ii) **ST Segment Depression**



a) Isoelectric point taken on PQ Segment

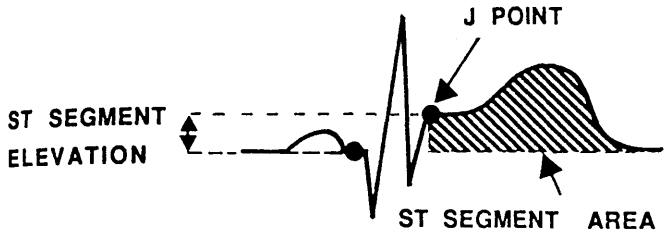
b) in (ii) the end of the R wave is depressed to coincide with the negatively deviated J point. There is no S wave. For reproducibility using the digitizer the R wave duration is measured as shown - on the down stroke as it passes through the isoelectric line. AHA recommendations would measure R wave duration from upstroke to J point.

c) in (iii) the 'R' wave is more depressed than the J point - this extra deflection back to meet the J point is termed an S wave and the R wave duration is as shown.

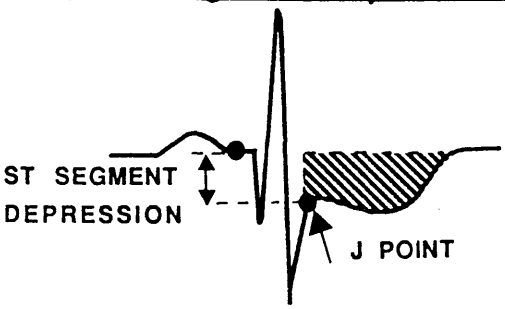
FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

3. Measurement of ST Segment Elevation and Depression (Amplitude and Area)

(i) ST Segment Elevation



(ii) ST Segment Depression

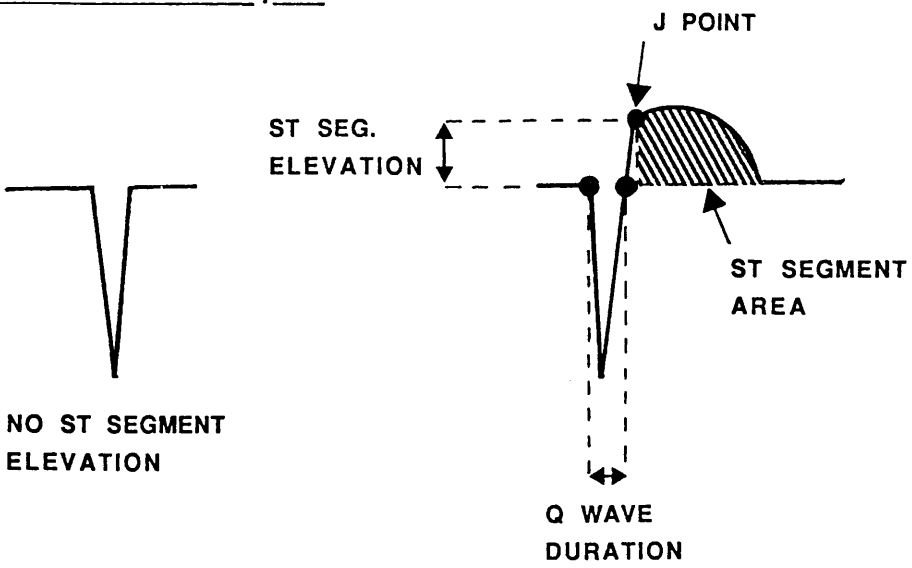


a) Isoelectric line taken at PQ Segment

b) Amplitude (mv) of ST depression/elevation taken at J point with reference to isoelectric point

c) Area of depression/elevation taken by tracing digitizer pen round ST-T contour. Digitizer automatically drops perpendicular to isoelectric line and computes area as shown by hatched lines. Elevation is expressed as a positive value, depression as a negative value.

(iii) ST elevation with QS complex

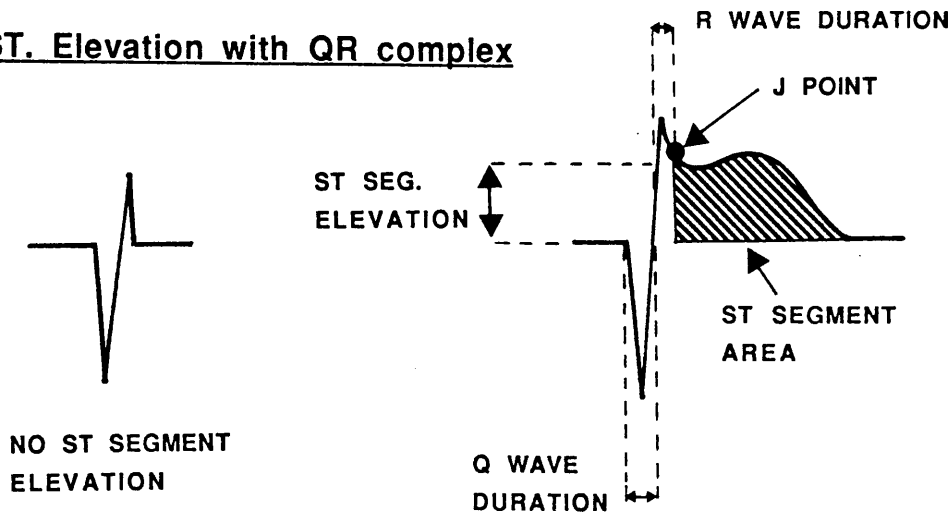


a) The terminal portion of the Q wave is elevated above the isoelectric line as a function of ST Segment elevation. There is no R wave.
ST Segment elevation is measured from the J point as shown.
For reproducibility with the digitizer Q wave duration is measured where down stroke and up stroke cross the isoelectric baseline and not at the J point.

FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

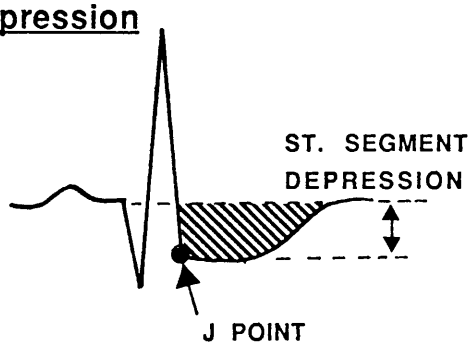
3. Measurement of ST Segment Elevation and Depression - (Continued).

(IV) ST. Elevation with QR complex

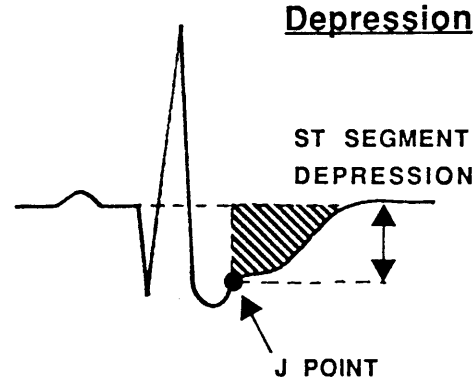


a) If the terminal portion of the QRS complex deflects back down to the J point which is elevated then by definition there is an R wave present

(V) QR Complex with ST Depression



(VI) QRS Complex with ST Depression



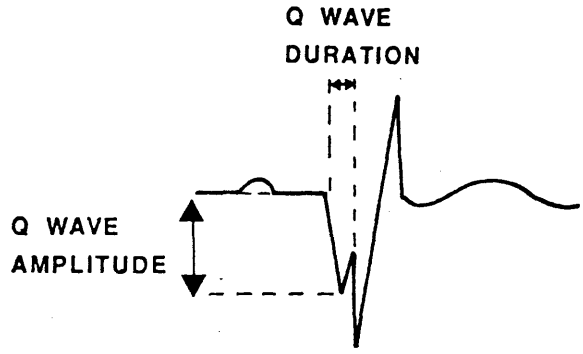
a) in (V) the end of the R wave is depressed to coincide with the negatively deviated J point. There is no S wave. Measurements for ST depression are taken as shown.

b) in (VI) the deflection of the slurred terminal portion of the QRS complex back to meet the J point is termed an S wave. Measurements for ST depression are taken as shown.

FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

4. Measurement of notched Complexes

(i) Notched Q waves



a) A 'notch" is said to occur if there is a reversal in direction of the initial deflection ≥ 0.05 m Volts.

b) The duration and amplitude of a 'notched' Q wave are measured from the initial deflection as shown.

FIGURE 12: SET OF GUIDELINES FOR DIGITIZED MEASUREMENTS OF ECG DATA

5.4. INTRA AND INTER OBSERVER VARIATION

5.4.1 Aim

The purpose of this study was to validate the technique and ensure that both inter and intra observer variation was sufficiently small to allow more than one person to enter data (KJH and AMcK) which could be used in future analysis.

5.4.2. Methods

One hundred ECG's were analysed from a total of 10 patients. The ECG's analysed in this study were chosen to represent the spectrum of ECG's which would be analysed in thrombolytic patient studies i.e. hyperacute changes of myocardial infarction, established infarcts and infarcts in evolution. This allowed the estimation of the inter and intra observer variation for ST segment elevation and depression, and Q wave duration, as well as the other normal parameters of a 12 lead ECG. The ECG data from this study are shown in Appendix V. Each of the 10 patients had a 12 lead ECG performed in the supine position, and 9 identical copies made (memory facility on Hewlett Packard 4700A). This was necessary for the study as digitization of an ECG can leave marks from the pen which may bias a second observer or the same observer the second time round. The ECG's were split into 2 sections of 50 (10 x 5) and put into a random order before each section was analysed by one observer (KJH and AMcK). No conferring was allowed, and the data stored on computer.

5.4.3. Analysis

Once all the ECG data had been digitized, the data were transferred on to magnetic tape for further analysis on the University mainframe computer (ICL.2980). For each of the 10 ECG's, 11 leads were analysed per ECG, with a total possibility of 9 parameters per lead (ST amplitude and area (elevation or depression) Q wave amplitude and duration, S wave amplitude, R wave amplitude and duration, R/S and R/Q ratios) and a further 2 parameters per ECG (heart rate and QRS score). Not all leads had all parameters i.e. no Q wave or ST segment deviation, but this gives a potential number of measurements for the 10 ECG's as 1,010 - each of which was repeated 5 times by each observer. Grouping the measurements either across all leads or across all ECG's does not make sense in electrocardiographic terms due to the expected degree of variation between ECG's (chosen specially to represent a spectrum of myocardial infarction), and across lead types. Therefore a "cell" consisting of one parameter for one lead for one ECG was analysed separately. Where parameters had not existed, as in the case of a lead without a Q wave, this was given a score of 0.00 and omitted from further analysis. The mean and standard deviations were calculated for each cell, and coefficients of variation calculated. This gives a measure of the inter and intra observer variation. The formula used and worked examples are shown in Figures 13 and 14 respectively. This method expresses the standard

deviation as a percentage of the mean. To make the vast number of results manageable, they have been expressed as the percentage of total measurements made, which fall within a coefficient of variation of <10% and <20%.

INTRAOBSERVER VARIATION

$$CV = \frac{SD}{x} \times 100\%$$

where

CV = coefficient of variation
SD = Standard deviation for one cell
x = mean value of 5 replicates for one cell

Example 1

ECG 3, Lead 1, observer 1, Parameter 4
[R wave amplitude]

x = 0.8790
SD = 0.111

$$cv = \frac{0.0111}{0.8790} \times 100\%$$

cv = 1.2%

Example 2

ECG 1, Lead 1, observer 1, Parameter 1
(ST deviation)

x = -0.134 (ST depression characterized as negative. The negative change is ignored in calculation of cv as it is solely a means of differentiating ST segment depression from elevation)

SD = 0.00909

$$cv = \frac{0.00909}{0.134} \times 100\%$$

cv = 6.8%

Example 3

ECG 1, Lead 1, observer 2, Parameter 1
(ST deviation)

x = -0.1394

SD = 0.00391

$$cv = \frac{0.00391}{0.1394} \times 100\%$$

cv = 2.8%

FIGURE 13: METHOD FOR DETERMINING COEFFICIENT OF VARIATION FOR INTRAOBSERVER VARIATION

INTER-OBSERVER VARIATION

$$cv = \frac{SD}{\bar{\bar{x}}} \times 100\%$$

$$cv = \frac{\sqrt{s^2}}{\bar{\bar{x}}}$$

$$cv = \frac{\sqrt{\sum_{i=1}^{2} \frac{(\bar{x}i - \bar{\bar{x}})^2}{n - 1}}}{\bar{\bar{x}}}$$

$$cv = \frac{\sqrt{\frac{(\bar{x}_1 - \bar{\bar{x}})^2 + (\bar{x}_2 - \bar{\bar{x}})^2}{n - 1}}}{\bar{\bar{x}}}$$

where $\bar{\bar{x}}$ overall mean for all measurements

$\bar{x}_1$ mean of 5 measurements for observer 1

$\bar{x}_2$ mean of 5 measurements for observer 2

Example

Working out inter-observer variation from examples 2 and 3 in Figure 13.

$\bar{\bar{x}} = -0.1367$

$\bar{x}_1 = -0.134$

$\bar{x}_2 = -0.1394$

$n = 2$

$$cv = \frac{\sqrt{\frac{(-0.134+0.1367)^2 + (-0.1394+0.1367)^2}{1}}}{-0.1367}$$

$cv = 2.7\%$

FIGURE 14: METHOD FOR DETERMINING COEFFICIENT OF VARIATION FOR INTER-OBSERVER VARIATION

5.4.4.Results: Intraobserver Variation

Of 2,020 possible cells, (both observers, all ECG's, all leads, all parameters) 1,565 measurements were made, the discrepancy reflecting leads which did not exhibit Q waves, S waves or ST segment deviations from baseline. Standard deviations of these measurements expressed as a percentage of the mean were <10% in 78% of cases. Only 4% of all measurements made had coefficients of variations >20%. This data is displayed graphically in Figure 15.

The individual parameters were then examined to see if there was one particular variable which the observers found difficult to measure, which would result in persistently high coefficients of variation. From Table 15 it can be seen that in general all measurements perform well. Q wave duration and amplitude have the least amount of cases with a coefficient of variation of <10% and this may reflect the difficulty in measuring small Q waves in evolution. However, well over 90% of both measurements (duration and amplitude) have a coefficient of variation of <20%. The QRS score has been omitted from this table as in contrast to other parameters measured, a score of zero should be taken into account as this would be the score expected if the ECG did not show evidence of an established myocardial infarction.

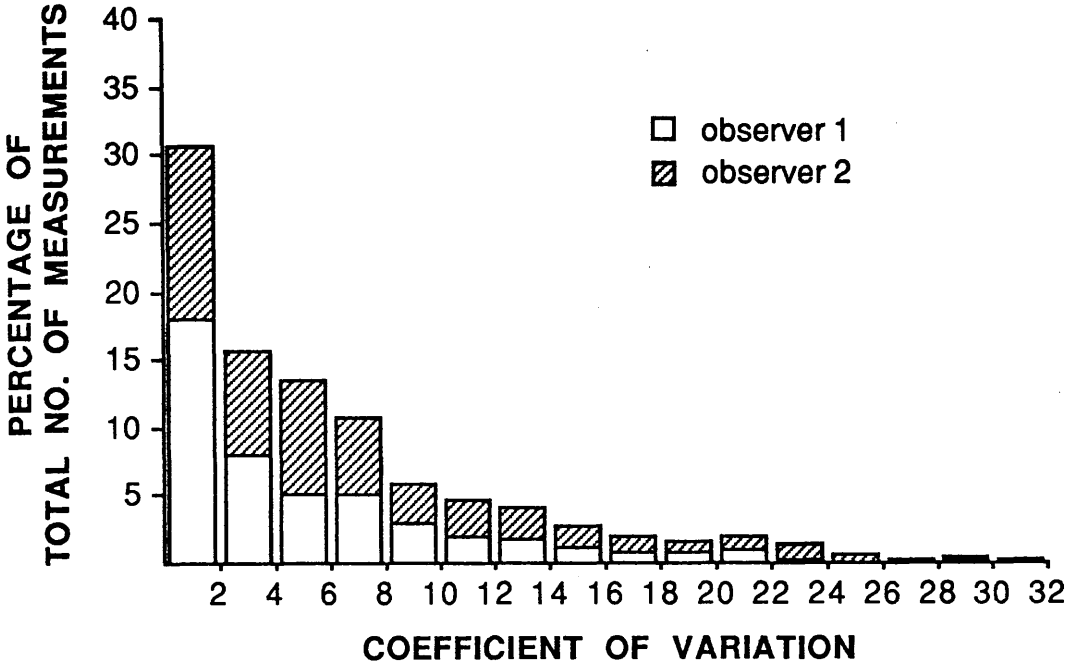


FIGURE 15: INTRAOBSERVER VARIATION - SPREAD OF COEFFICIENTS OF VARIATION

Parameter	Total No. Measurements	Coefficient of Variation <10%	<20%	>20%
ST amplitude (elevation and depression)	133	78%	90%	10%
ST area (elevation and depression)	134	84%	96%	4%
Q wave amplitude	74	70%	97%	3%
R wave amplitude	205	96%	99%	1%
S wave amplitude	148	91%	97%	3%
Q wave duration	74	59%	93%	7%
R wave duration	205	77%	98.5%	1.5%
Heart Rate	220	100%	100%	0%

TABLE 15: INTRAOBSERVER VARIATION: COEFFICIENTS OF VARIATION FOR DIFFERENT ECG PARAMETERS

5.4.5. Results: Interobserver Variation

Results for interobserver variation have been analysed in a similar fashion as for intraobserver variation. Out of a total possible 1,010 cells per observer (1 observer, all ECG's, all leads, all parameters), 772 had been measured and coefficients of variation calculated, 80% of this total having a coefficient of variation <10% and only 5% having a coefficient of variation >20%. These results are shown graphically in Figure 16. Note that although ST segment depression is characterized and differentiated from ST segment elevation by a negative sign, this does not influence the calculation of the coefficients of variation which by convention are always reported as positive.

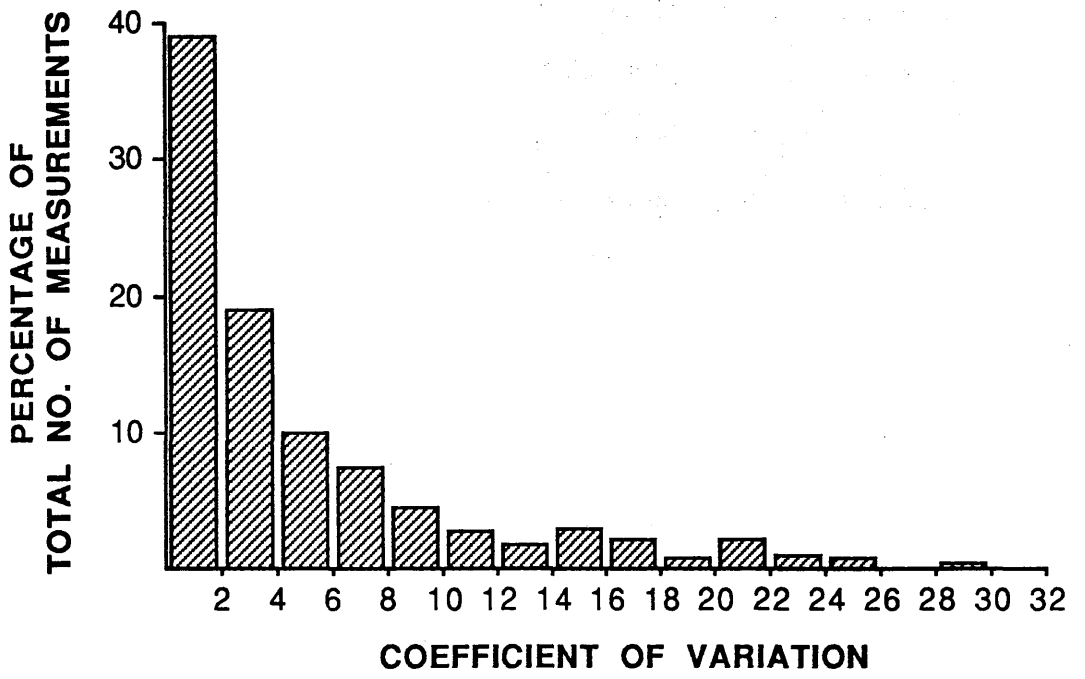


FIGURE 16: INTEROBSERVER VARIATION - SPREAD OF COEFFICIENTS OF VARIATION

5.4.6. Computed QRS Score

The inter and intraobserver variations for the Simplified Selvester QRS score computed automatically for each ECG were examined. Significant differences in the QRS score obtained could arise by the arbitrary cut off levels for "significant" and "non significant" Q waves (e.g. Lead II, Q wave $\geq$30 m.secs is significant and scores + 1, Q wave $<$30 m.secs is non scoring). If observer 1 recorded an average Q wave duration of 29.5 m.secs for lead II and observer 2 recorded an average duration of 30.3 m.secs for the same lead, this gives a very satisfactory interobserver variation of 1.1%, but a difference of 1 in the ultimate QRS score. The scores obtained for each of the 10 ECG's by each observer are shown in Table 16.

Because of the inherent difference in the 10 ECG's chosen for analysis, the score for each ECG was examined separately, a score of 5/5 meaning that all replicates of one ECG scored the same. When these results were grouped together the QRS scores were in complete agreement in 94% of cases for observer 1 and 78% cases for observer 2. Previous work by Anderson et al. (1983) has highlighted the problem of minor fluctuations in R wave and Q wave dimensions, giving rise to frequent transient 1 point variations and defined a "QRS change" as a score increase or decrease of $\geq$2 points compared with a previous observation. In this study, scores $\pm$ 1 point difference resulted in agreement for observer 1 in 100% of cases and

observer 2 in 88% of cases. Comparing scores between observers showed complete agreement in 68% of cases and $\pm$ 1 in 90% of cases.

The biggest difference which occurs between scores for the same ECG between two observers is ECG No. 9 where observer 1 scores 7 and observer 2 scores 2 on the first analysis. This primarily arises due to differences in measured Q wave duration. Observer 1 measures the Q wave in lead II as 45 msecs (score +2) but observer 2 has measured the same Q wave as 38 msecs (Score +1). For lead AVF observer 1 measures Q wave duration as 42.5 msecs which also scores 2 and because the Q wave is significant and the R/Q ratio is less than 2 this adds another one to the score. Observer 2 however has measured this Q wave as being only 24 msecs in duration, which is regarded as non significant (cut off $\geq$ 30 msecs) and thus the R/Q ratio which has physically been measured as the same by the 2 observers is not taken into account, and a score of 3 is immediately lost due to misinterpretation of Q wave duration. The other one point difference is attributed to the R/S ratio in V_5 measured as 1.99 (score +1 as R/Q $\leq$2) by observer 1 and as 2.04 (score 0 as R/Q >2) by observer 2. These small differences which give rise to differences in the QRS score because of arbitrary cut off points will occasionally occur, and have to be accepted. The problem of misinterpretation of Q wave duration by almost 50% as

in the example above is considered a miss-hit as all other ECG's by the same observer have much longer Q wave durations. With further experience this type of miss-hit should be recognised and rectified at the time.

ECG NO.	REPLICATES (OBSERVER 1, OBSERVER 2) 1	2	3	4	5
1	2,4	2,2	3,3	2,4	2,2
2	0,2	0,1	0,0	0,0	0,0
3	0,0	0,0	0,0	0,0	0,0
4	3,2	3,2	3,3	3,3	3,2
5	3,3	3,3	3,4	3,3	3,3
6	0,0	0,0	0,0	0,0	0,0
7	1,1	1,1	1,1	1,1	1,1
8	6,6	6,6	6,6	6,6	6,6
9	7,2	7,6	8,8	8,8	8,6
10	1,2	1,2	1,2	1,2	1,2

Observer 1 = KJH
Observer 2 = AMcK

TABLE 16: AUTOMATED SIMPLIFIED SELVESTER QRS SCORES FOR OBSERVER 1 AND OBSERVER 2

5.4.7. Conclusion

This study confirms that digitizing electrocardiographic parameters from a 12 lead ECG for subsequent storage and analysis is feasible, with very good intra and interobserver variation. This allows the system to be utilized by doctors and technicians trained in electrocardiography, who are familiar with the rules for defining wave forms already discussed in this chapter. This facilitates the analysis of large quantities of data such as that generated by large clinical trials. The study was designed especially to examine the variation in technique when clearly abnormal ECG's were digitized and has successfully validated its application in acute myocardial infarction, and has been shown to be sensitive enough to detect the quantitative changes in electrocardiographic parameters seen after thrombolysis.

CHAPTER 6

COMPARISON BETWEEN ANISTREPLASE AND STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

RESULTS I - DEMOGRAPHIC DATA

- ANGIOGRAPHIC PATENCY DATA

6.1. INTRODUCTION

The next 3 chapters present the results of a randomised trial conducted in Stobhill Coronary Care Unit comparing streptokinase and anistreplase, and to which the ECG methodology described in the previous chapter was prospectively applied. The primary end point of the study was to compare angiographic patency rates at 90 minutes and at 24 hours following therapy. The 12 lead electrocardiographs arising from this trial were digitized, providing a large data base with which to investigate those electrocardiographic parameters best indicating reperfusion and myocardial salvage. The analysis of each 12 lead ECG on presentation also provided a detailed account of those ECG changes occurring in the early phase of acute myocardial infarction which could be correlated with acute angiographic anatomy. This chapter details the study methodology, patient demographic data and presents the angiographic patency results. Chapter 7 deals with the admission ECG relating the findings to angiographic correlates. The results of analysis of the electrocardiographic markers of reperfusion and infarct evolution are presented in chapter 8.

6.2. AIM

The aim of this study was to investigate if there was any difference in patency rates between 1.5 M.U. streptokinase

given over one hour and 30 U anistreplase given as an intravenous bolus dose over 5 minutes in patients with acute myocardial infarction of ⩽6 hours duration.

6.3. PATIENTS AND METHODS

A copy of the study protocol is provided in appendix I, with a list of inclusion and exclusion criteria. One hundred and twenty-eight patients (101 M, 27F, age range 31-70, mean age 55.5 years) were recruited between April 1987 and December 1988. Individual patient details are listed in appendix VI. The size of the trial was calculated on the numbers which would be required to show a significant difference between treatments with adequate power assuming a patency of 80% for anistreplase based on previous work conducted in Stobhill (Hillis et al., 1987) and published work suggesting a patency rate of 55% for streptokinase (Verstraete et al. 1985a). Following written informed consent, the patients were randomised in a double-blind, double-dummy fashion to receive either 1.5 M.U. streptokinase intravenously over one hour or 30 U anistreplase (Beechams Pharmaceuticals) as an intravenous bolus over 5 minutes.

Patients underwent coronary angiography at 90 minutes following drug administration. The artery believed to be infarct-related, based on the admission ECG, was injected first, and this first injection scored according to the TIMI scale, a score of 0-1 denoting non-reperfusion and a

score of 2-3 indicating a patent artery (Williams et al., 1986; Appendix VII). The other coronary arteries were then injected in standard angiographic views. At the end of the procedure a femoral sheath was left in situ, and coronary angiography was repeated 24 hours after treatment, with left ventriculography being performed where possible. The coronary angiograms were reviewed by the consultant in charge of the patient to facilitate decisions regarding further therapy, and then independently scored on the TIMI scale by a consultant cardiologist experienced in scoring coronary angiograms who was not involved in the study and who was blinded to treatment allocation. This independent score is presented as final patency data.

Intravenous heparin was commenced in all patients 3-4 hours after onset of therapy titrating the dose against the thrombin time. If, at 24 hours the infarct-related artery was not patent, heparin was discontinued. If patency was confirmed at 24 hours, heparin was continued and warfarin introduced. Heparin was stopped in all cases for a short period after the second angiogram to allow the coagulation screen to normalize, enabling removal of the femoral sheath.

Results are expressed as percentages of patent arteries ±95% confidence intervals, calculated from the total number of angiograms performed. Patients not undergoing angiography were excluded from analysis, a technique used in other studies of similar design (Verstraete et al., 1987). Qualitative differences between groups were examined using the chi-squared test where appropriate and quantitative differences assessed using unpaired t-tests.

6.4. RESULTS

6.4.1. Baseline Characteristics

The baseline characteristics for the 128 subjects recruited are shown in Table 17 according to the thrombolytic agent received. There were no significant differences in the male to female ratio, mean age, infarct distribution or time to therapy between the two groups. There was a slightly higher incidence of patients in the streptokinase treated group having had a previous myocardial infarction distant to the current site (16% vs 6%), but this did not reach statistical significance.

	STREPTOKINASE	ANISTREPLASE	
TOTAL NO. OF PATIENTS	63	65	
SEX — FEMALE	11 (17%)	16 (25%)	NS
SEX — MALE	52 (83%)	49 (75%)	
MEAN AGE (yrs)	55.8±8.	55.3±8.1	NS
INFARCT RELATED ARTERY (by angiography)			
LAD	29 (46%)	25 (38%)	
RCA	27 (43%)	28 (43%)	NS
Cx	3 (5%)	9 (14%)	
NOT DETERMINED	4 (6%)	3 (5%)	
MEAN TIME TO THERAPY	209±80 min.	199±77 min.	NS
PREVIOUS M.I.	10 (16%)	4 (6%)	NS

TABLE 17: BASELINE CHARACTERISTICS OF PATIENTS RANDOMISED TO STREPTOKINASE OR TO ANISTREPLASE

6.4.2. Angiographic Patency

No pre-treatment angiogram was performed and so the results are presented as patency rates. Details of angiographic findings are shown in Table 18 for both 90 minutes and 24 hours. A total of 116 angiograms were performed at 90 minutes post therapy and 114 at 24 hours following therapy, giving a total angiography rate of 91% and 89% respectively. Four patients died within 90 minutes of receiving thrombolytic therapy (anistreplase 1, streptokinase 3). Of the remaining 8 angiograms not performed at 90 minutes, 3 were due to the patients being too haemodynamically unstable, 2 were due to extensive bruising round the femoral vein and artery (one from a Swan Ganz insertion and one from a femoral puncture for blood gases during earlier resuscitation), arterial access was not obtained in a further 2 patients and in another 1 patient who received streptokinase there was extravasation of therapy 20-30 minutes after infusion onset and the patient was withdrawn from the study. By the 24 hour angiogram a further 3 patients had died (anistreplase 2, streptokinase 1). Of the remaining 7 angiograms not performed at this time, poor patient condition accounted for 2, problems with arterial access for 1 and haematoma formation round the femoral sheath in a further 2 patients necessitated early removal of the sheath in 1 and inability to pass the guide wire through the sheath in the other. One patient had sustained a cerebrovascular accident following the 90 minute angiogram and it was

considered unethical to repeat the 24 hour angiogram, and the remaining patient had been withdrawn due to extravasation of drug.

Of the angiograms performed 32 of 58 patients (55%) receiving anistreplase and 31 of 58 (53%) receiving streptokinase had patent infarct-related arteries at 90 minutes (95% confidence intervals 42-68% for anistreplase and 40-66% for streptokinase). By 24 hours, 81% of patients receiving anistreplase and 87.5% of patients receiving streptokinase had patent arteries (Figure 17). One patient in each treatment group had angiographic evidence of reocclusion at 24 hours. Both had occlusion of the right coronary artery, the TIMI score being reduced from 2 at 90 minutes to 0 at 24 hours in the patient who received streptokinase and from 3 to 0 in the patient who had anistreplase.

All patients fulfilled ECG criteria for entry into the study, but two patients subsequently failed to show a rise in cardiac enzymes (patients 58 and 80). Coronary angiography revealed normal coronary arteries in one patient (80) and minor insignificant irregularities in the other (58). Both patients received streptokinase and their exclusion does not significantly alter the patency rates reported (52% vs 53% NS).

		STREPTOKINASE		ANISTREPLASE	
Total No. of Patients		63		65	
90 MINUTE ANGIOGRAM					
	TIMIGRADE				
NON REPERFUSION	0	21	(47%)	22	(45%)
	1	6		4	
					NS
REPERFUSION	2	7	(53%)	10	(55%)
	3	24		22	
ANGIO NOT PERFORMED		5		7	
24 HOUR ANGIOGRAM					
	TIMIGRADE				
NON REPERFUSION	0	4	(12.5%)	10	(19%)
	1	3		1	
					NS
REPERFUSION	2	11	(87.5%)	8	(81%)
	3	38		39	
ANGIO NOT PERFORMED		4		6	

TABLE 18: ANGIOGRAPHIC DETAILS FOR PATIENTS RANDOMISED TO STREPTOKINASE OR ANISTREPLASE AT 90 MINUTES AND AT 24 HOURS

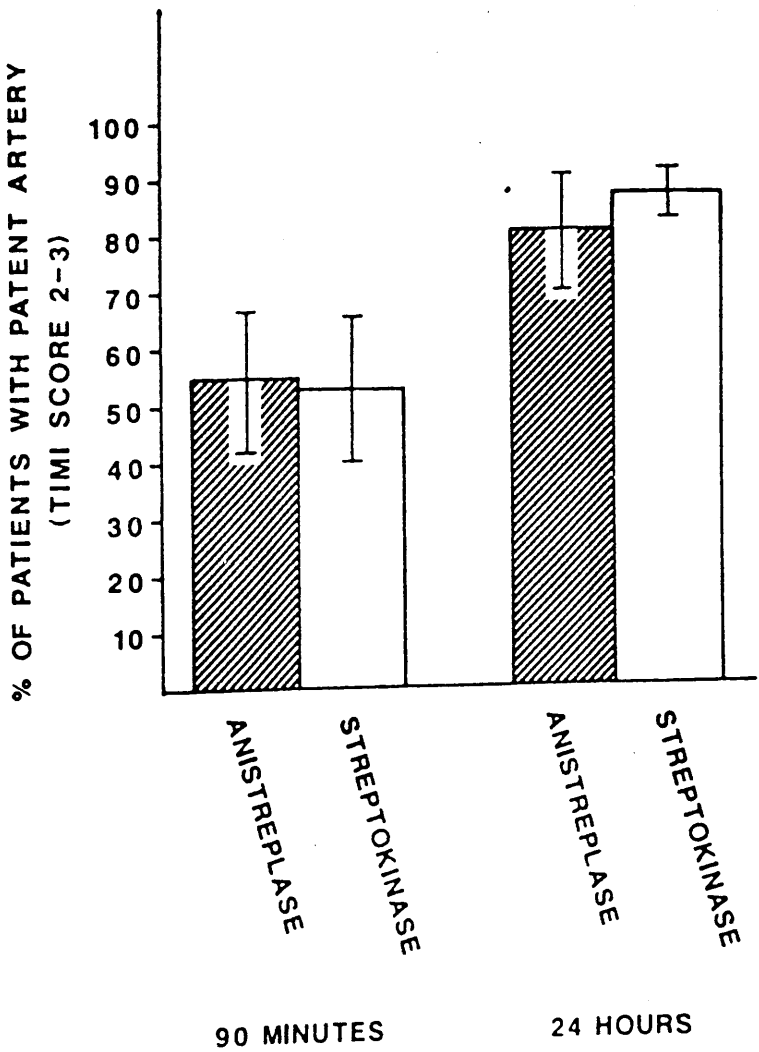


FIGURE 17: PATENCY DATA OF INFARCT RELATED ARTERY AT 90 MIN AND 24 HOURS WITH 95% CONFIDENCE INTERVALS SHOWN

6.4.3. Influence of Time to Therapy on Patency Rates

Figure 18 shows the patency rate at 90 minutes and 24 hours related to the time to therapy from symptom onset. Very few patients (n=3) were admitted and treated within the first hour, the majority of patients (n=71) being treated between 2 and 4 hours from onset of pain. Although from the table it appears that there is initially a decreasing patency rate with increasing time to therapy i.e. for anistreplase 67% at 61-120 min, 47% at 121-180 minutes and 38% at 181-240 minutes, this is not borne out as the highest patency rate is 78% for the next time interval 241-300 minutes. Somewhat paradoxically looking at 24 hour patency rates for early (0-3 hours) and late groups (3-6 hours) in Table 19, it is the group presenting late which has the higher patency rate i.e. 89% versus 78%. This is true irrespective of which agent is used i.e. 94% versus 78% for streptokinase and 84% versus 78% for anistreplase. However, as subdividing the treatment groups in this way results in smaller numbers, the 95% confidence intervals of these patency rates are wide and there is no significant difference in patency rates obtained dependent on time to therapy.

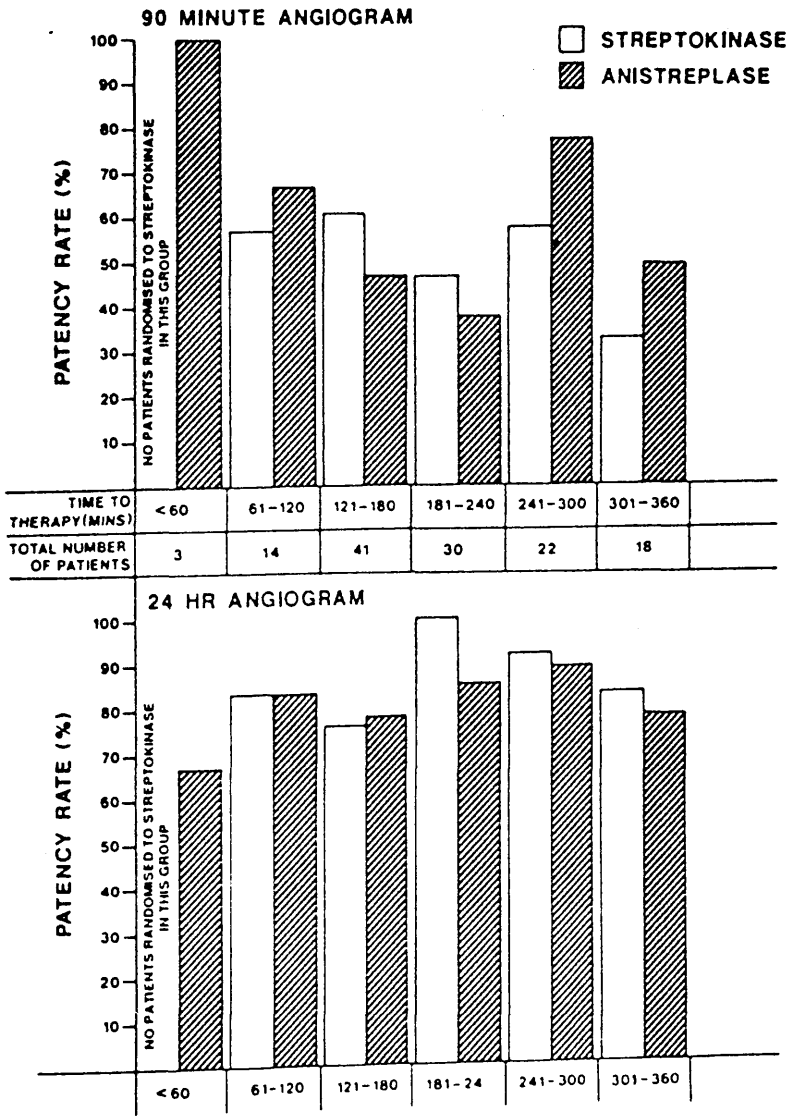


FIGURE 18: PATENCY DATA RELATED TO TIME TO THERAPY FROM SYMPTOM ONSET AT 90 MINUTES AND AT 24 HOURS

	TIME TO THERAPY (HOURS)		
	0-3 Hrs	3-6 Hrs	
90 MINUTE ANGIO			
Streptokinase	15/25 (60%)	16/33 (48%)	NS
Anistreplase	16/28 (57%)	16/30 (53%)	NS
24 HR ANGIOGRAM			
Streptokinase	18/23 (78%)	31/33 (94%)	NS
Anistreplase	21/27 (78%)	26/31 (84%)	NS

TABLE 19: PATENCY RATE RELATED TO TIME TO THERAPY FROM SYMPTOM ONSET

6.4.4. Haemodynamic Data

Satisfactory blood pressure data was obtained every 2 minutes for the first 90 minutes post treatment in 106 patients (anistreplase 48, streptokinase 58). Forty-two percent of patients who received anistreplase and 45% of patients who had streptokinase experienced an early fall in blood pressure as previously defined. This fall in blood pressure was rarely associated with symptoms or required specific treatment. In general nitrate therapy was stopped transiently until the blood pressure recovered, but none of the patients required treatment with dopamine or dobutamine.

6.4.5. Adverse Events

Table 20 documents those adverse events occurring in both treatment groups until hospital discharge. Bleeding problems were numerically the most important, but out of the 21 reported, 81% were related to the site of arterial puncture for coronary arteriography. There was no difference in incidence of bleeding between the two groups. However there was a higher incidence of skin rash in patients receiving streptokinase, and in 4 of these it took the form of a vasculitic rash which lasted about 2 weeks. One patient in each treatment group received therapy for anaphylaxis related to the injection or infusion.

The single cerebrovascular accident reported in the anistreplase group refers to a transient ischaemic attack which resolved completely in 24 hours. Two cerebrovascular accidents occurred in the streptokinase treatment group, 1 presenting after the 90 minute angiogram and the other at 48 hours following therapy. This latter patient subsequently died in cardiogenic shock but the former patient has made a reasonable recovery, with only a mild residual left hemiparesis. Neither patient underwent CT scanning.

EVENT	STREPTOKINASE	ANISTREPLASE
Total No. of patients receiving treatment	63	65
A. Skin-rash		
1. Vasculitic	4	0
2. Mild, transient	2	1
B. Anaphylaxis -related to i.v. administration requiring i.v. treatment	1	1
C. Bleeding		
1. From catheter site		
(a) No intervention	5	2
(b) Anticoagulants stopped ± protamine	3	5
(c) Required transfusion	1	1
2. From other sites		
(a) Venepuncture	0	1
(b) Haematemisis	1	2
D. Cerebrovascular accident	2	1*
E. Further clinical events		
1. Reocclusion (ECG + enzymes)	3	2
2. Refractory arrhythmias	0	1
3. Left ventricular failure	0	1
4. Angioplasty prior to discharge	0	2
F. Miscellaneous		
1. Sore throat	0	1
2. Extravasation of drug (full treatment not given)	1	0

* refers to TIA resolving within 24 hours

TABLE 20: ADVERSE EVENTS TO HOSPITAL DISCHARGE

6.4.6 Clinical Evidence of Reocclusion

There were a total of 5 episodes with clinical evidence of reocclusion after the 24 hour angiogram had been performed, and prior to hospital discharge (Table 20). Two patients died, 1 had emergency angioplasty and the remaining 2 had no intervention and both made an uncomplicated recovery.

6.4.7. Mortality Rates

There were 10 deaths in total up to hospital discharge, 6 in the streptokinase group (9.5%) and 4 in the anistreplase group (6%). The majority of these deaths occurred within the first 24 hours in patients with extensive infarction (anistreplase 3, streptokinase 4). Four of these deaths occurred within the first 90 minutes of treatment, 1 of which was due to cardiac tamponade from a ruptured posterior ventricular wall. Of the 3 deaths occurring between 24 hours and hospital discharge (anistreplase 1, streptokinase 2) 2 were due to reocclusion and extension of the infarct occurring at 2 days post treatment in the patient receiving streptokinase and at 5 days in the patient receiving anistreplase. The third patient died of cardiogenic shock and also sustained a cerebrovascular accident.

6.5. DISCUSSION

The results of this study show that there is no difference in the 90 minute patency rates between patients receiving 30 U anistreplase and 1.5 M.U. streptokinase intravenously for acute myocardial infarction of ≤6 hours duration. The percentage patency rates were 55% and 53% for the two treatment groups respectively. In an attempt to shorten the delay for thrombolytic therapy to be administered, none of the patients received a pre-treatment angiogram and therefore patency rates and not reperfusion rates are reported. According to the data of de Wood et al. (1980) partial occlusion at presentation may result in a patency rate which over-estimates the true reperfusion rate by at least 13%.

The observed patency rate of 55% with anistreplase in this study is similar to the data reported by the Anderson group of 51% reperfusion at 90 minutes (Anderson et al., 1988) but is at variance with our previously published work (Hillis et al., 1987) and with the higher rates of 64% reperfusion at 90 minutes reported by Bonnier et al. (1988), 72% patency by Brochier et al. (1987), and 86% patency by Lopez-Sendon et al. (1988). The variation in these results can be accounted for to some extent by differences in mean time to therapy, total patient numbers recruited and the exact timing of the 90 minute angiogram. Timing of this is critical as it would seem that the increase in reperfused coronary arteries resulting in a

difference between 55% patency at 90 minutes and 81% at 24 hours may well be occurring in the few hours after therapy when the fibrinolytic effect is at its peak. In our present study it was the first injection into the infarct-related artery which was assessed for patency status, although in several cases the artery was seen to reperfuse during serial injections. In our previous study (Hillis et al., 1987) coronary angiography was carried out between 90 and 180 minutes post treatment, and this may account for the discrepancy in patency rates between the two studies.

The patency rate of 53% for 1.5 M.U. of streptokinase is higher than that of 35% previously reported in the TIMI (Phase I) Trial (TIMI Study group., 1985). This is probably due to the difference in mean time to therapy being 4.8 hours in the TIMI Phase I Trial and 3.5 hours in the present study. The European Co- operative Study Group documented a patency rate of 55% treating at a mean of 2.6 hours from symptom onset (Verstraete et al., 1985a). There is well documented data pooled from multiple studies showing a decrease in incidence of reperfusion with streptokinase in relation to time to treatment (Sherry, 1987). A similar phenomenon has been suggested for anistreplase (Anderson et al., 1988). Subdividing the patients in this study into 6 groups dependant upon the time from symptom onset results in subsets with very small

numbers. Nevertheless, there appears to be almost a biphasic reperfusion curve with a second peak occurring at the 241-300 minute time interval. A hypothesis to explain this may be that patients presenting later may have less clamant symptoms, and may be more likely to have a sub total occlusion i.e. TIMI grade I. This sub group are known to have a higher incidence of reperfusion following thrombolytic therapy (Anderson et al., 1988). Despite this second peak, dividing the patients into an early (0-3 hours) and late (3-6 hours) group showed patency rates at 90 minutes of 60% and 48% respectively for streptokinase, compared with 57% and 53% respectively for anistreplase. It is of interest that the AIMS Trial Study Group (1988) reported similar reduction in mortality irrespective of whether the patients were treated early (0-4 hrs) or late (4-6 hrs).

No intervention was performed other than standard anticoagulation with heparin in any patient between 90 min and 24 hours, allowing an accurate reocclusion rate to be calculated at the 24 hour angiogram. This is very low, only 1 patient in each treatment group showing evidence of reocclusion. This is similar to a 24 hour anistreplase reocclusion rate reported by Bonnier et al, (1988). Evidence of reocclusion prior to hospital discharge (confirmed by ECG and enzyme changes) took place in a further 3 patients (5%) who received streptokinase and 2 patients (3%) who had received anistreplase. This seems

to be in keeping with the incidence of reinfarction reported by GISSI of 4.1% (1987). Although these figures indicate reinfarction, a higher percentage of patients undetectable in this type of study design may have angiographic evidence of re-thrombosis and reocclusion - a discrepancy recognised by and reported by Geltman (1987).

A transient drop in blood pressure which was usually well tolerated was observed in slightly less than half of all patients. This is a high incidence compared to episodes of hypotension reported in the AIMS Study (8 out of 502 (1.5%)) (1988). Although hypotension is a common occurrence, this transient drop in blood pressure does not require treatment and may go unnoticed, suggesting that the haemodynamic response to bolus anistreplase may have been overemphasized.

Catheter-related haemorrhage formed the most substantial part of bleeding complications, but only 1 person in each group developed a haematoma such that transfusion was required. Although a serum sickness type illness with associated vasculitic rash is now a recognised complication of streptokinase therapy (Weatherbee, 1984; Noel et al., 1987; Gemmill et al., 1988) a recent report suggested it also occurred with anistreplase therapy (Bucknall et al., 1988). Although none of the patients in this study receiving anistreplase developed a vasculitic

rash, it is likely that it is the streptokinase moiety which is responsible, and as such anistreplase might be expected to be implicated in a similar type of reaction.

In conclusion, this study has shown that 30 U anistreplase given as an intravenous bolus is as effective in obtaining coronary artery patency at 90 minutes as 1.5 MU streptokinase given as an infusion over 1 hour. Patency rates at 90 minutes are 55 and 53% respectively, and 81 and 87.5% respectively at 24 hours. There is a very low reocclusion rate in patients obtaining reperfusion who receive no other intervention other than standard anti-coagulation with heparin and warfarin. This is true irrespective of which agent was used. As anistreplase is as effective as intravenous streptokinase at obtaining a patent artery within 6 hours of onset of acute myocardial infarction, its major advantage lies in its bolus route of admin-istration, making it an easy treatment to give in an out-of-hospital setting. Whether further saving of time to therapy will result in better reperfusion or patency rates and a decrease in mortality has still to be proven.

CHAPTER 7

COMPARISON BETWEEN ANISTREPLASE AND STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

RESULTS II - THE 12 LEAD ELECTROCARDIOGRAPH IN ACUTE MYOCARDIAL INFARCTION

7.1. INTRODUCTION

The accuracy of the 12 lead ECG in localising acute myocardial infarction has previously been discussed in Chapter I Section B. Initially this was based on a series of post mortem examinations (Myers et al., 1948 a-b, 1949 a-e) but has been added to by studies comparing ECG findings with the results of angiography early in the course of acute myocardial infarction (Blanke et al., 1984b). Other workers have retrospectively studied patients with single vessel disease to further clarify the situation (Fuchs et al., 1982), but have performed angiography at a considerable distance from the time of infarction , and have used the presence or absence of Q waves rather than the earlier changes in ST segment elevation to indicate the anatomical location of the occlusion. Despite the number of studies which have performed acute angiography early in the course of myocardial infarction, usually in the context of thrombolysis, few have correlated findings with a comprehensive analysis of the 12 lead ECG at presentation. Most studies concentrate on the degree of ST segment elevation but the presence and extent of reciprocal ST segment depression and its relationship to arteriographic findings is not well documented. Work by Bar et al. (1987) using ECG data from the Netherlands Interuniversity Group (Simoons et al., 1985) showed that the admission ECG was of some value in predicting which patients would benefit most from thrombolysis. Not suprisingly those

patients with the highest ST segment elevation and no Q waves (both anterior and inferior infarction) fared best, but another group presenting early with high ST segment elevation who also had already developed Q waves had an impressive degree of infarct limitation. Thus, the admission ECG is not only of value in the diagnosis of acute myocardial infarction, but may highlight patients who would benefit especially from thrombolysis. It is therefore of value to study the ECG on admission, and to correlate the findings with acute angiographic anatomy. This chapter presents the observational changes in ST segment elevation and depression at presentation in patients with an acute myocardial infarction of $\leq$ 6 hours duration.

7.2. PATIENTS AND METHODS

The patient group consisted of that group recruited for the anistreplase/streptokinase comparison study detailed in Chapter 6. Of the initial 128 patients only 125 had ECGs suitable for analysis. The 3 patients who did not (patients 13, 53 and 115) all had a complete right bundle branch block pattern, and in addition, patient No. 115 also had left axis deviation and died soon after starting therapy. Twelve lead ECG's were performed on admission and at 2, 4, 16, 18 and 24 hours following therapy using the method discussed in Chapter 2. These electrocardiograms were digitized according to the method described in Chapter 5, and each patient coded for age, sex, infarct related artery, patency data at 90 minutes and at 24 hours, the drug given (anistreplase or streptokinase), the time to therapy and finally the presence of a previous infarct. Data were then transferred to a mainframe computer (ICL2980) and analysed using MINITAB. If a patient developed transient bundle branch block or pacemaker dependence, the ECG showing this was not digitized, but the subsequent one was included if the patient had reverted to sinus rhythm with normal conduction.

Each coronary angiogram was scored for degree of perfusion of the infarct related artery, as described in Chapter 6, but in addition all arteries were individually scored for disease using the following scale: 0, normal; 1, <50%; 2,50-90%; 3,91-99% (complete filling); 4,99% (incomplete filling); 5,100%; 6,absent; 7,unknown.

7.3 RESULTS

7.3.1. Collection of ECG data

The total potential number of ECG's arising from this study is 750 (i.e. 125 x 6). Of this total, 50 have not been digitized, in 16 of these the patient had died prior to the ECG being recorded. The remaining 34 ECG's were not digitized either because of a temporary conduction defect, because of poor quality tracing or because the ECG was not recorded. This results in a 95.5% complete collection of all possible data. The admission ECG has not been digitized in two patients, although the ECG series for each of these patients is otherwise complete. In one, (patient No.35), the admission ECG was lost following randomisation, and in another patient (patient No.103), a temporary conduction defect precluded digitization. Both patients have been eliminated from analysis.

Patients who did not have the infarct-related artery identified by coronary angiography are not included in the analysis. A small number of patients (n=5) did not undergo angiography at 90 minutes, but had the infarct-related artery identified at 24 hours, and these patients are included. A total of 117 admission ECG's have been analyzed, 51 patients having occlusion of the left anterior descending artery (LAD), 54 patients having occlusion of the right coronary artery (RCA) and 12 patients presenting with occlusion of the circumflex artery (Cx).

7.3.2. Distribution of ST segment shift on admission ECG in relation to infarct-related artery

Figures 19-21 show the percentage of all leads (excluding AVR) showing some degree of ST segment elevation and, or depression on the admission ECG as measured on the digitizer and divided on the basis of the infarct-related artery.

Figure 19 shows that for the 51 patients with LAD occlusion, 98% have ST segment elevation in V_2 and 100% had ST segment elevation in V_3. A substantial percentage of those patients also showed ST segment elevation in classically termed inferior leads (14% for lead III, 21.5% lead II), but by far the most common finding was of reciprocal ST segment depression, lead II showing ST segment depression in 47%, lead III in 69%, and AVF in 67%.

For the 54 patients who had an occlusion of the RCA, 100% of those patients had ST segment elevation in leads III and AVF and 93% in lead II. Of particular interest was the high percentage of leads showing reciprocal changes on the admission ECG, 100% of patients with an RCA occlusion had ST segment depression in AVL, 87% in lead I, 80% in V_2 and 78% in V_3 (Figure 20).

Figure 21 shows the distribution of ST segment shift on the admission ECG for 12 patients with a Cx occlusion. Although numbers are smaller than in the other two groups, it can be seen that there is no simple method of separating out Cx occlusion from RCA occlusion. 100% of patients had ST segment elevation in II and AVF and the incidence of reciprocal anterior ST segment depression was 84% in V_2 and 75% in V_1 and V_3. Patients with RCA occlusion never demonstrated ST segment elevation in I and AVL but 42% and 17% of patients with Cx occlusion demonstrated ST segment elevation in those leads respectively. Taking ST segment elevation in Lead 1 as a marker for Cx occlusion gives a test with a specificity of 100%, but a low sensitivity of 42%. Fifty-eight per cent. of Cx occlusions will not have ST elevation in lead I at presentation.

Although all patients fulfilled the ECG criteria for inclusion into the study ($\geq$ 1mm ST elevation in 2 limb leads or $\geq$ 2mm ST elevation 2 precordial leads), the data shown in figures 19-21 reflects any deviation from the isoelectric line, and may in some leads represent small changes which are less than the conventionally accepted cut-off points designating "significant" ST segment shift. To compare the incidence of reciprocal change between this data base and that reported in the literature requires that the same criteria for definition of reciprocal change is applied. Reciprocal change is most commonly described

as more than 1 mm horizontal or sloping ST segment depression in leads remote from the site of infarction. Table 21 shows the decreasing incidence of reciprocal change with increasingly stringent cut-off limits for significant ST depression. Assuming ST depression of $\geq$ 1mm to be significant, results in a true incidence of reciprocal change of 55% in lead III in anterior infarction, 89% in AVL and 72% in V_2 for inferior infarction, and 75% in V_3 for Cx occlusion. The relationship between reciprocal change and coronary artery anatomy is discussed in Section 7.3.6.

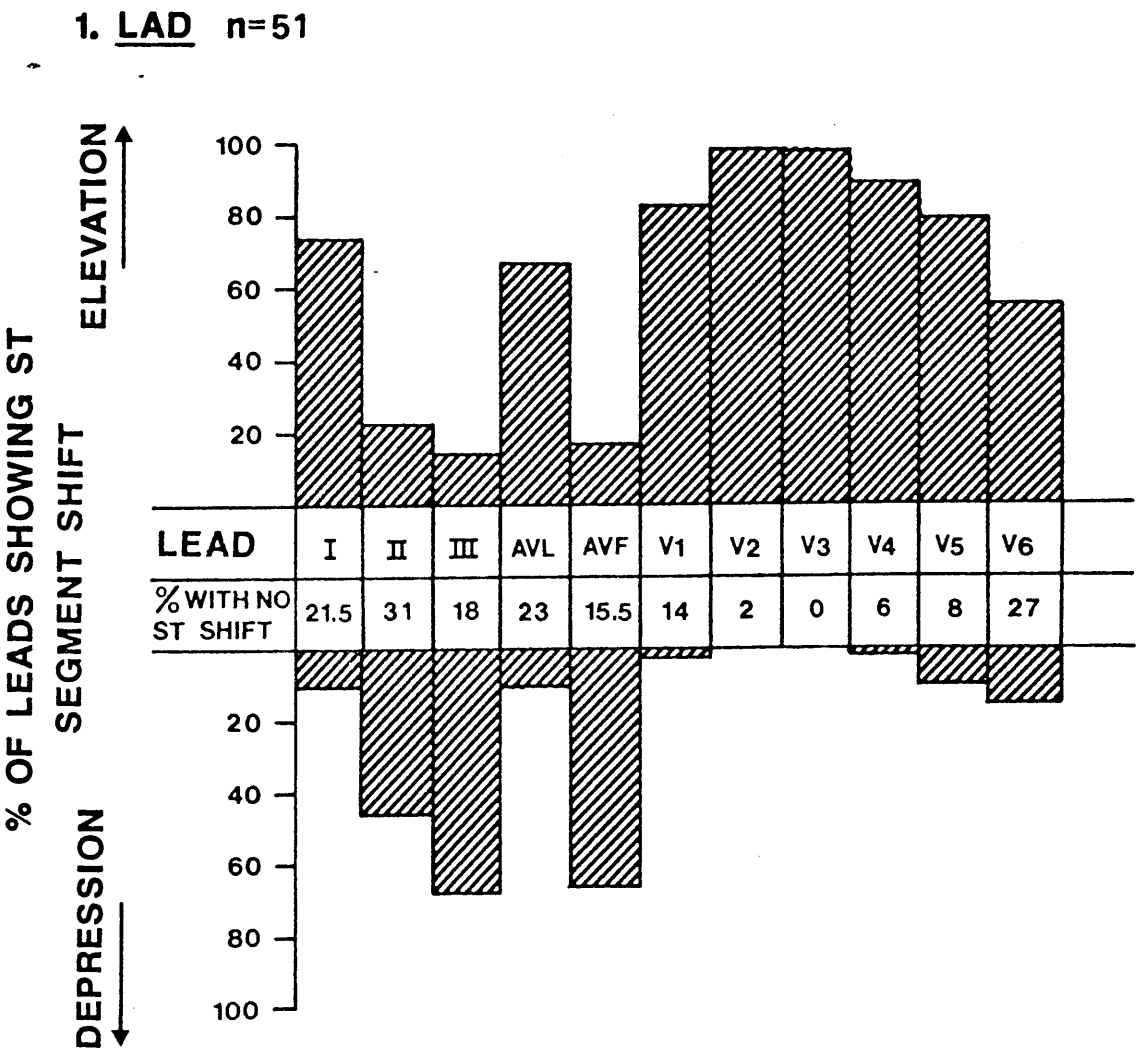


FIGURE 19: DISTRIBUTION BETWEEN ST SEGMENT SHIFT AND INFARCT RELATED ARTERY ON ADMISSION ECG:1: LAD OCCLUSION

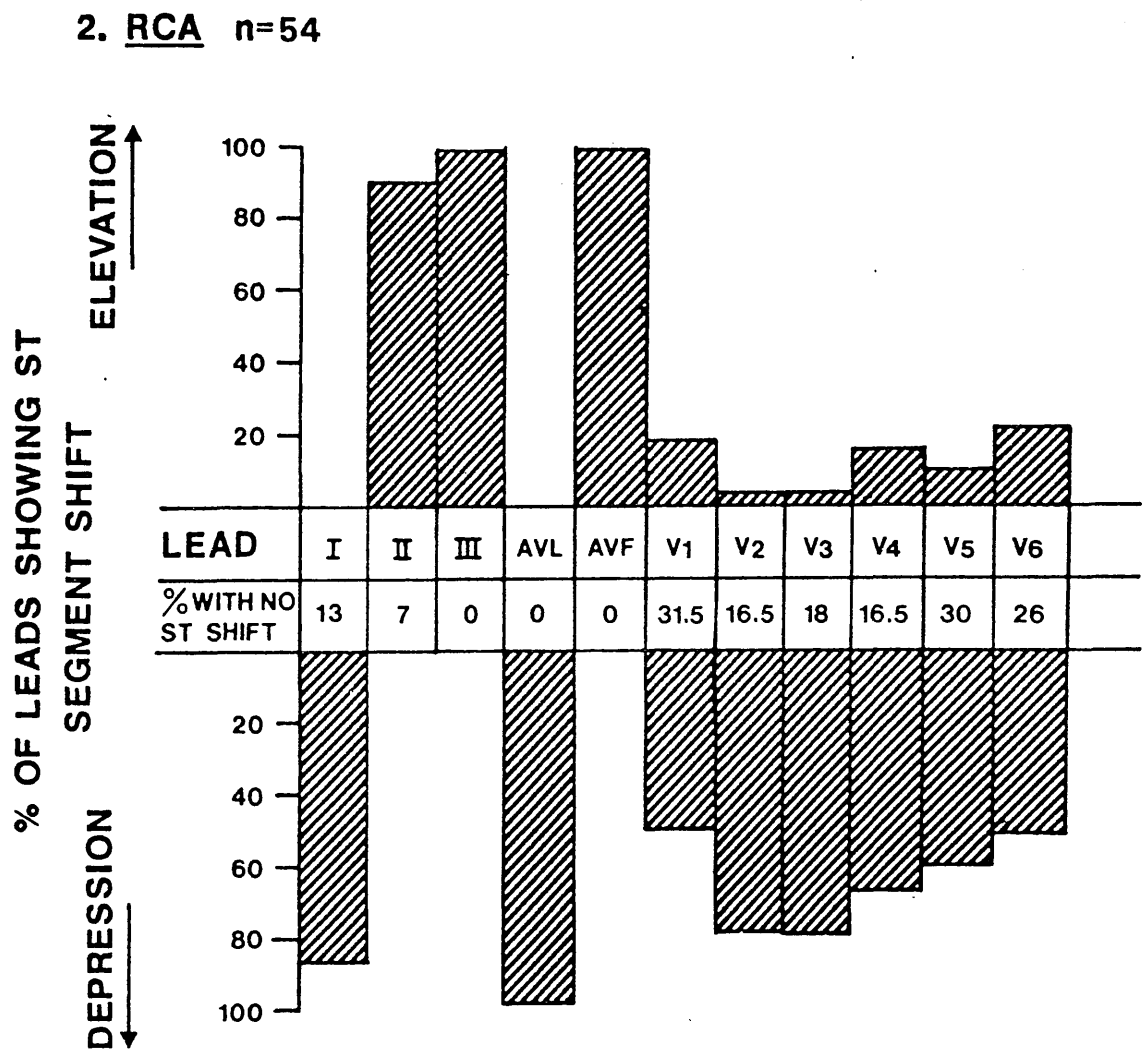


FIGURE 20: DISTRIBUTION BETWEEN ST SEGMENT SHIFT AND INFARCT RELATED ARTERY ON ADMISSION ECG:2: RCA OCCLUSION

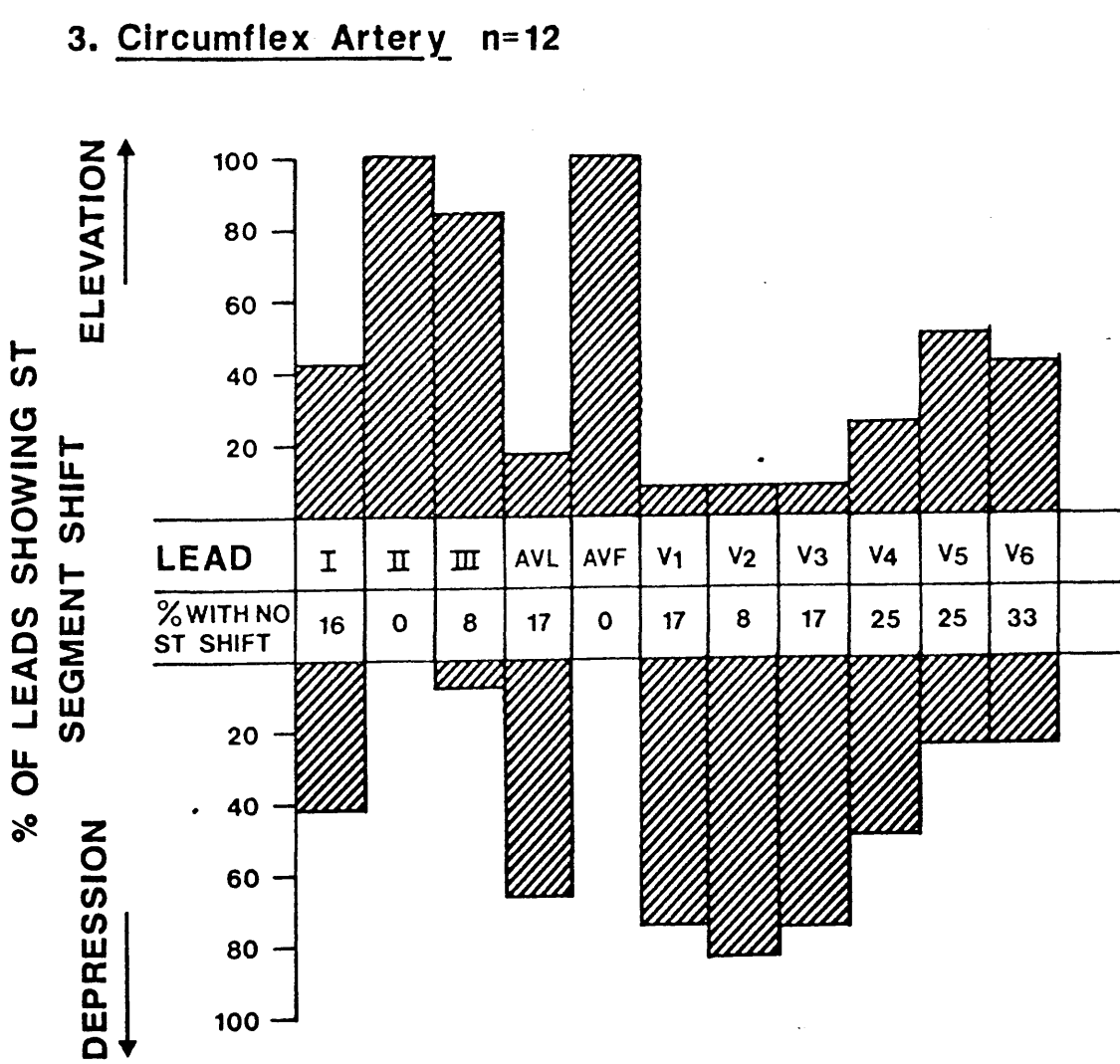


FIGURE 21: DISTRIBUTION BETWEEN ST SEGMENT SHIFT AND INFARCT RELATED ARTERY ON ADMISSION ECG:3: Cx OCCLUSION

INFARCT RELATED ARTERY	LEAD	LIMITS FOR DEFINITION OF RECIPROCAL CHANGE NONE	≥ 0.5 MM	≥ 1 MM	≥ 2 MM
	II	47%	39%	14%	2%
L.A.D.	III	69%	65%	55%	14%
(n=51)	AVF	67%	65%	39%	6%
	I	87%	85%	67%	30%
	AVL	100%	100%	89%	61%
	V1	50%	44%	27%	4%
R.C.A.	V2	80%	80%	72%	48%
(n=54)	V3	78%	78%	69%	41%
	V4	69%	67%	57%	22%
	V1	75%	67%	50%	33%
Cx	V2	83%	83%	67%	50%
(n=12)	V3	75%	75%	75%	58%
	V4	50%	50%	33%	17%

TABLE 21: VARYING INCIDENCE OF RECIPROCAL CHANGE RELATED TO DEGREE OF ST SEGMENT DEPRESSION.

7.3.3. Degree and location of maximum ST segment shift

Figure 22 shows a bar histogram detailing which single lead from the 12 lead admission ECG showed the maximum degree of ST segment elevation, and also which one lead showed the maximum degree of reciprocal change for each patient presenting with an acute coronary occlusion. Figures 23-25 show the mean ($\pm$ SD) values of ST segment elevation and depression for each of the leads for LAD, RCA, and Cx occlusions respectively. Results are expressed in mm rather than mV for convenience. It can be seen that the most "dynamic" leads (i.e. those resulting in most ST segment shift) are leads V_2 and V_3 for elevation in an LAD occlusion (mean ST elevation; 4.7 ± 2.4 mm for V_2, 5.5 ± 3.2 mm for V_3), and lead III in a RCA occlusion (3.7 ± 2.3 mm). Reciprocal changes tend to be of similar magnitude across several leads (-2.5 ± 1.5 mm for AVL, -2.5 ± 1.5 mm for V_2 and -2.5 ± 0.17 mm for V_3 in RCA occlusion) except in Cx occlusion, where V_2 and V_3 have a higher mean value of ST segment depression (i.e. -3.3 ± 2.6 mm and -3.6 ± 2.4 mm respectively).

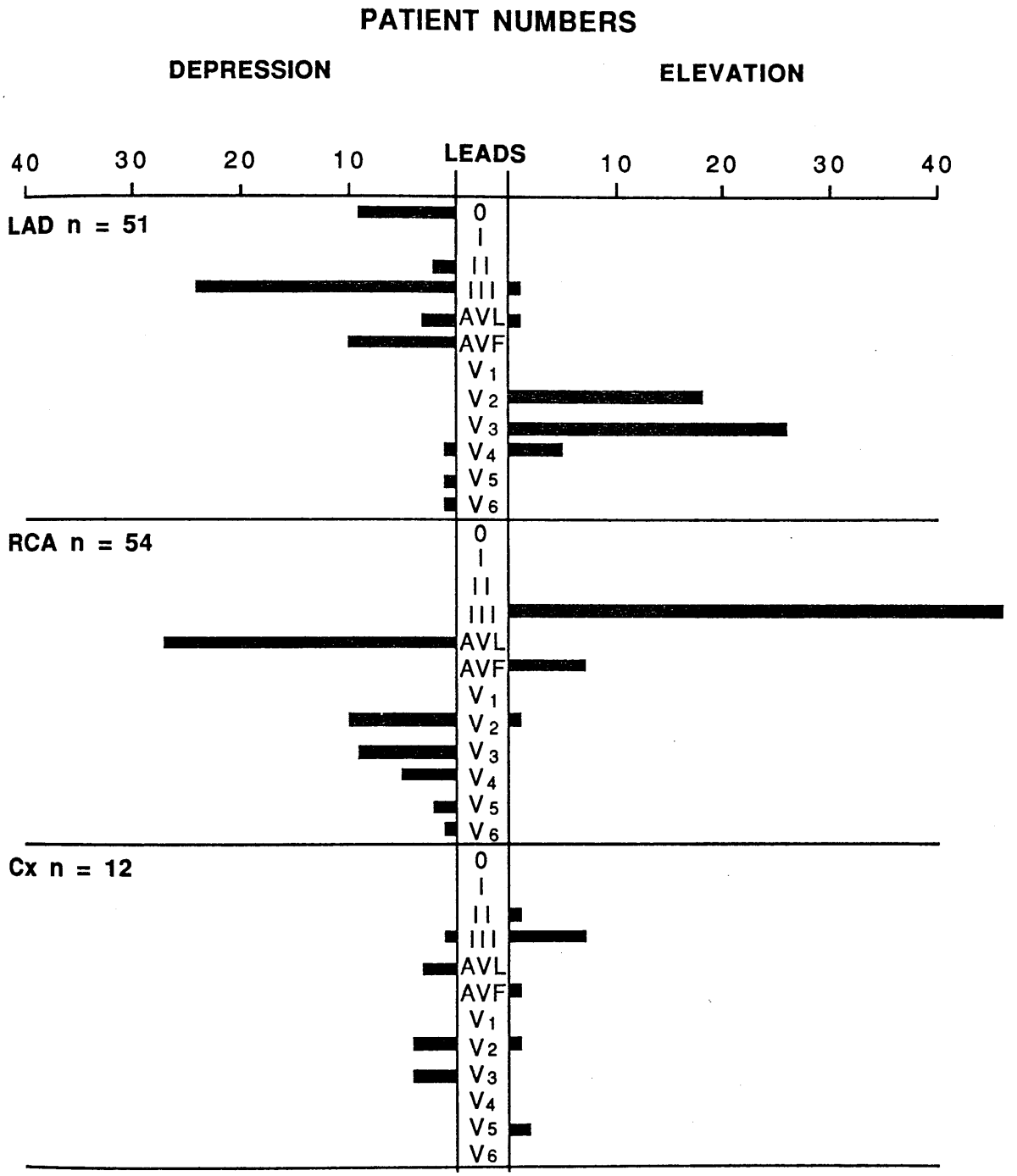


FIGURE 22: DISTRIBUTION OF LEADS SHOWING MAXIMUM ST SEGMENT DEVIATION (ELEVATION AND DEPRESSION) ON ADMISSION ECG

1. Infarct Related Artery = LAD n=51

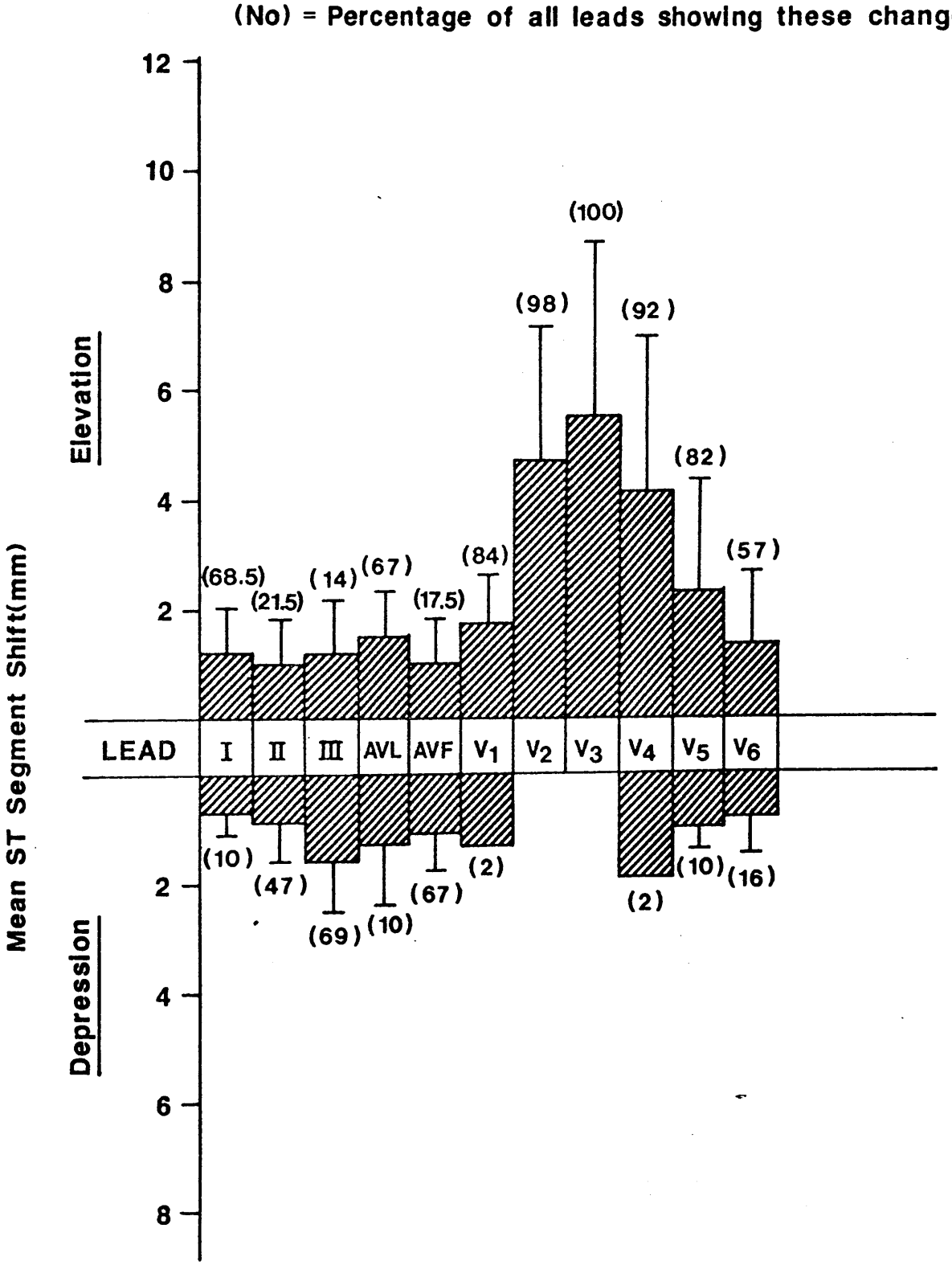


FIGURE 23: MEAN ST SEGMENT SHIFT FOR EACH LEAD ON ADMISSION ECG: LAD OCCLUSION

2. Infarct Related Artery = RCA n=54

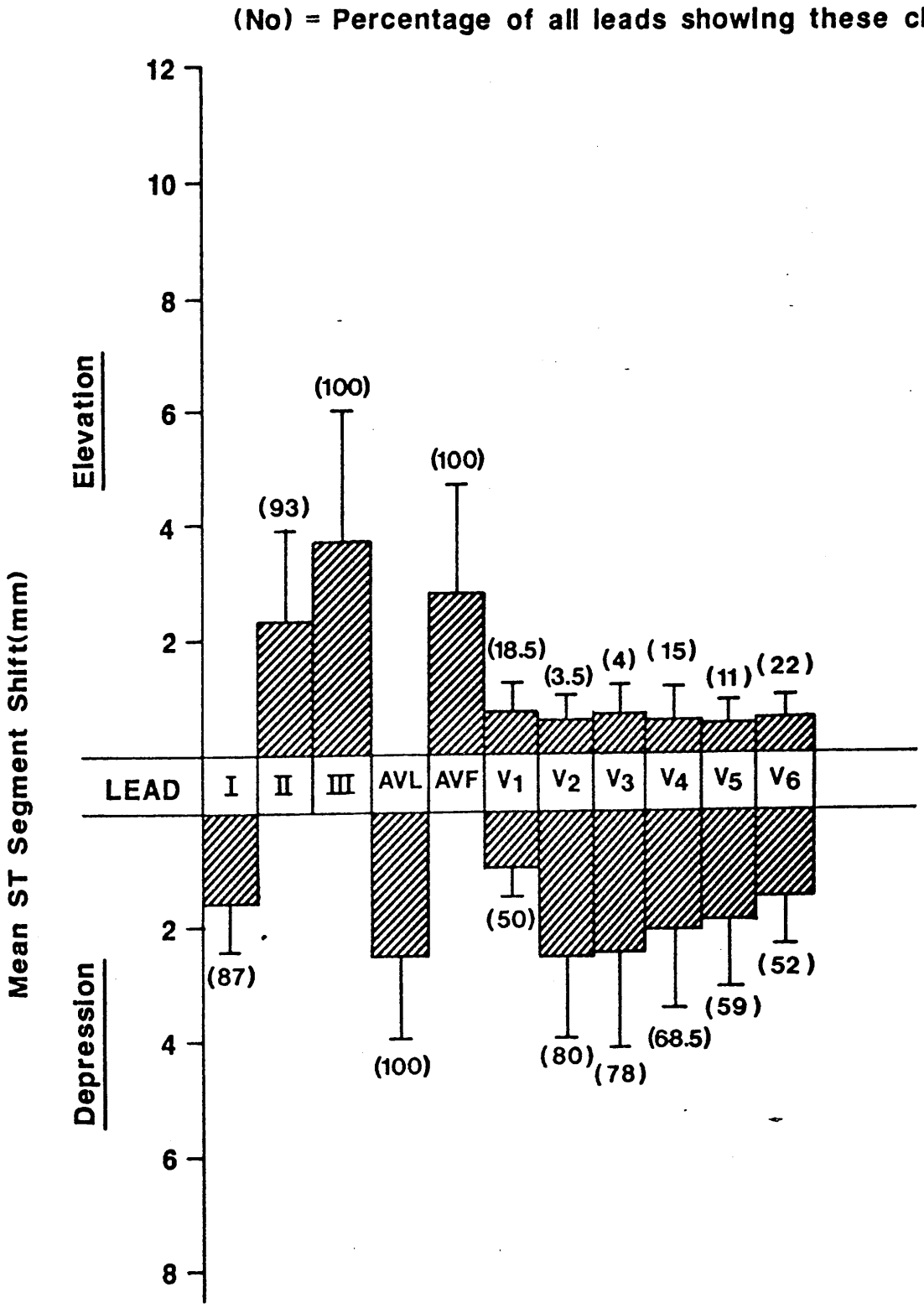


FIGURE 24: MEAN ST SEGMENT SHIFT FOR EACH LEAD ON ADMISSION ECG: RCA OCCLUSION

3. Infarct Related Artery = Cx n=12

(No) = Percentage of all leads showing these changes.

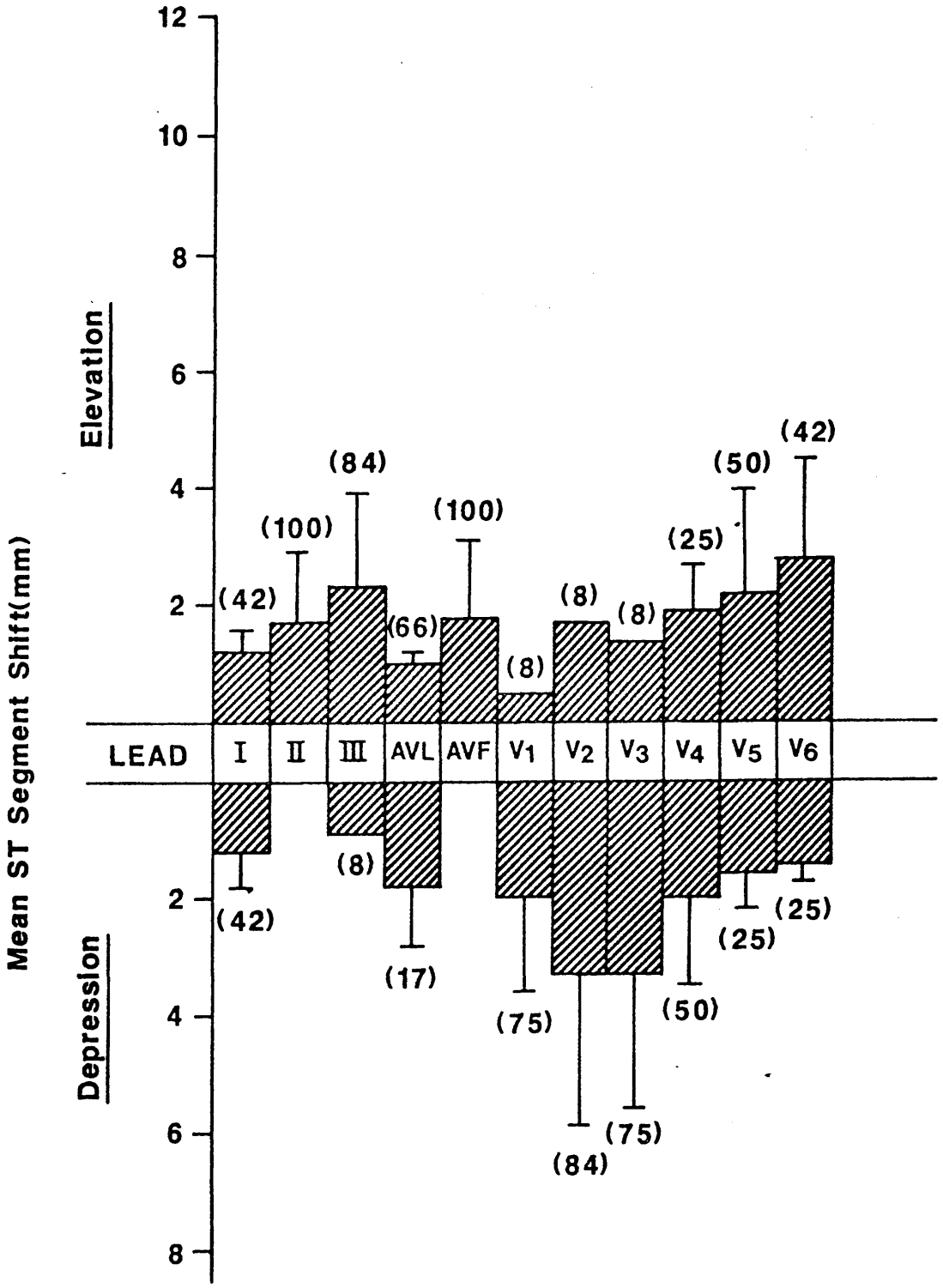


FIGURE 25: MEAN ST SEGMENT SHIFT FOR EACH LEAD ON ADMISSION ECG: Cx OCCLUSION

7.3.4. Influence of time to presentation on extent of ST segment shift

Figure 26 and 27 are scattergrams showing respectively, the relationship between the sum of ST segment elevation and time to therapy, and the sum of ST segment depression and time to therapy for all patients recruited to the study (n=123). It should be noted that the X axis represents the time to therapy in minutes, and not the exact time of recording of the presentation ECG. The interval between these two events is on average about 30 minutes and is constant for all cases. The use of "time to therapy" on the X scale should not influence any correlation which exists, the only effect being to move all points 30 minutes to the right.

There is no relationship between $\sum$ST elevation on admission and time to therapy (Figure 26 r=-0.031). Figure 27 does however show an inverse relationship between the extent of $\sum$ST depression and time to therapy (r=-0.27) suggesting that the earlier the patient presents, the more marked will be the degree of ST segment depression. Although this r value of -0.27 carries a p value <0.01, it can be seen from the scattergram, and also from the r value, that this is not a strong relationship, and it is unwise to attach much significance to it. Similarly, from Table 22 it can be seen that by subdividing the groups according to the infarct-related artery, or by looking at $\sum$ST area (mm^2) or the single

lead with maximal ST segment shift, both for elevation and depression, results in weak correlations, suggesting little in the way of any true relationship. The RCA appears to have the strongest correlation between the extent of ST segment shift (both elevation and depression) and time to therapy.

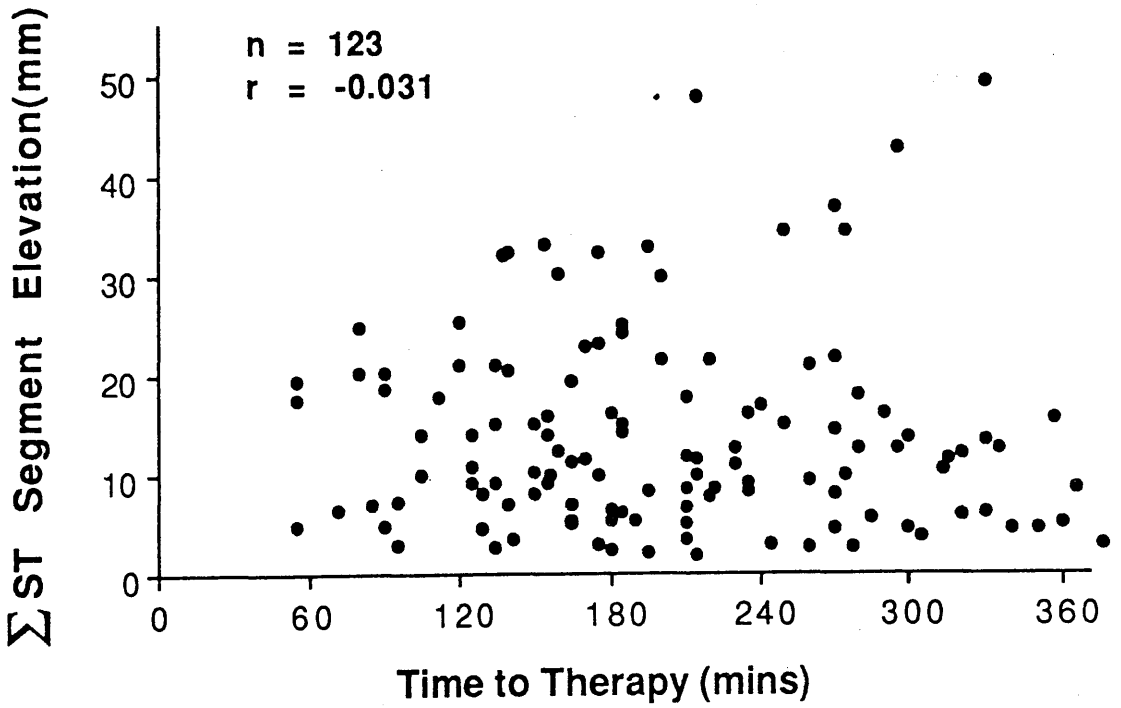


FIGURE 26: INFLUENCE OF TIME TO THERAPY ON ∑ST SEGMENT ELEVATION

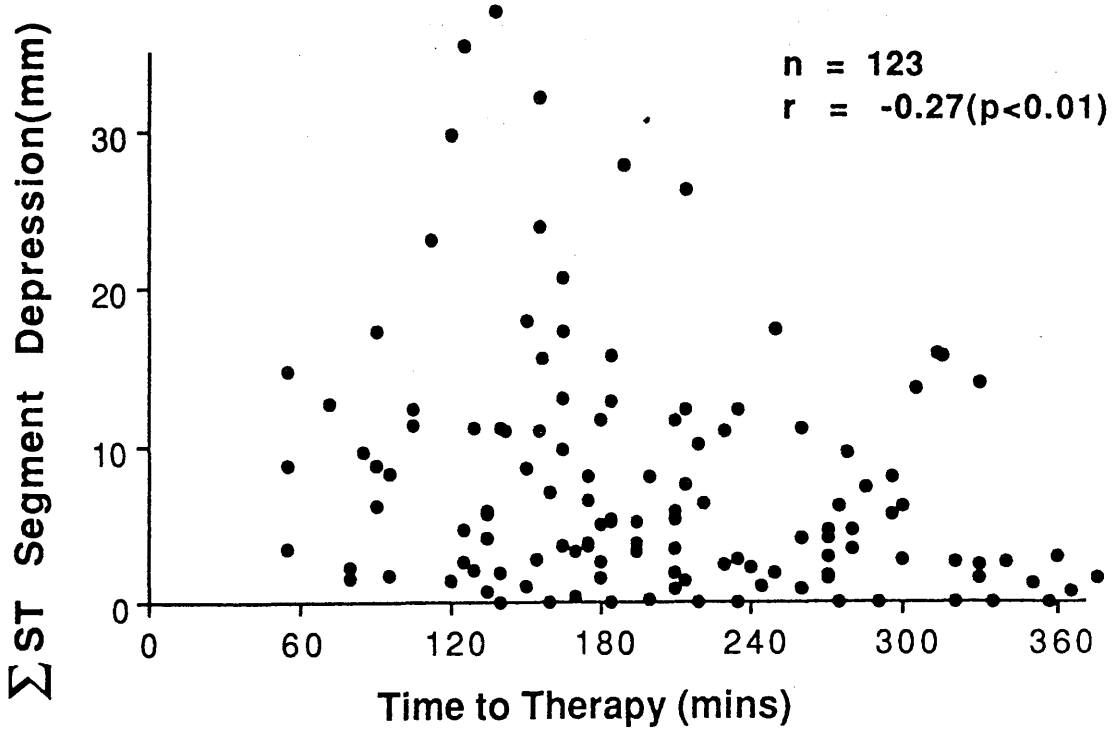


FIGURE 27: INFLUENCE OF TIME TO THERAPY ON ∑ST SEGMENT DEPRESSION

PARAMETER	r value			
	all patients	Infarct related artery LAD	RCA	Cx
$\sum^{n}$ ST elev (mm)	-0.03	0.01	-0.28*	-0.29
$\sum^{n}$ ST dep (mm)	-0.27**	-0.21	-0.28*	-0.26
$\sum^{n}$ ST elev area (mm^2)	-0.09	-0.11	-0.28*	-0.01
$\sum^{n}$ ST dep area (mm^2)	-0.26**	-0.25	-0.28*	-0.04
Maximal ST elev^{n} (mm) (single lead)	-0.08	-0.03	-0.31*	-0.29
Maximal ST dep^{n} (mm) (single lead)	-0.29	-0.20	-0.34*	-0.3

* $p<0.05$

** $p<0.01$

TABLE 22: CORRELATION COEFFICIENTS BETWEEN TIME TO THERAPY AND ST SEGMENT SHIFT

7.3.5. Relationship between degree of ST segment elevation and extent of reciprocal change.

As there was a high incidence of reciprocal change in this infarct group (ST depression $\geq$ 1 mm in leads remote from infarct territory in 55% LAD occlusions and 89% RCA occlusions), the relationship between the extent of ST segment elevation and the degree of reciprocal change was examined. Table 23 shows correlation coefficients for each of the ECG parameters measured. The best correlation for all arteries arises by taking the single lead with maximum ST elevation and comparing it with the single lead showing maximum ST segment depression. These correlations are shown for each of the infarct-related arteries in Figure 28. Taking the leads previously shown to be most dynamic (V_3 and lead III - Figure 22) results in similarly close correlations with a better correlation coefficient for LAD occlusion (Table 23, $r=-0.41$ $p<0.05$).

Parameter (Elevation vs Depression)	INFARCT RELATED ARTERY LAD (n=51)	RCA (n=54)	Cx (n=12)
$\sum$ST height (mm)	0.11	0.63**	0.60*
Single max. ST shift	0.32*	0.87**	0.82**
$\sum$ST area (mm2)	0.14	0.52**	0.21
Single max ST area (mm2)	0.26	0.90**	0.65*
Lead III vs V3	0.41*	-0.62**	-0.84**

*p<0.05
**p<0.01

TABLE 23: CORRELATION COEFFICIENTS FOR VARYING ECG PARAMETERS RELATING EXTENT OF ST SEGMENT ELEVATION TO DEGREE OF ST DEPRESSION.

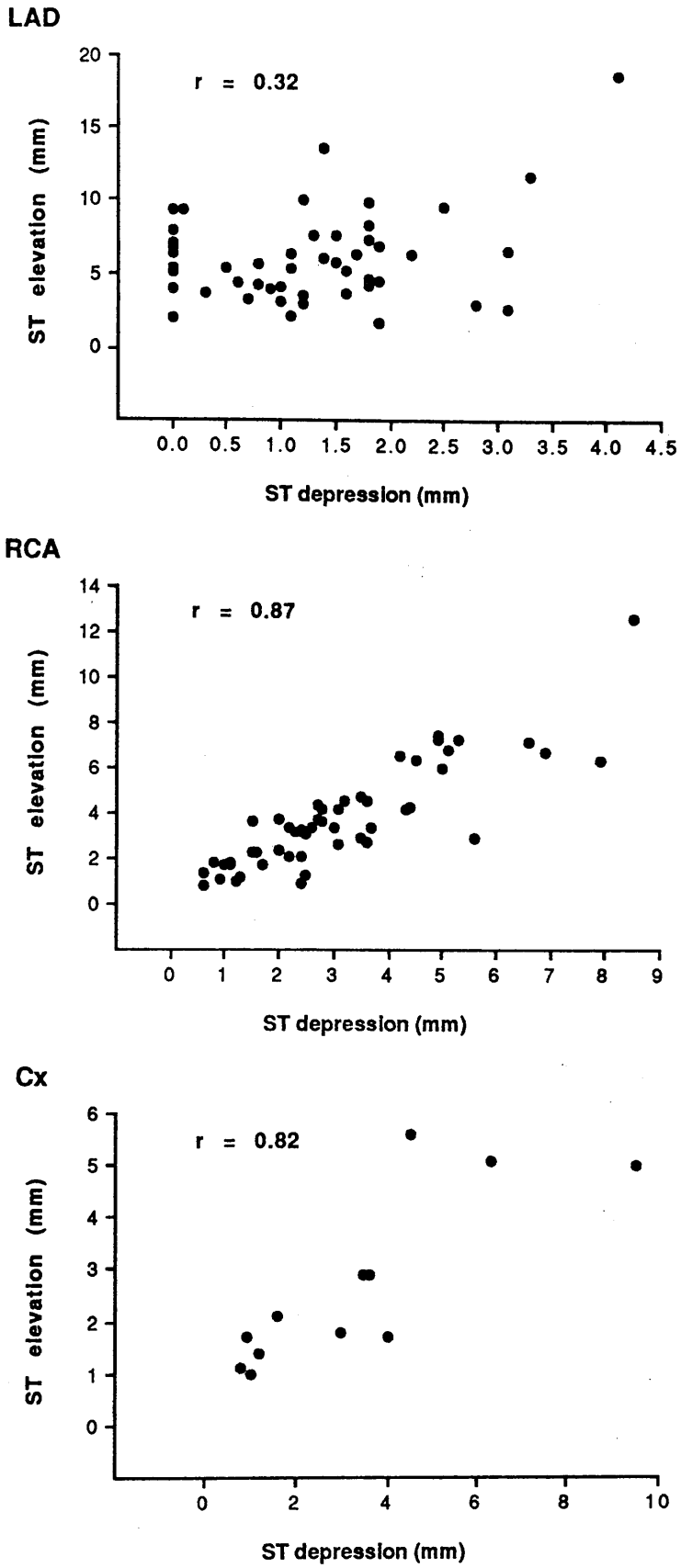


FIGURE 28: CORRELATIONS BETWEEN ST ELEVATION AND DEPRESSION USING A SINGLE LEAD WITH MAXIMAL SHIFT FOR LAD, RCA AND Cx OCCLUSION

7.3.6. Relationship between reciprocal change and arteriographic findings.

Full angiographic data and an admission ECG are available in 114 cases. The two patients with negative enzymes (patients 58 and 80) have been excluded, as has patient 107, who underwent angiography, but the quality of the investigation, although adequate to determine perfusion in the infarct-related artery (IRA), precluded interpretation of the extent of arterial disease. A vessel was considered significantly diseased if there was a stenosis >50% of the luminal diameter present.

Forty-three per cent of patients had single vessel disease, 36% double vessel disease, and 14% triple vessel disease (Table 24). Eight patients (7%) at the 90 minute angiogram are described as not having significant disease in any vessel. Those patients all had a rise in cardiac enzymes, and 7 out of 8 had a lesion in the infarct-related artery of <50%. One patient (No.69) had entirely normal arteries. In all eight cases the IRA could be confidently identified by slow clearing of dye from the infarct territory, or by persistent staining of dye at the site of presumed thrombus.

Reciprocal change defined as a ≥ 1 mm ST depression in leads remote from the site of infarction occurred in 55% of LAD occlusions. In patients with RCA occlusion, 89% had reciprocal changes in AVL and 43 of those 48 patients

also showed significant reciprocal change in the anterior leads. Table 25 shows the incidence of patients with and without reciprocal change related to the degree of vessel disease. Identification of which arteries, other than the IRA, were significantly diseased are shown in Table 26.

From these tables it can be seen that in patients with a single LAD lesion causing infarction and no other arterial disease, over half of these patients (16 vs 12) had reciprocal changes in the inferior leads, which clearly does not reflect coexisting disease in the distribution of the RCA. All patients with coexisting arterial disease and a RCA occlusion showed evidence of reciprocal change, but this is unlikely to be directly attributable to coexisting disease as 19 of 24 patients with single vessel RCA occlusions also showed marked reciprocal change. Of the 5 patients with RCA occlusions who only showed ST depression in AVL and not in the anterior leads, 1 had single vessel disease, 2 had coexisting LAD disease and 2 had coexisting Cx lesions. There was no relationship between the incidence of reciprocal change and the dominance of the arterial circulation. The values for Cx occlusion with and without coexisting disease do not show any pattern.

Infarct Related Artery	EXTENT OF VESSEL DISEASE 3VD	2VD	1VD	OVD
LAD (n=49)	6 (12%)	14 (29%)	24 (49%)	5 (10%)
RCA (n=53)	7 (13%)	22 (41.5%)	22 (41.5%)	2 (4%)
Cx (n=12)	3 (25%)	5 (42%)	3 (25%)	1 (8%)
ALL ARTERIES (n=114)	16 (14%)	41 (36%)	49 (43%)	8 (7%)

TABLE 24: INCIDENCE OF SINGLE, DOUBLE AND TRIPLE VESSEL DISEASE.

Infarct Related Artery	EXTENT OF VESSEL DISEASE 3VD	2VD	1VD	OVD
LAD (all patients)	6	14	24	5
With reciprocal change	2	8	16	1
No reciprocal change	4	6	8	4
RCA (all patients)	7	22	22	2
With reciprocal change	7	22	18	1
No reciprocal change	0	0	4	1
Cx (all patients)	3	5	3	1
With reciprocal change	3	3	3	0
No reciprocal change	0	2	0	1

TABLE 25: INCIDENCE OF SINGLE, DOUBLE AND TRIPLE VESSEL DISEASE IN PATIENTS WITH AND WITHOUT RECIPROCAL CHANGE ON THE ADMISSION ECG.

Infarct Related Artery	Distribution Of Vessels Affected	R.C. Present	R.C. Absent
LAD	IRA ONLY (IVD+OVD)	16	12
	RCA+IRA	6	3
	Cx+IRA	2	3
	RCA+Cx+IRA	2	4
	RCA ALONE (IRA <50%)	1	0
RCA	IRA ONLY (IVD+OVD)	19	5
	LAD+IRA	13	0
	Cx+IRA	9	0
	LAD+Cx+IRA	7	0
Cx	IRA ONLY (IVD+OVD)	3	1
	LAD+IRA	2	1
	RCA+IRA	1	1
	LAD+RCA+IRA	3	0

TABLE 26: DISTRIBUTION OF ADDITIONAL ARTERIAL STENOSES IN PATIENTS WITH AND WITHOUT RECIPROCAL CHANGE.

7.4. DISCUSSION

This chapter describes the features of the admission ECG in 125 patients recruited to the anistreplase/ streptokinase comparison study, all of whom had sustained an acute myocardial infarction of ⩽6 hours duration. Of these 125 patients, 119 underwent acute angiography which identified the infarct-related artery allowing comparison between the admission ECG and coronary anatomy at the time of infarction.

The group of patients studied here are pre-selected in that they all fulfilled the ECG criteria for the study before being randomised (i.e. ⩾1 mm ST elevation in 2 limb leads or ⩾2 mm ST elevation in 2 precordial leads). This explains the high percentage of patients presenting with a "classical" picture of infarction in this study; 100% of RCA occlusions had ST elevation in leads II and AVF, and 100% and 98% of LAD occlusions had ST elevation in V_3 and V_2 respectively. If patients presenting with chest pain, not chosen on the basis of their ECG, but subsequently proven to have sustained infarction by positive enzymes, undergo angiography, the number of patients correctly showing "classical" ECG changes of anterior myocardial infarction drops to 93% and to 77% for patients correctly showing classical changes of inferior myocardial infarction (Blanke et al., 1984b).

Patients with an acute circumflex occlusion could not be

differentiated from those with an acute RCA occlusion on the basis of the 12 lead ECG. The presence of ST segment elevation in lead I was 100% specific for Cx occlusion, but only 42% sensitive, and the values are calculated in a relatively small number of Cx occlusions (n=12). This confirms the findings of previous studies which have been unable to distinguish RCA from Cx occlusion based on ECG criteria (Fuchs et al., 1982; Blanke et al., 1984b).

This study has shown that there is no relationship between the extent of ST segment shift and the age of the infarct over the 6 hour time window examined. Bar et al. (1987) reporting for the Netherlands Interuniversity Cardiology Institute had a large proportion of patients (n=70) who infarcted in hospital, and who underwent very early electrocardiography and suggested that the degree of ST segment elevation is higher in the hyperacute phase than in a later period. Only 3 patients were randomised in this study within the first hour, and with previous work showing that the degree of ST segment elevation in patients with an acute infarction is stable 1-4 hours after the onset of pain (Foerster et al., 1977), these factors may well explain why no relationship has been detected.

Reciprocal changes in acute myocardial infarction, although first described by Wolferth et al. in 1945 continue to be the subject of much debate. There are several schools of thought involving the mechanism and significance of this concomitant ST segment depression in association with acute infarction. It has been suggested it is simply a benign electrical phenomenon (Steinhaus et al., 1982;, Ferguson et al., 1984), a marker for extensive necrosis and bad prognosis (Pichler et al., 1983; Berland et al., 1986) or thirdly, an indicator of remote ischaemia or co-existing arterial stenoses (Salcedo et al., 1981; Jennings et al., 1983). The majority of published work addresses the significance of anterior ST segment depression in the context of acute inferior myocardial infarction (Betocchi et al., 1983; Tendera and Campbell, 1984; Cohen et al., 1984; Little et al., 1984). Few studies have examined the significance of reciprocal changes in anterior infarction, and those published are limited by small numbers (Pichler et al., 1983; Haraphongse et al., 1984). Dewhurst et al. (1985) examined the early electrocardiographic results in 100 patients sustaining a first myocardial infarction, and reported 'reciprocal changes' in 61% (33/54) of inferior infarctions and in 43% (20/46) of anterior infarctions. Reciprocal changes were recorded if occurring within 48 hours of the acute event. The population of patients in this present study are more acute, all presenting within 6 hours of onset of pain and this probably contributes to

the higher incidence of reciprocal change reported here, i.e. 89% of inferior infarctions had ST depression in AVL and 55% of anterior infarctions had ST depression in lead III. Tendera and Campbell (1984) divided reciprocal changes in inferior myocardial infarction into early (occurring within 4 hrs of chest pain onset) and late (>6 hours of chest pain), and looked specifically at incidence of ST depression in V_2. Although there was a higher incidence in the early group (62%) compared with the late group (21%) it was only those late reciprocal changes which helped to identify concurrent LAD stenoses or reduced LVEF. Although specific this was not sensitive, and based on a small cohort.

This finding, coupled with the overall high incidence of reciprocal changes early in the course of myocardial infarction reported here may support the theory that ST depression on the admission ECG occurring soon after symptom onset is simply a mirror image of ST segment elevation, and may be an index of total ischaemia, rather than specifically pinpointing co-existing disease. Certainly the close correlation found between ST segment elevation and depression in this study, whether examining the relationship between $\sum$ST elevation and depression, single leads with maximal ST shift or simply lead III versus V_3 supports the electrocardiographic mirror image theory. This confirms work by Camara et al. (1983)

performed in a smaller number of patients (n=25) presenting at 3.97±4.8 hours of pain onset, and which showed a significant correlation between ST segment elevation and depression in both anterior and inferior infarction (r=0.93, r=0.55 respectively).

The evidence based on the relationship of ECG changes to coronary anatomy in the 114 patients in this study, clearly indicates that the phenomenon of reciprocal change is totally independent of coexisting arterial stenoses. This again confirms the studies by Little et al. (1984) and of Berland et al. (1986) who confined their observations to inferior infarctions undergoing angiography for coronary thrombolysis.

In addition to the above data it would seem that resolution of ST segment depression closely follows that of ST elevation (Chapter 8). All these features together tend to support the hypothesis that reciprocal ST depression during early acute transmural myocardial infarction does not reflect remote ischaemia. Not only does the work of Lew et al. (1987) agree with this point, he and his co-workers showed that inferior wall ischaemia in anterior myocardial infarction, documented by thallium 201 scintigraphy and by contrast ventriculography was more likely to be associated with isoelectric or elevated ST segments compared to anterior infarction with no inferior ischaemia. The group of patients whose LAD

artery supplied the left ventricular wall up to and including the apex, but not the inferior wall, had a significantly greater degree of ST segment depression in the inferior leads compared with patients who had definite ischaemia of their inferior wall. This led the group to suggest that by using a ratio of ST segment depression in AVF to ST elevation in V_2, less negative than -0.2 would lead to identification of patients with anterior infarction and concomitant inferior wall ischaemia due to an LAD occlusion which either supplies the inferior wall or is the source of collateral flow to a previously occluded RCA. This sub group of patients are at high risk from extensive infarction and would benefit from early thrombolysis.

In conclusion, this chapter has concentrated on the acute ECG changes occurring in a group of patients presenting with myocardial infarction of $\leq$ 6 hours duration undergoing thrombolysis. The advantage in studying this group has been in being able to use the coronary angiogram performed post therapy and to correlate these findings with the admission ECG in a large number of patients. Although many recent thrombolytic trials perform acute angiography to determine success of therapy, a comprehensive analysis of coronary anatomy in relation to the ECG has not been performed. In particular this study has helped to clarify thinking in a number of areas.

Firstly, that within the time window 1-6 hours, the height of ST segment elevation does not bear any relation to the age of the infarct, secondly, that there is a high incidence of reciprocal change early in the course of infarction, and thirdly, that this is not related to coexisting disease or remote ischaemia, but is an electrocardiographic mirror phenomenon.

CHAPTER 8

COMPARISON BETWEEN ANISTREPLASE AND STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

RESULTS III - ELECTROCARDIOGRAPHIC DETERMINANTS OF REPERFUSION AND INFARCT EVOLUTION

8.1 INTRODUCTION

Since the initial work of this thesis was first presented in 1985 (Hogg et al., 1985) the publication of well conducted mortality studies (GISSI, ISIS II, AIMS and ASSET) has assured the place of thrombolysis in acute myocardial infarction in all hospital practices. This has made it even more important to know how useful the 12 lead ECG is as a non invasive indicator of reperfusion and of myocardial salvage. The work presented in Chapter 3 introduced the concept of using a simple formula (Fractional Change) to calculate the percentage fall in ST segments and showed it to be a specific and sensitive non invasive test of reperfusion. Chapter 4 demonstrated that the QRS score was reduced in patients achieving reperfusion compared with a group of controls who received no lytic agent. The limitation of both chapters was that this initial work was conducted in relatively small patient numbers, and Chapter 4 confined itself to the examination of anterior infarcts only. In addition, the total number of non reperfusions were low (n=8 and n=3 in Chapters 3 and 4 respectively) making statistical comparison between reperfusions and non reperfusions impossible (chapter 4). The aim of this study was to investigate and validate using a large patient group consisting of both anterior and inferior infarctions, reperfusions and non-reperfusions, the results achieved in earlier work. In addition, the creation of an electrocardiographic data base backed up with acute

angiographic findings allowed comparison of different methodologies. The heterogeneity of methods used between groups of workers (Table 12) has confused the literature, and the aim was to determine the simplest, most specific and sensitive tests to be of value to physicians treating patients with thrombolytic agents.

8.2 PATIENTS AND METHODS

The patient group is that described in Chapters 6 and 7 and listed in appendix VI. The patency data reported in Chapter 6 by convention was based on the first injection into the infarct-related artery. Some arteries were seen to reperfuse during the angiogram, and for this part of the study which relates the ECG determinants of reperfusion and myocardial salvage to angiographic findings, it is the patency at the end of the catheterisation procedure which is used. The list of patients who had a change in patency during angiography are shown in Table 27. Although 10 patients have a change of greater than 1 in the TIMI Grade, only 6 are considered to have reperfused during the procedure (TIMI 2 or 3) resulting in a patency rate of 55% for streptokinase and 64% for anistreplase at the end of the procedure. The 95% confidence intervals are 42-68% and 52-76% respectively, showing there is no significant difference in patency rates between treatments.

Fractional Change was calculated on computer according to the formula described in Chapter 3. The ability of the ECG to determine reperfusion is expressed in terms of sensitivity and specificity using the same method as previously. Sensitivity measures the ability of the test to detect genuine cases of reperfusion and specificity measures the ability of the test to detect genuine cases of non- reperfusion. Other ECG parameters were analysed

on a main frame computer (ICL2980) using the statistical package MINITAB. Data are presented as mean $\pm$ SE and statistical comparisons between groups analysed by analysis of variance (ANOVA) using RUMMAGE and Bonferoni multiple comparisons with 95% confidence limits for statistical significance. For these analyses, the Q and R wave parameters were normally distributed and did not need to undergo transformation. However, the parameters of ST height and area required to undergo a square root transformation prior to ANOVA.

Each angiogram was assessed for presence or absence of collateral supply. Collaterals were graded according to the extent to which the epicardial arterial segment distal to the target stenosis (or acute occlusion) was retrogradely opacified (Rentrop et al., 1985). Grades of collateral filling from the contra-lateral vessel were : 0=none; 1=filling of side branches but no visualisation of epicardial vessel; 2=partial filling of epicardial segments; 3=complete filling of the epicardial segment distal to the stenosis or occlusion.

Patient No.	Drug	Timi Grade First Injection	Timi Grade Last Injection
5	APSAC	0	2
9	APSAC	0	2
22	SK	0	1
27	APSAC	0	1
29	SK	0	1
35	SK	0	1
39	APSAC	0	2
54	APSAC	0	3
55	SK	1	2
119	APSAC	1	2

APSAC = anistreplase

SK = streptokinase

TABLE 27: PATIENTS WITH CHANGE IN TIMI GRADE OF PERFUSION DURING 90 MINUTE ANGIOGRAM

8.3 RESULTS

8.3.1. Resolution of ST Segment Shift Over 24 Hours

Figure 29 shows the pattern of resolution of ST segment elevation (mean±SE) over a 24 hour period both for $\sum$ST height and $\sum$ST area, depending on coronary patency assessed at the 90 minute angiogram from a total of 107 patients (reperfusions n=66, non reperfusions n=41). There is no difference between baseline values on admission, and although both groups show a significant fall in ST segment elevation from baseline by 2 hours, there is a significantly greater reduction in $\sum$ST elevation (area and height) at 2 hours in those patients with a patent artery compared to non reperfusions ($\sum$ST height 4.6±0.46 mm vs 10.7±1.6 mm at 2 hours, $p<0.05$, $\sum$ST area 32±4.2 mm^2 vs 65.3±8.7 mm^2 at 2 hours, $p<0.05$). This difference between groups is still apparent at 4 hours ($\sum$ST height 4.6±0.46 mm vs 7.5±1.1 mm, $p<0.05$, $\sum$ST area 34±4.2 mm^2 vs 49.8±7.5 mm^2, $p<0.05$), but thereafter although the patients with patent arteries tend to have lower values, there is no significant difference between the two groups. Although there is no difference in the absolute value to which ST segment elevation returns, it is the rate of fall in the first 2-4 hours which differentiates patent from non patent arteries.

The resolution of ST segment depression is similar to that of ST elevation over the same time scale, but the only significant difference between groups is for $\sum$ST

depression (mm) at 2 hours (2.8±0.48 mm vs 4.8±1.1 mm, $p<0.05$), suggesting that the rate of resolution of ST depression is not as helpful in separating out patent from non patent arteries at the 90 minute time point (Figure 30). However, a significant proportion of the "non reperfusions" at 90 minutes (28 of 41) were found to have a patent artery at 24 hours, and only 13 patients did not reperfuse at all. The comparison between these two groups in shown in Figure 31 for $\sum$ST elevation (mm). The subgroup of patients who reperfused later than 90 minutes have a higher baseline value than the non reperfusions (16.4±2.4 mm vs 11.3±2.4 mm, $p<0.05$). Nevertheless the graph shows the gradual decline in ST segments for persistently occluded vessels over 24 hours. Although the trend is of a definite decline, none of the values at any time point is significantly different from baseline. This is in contrast to the group who reperfused late where the fall from baseline is statistically significant at all time points. Ninety percent of the total fall occurs within 4 hours, suggesting these patients reperfuse within this time scale.

These results show that patients who reperfuse or who obtain a patent artery early ($\leq$90 minutes)have faster resolution of ST segment elevation than patients shown to have an occluded artery, but within this latter group is a subset of patients who are shown to have a patent artery

by 24 hours and who show 90% of the fall in ST segments within 4 hours compared with the very gradual decline seen in people who never reperfuse. It is this fast fall in the first few hours following therapy which has been exploited as a non-invasive means of obtaining reperfusion and which will be discussed in the next section.

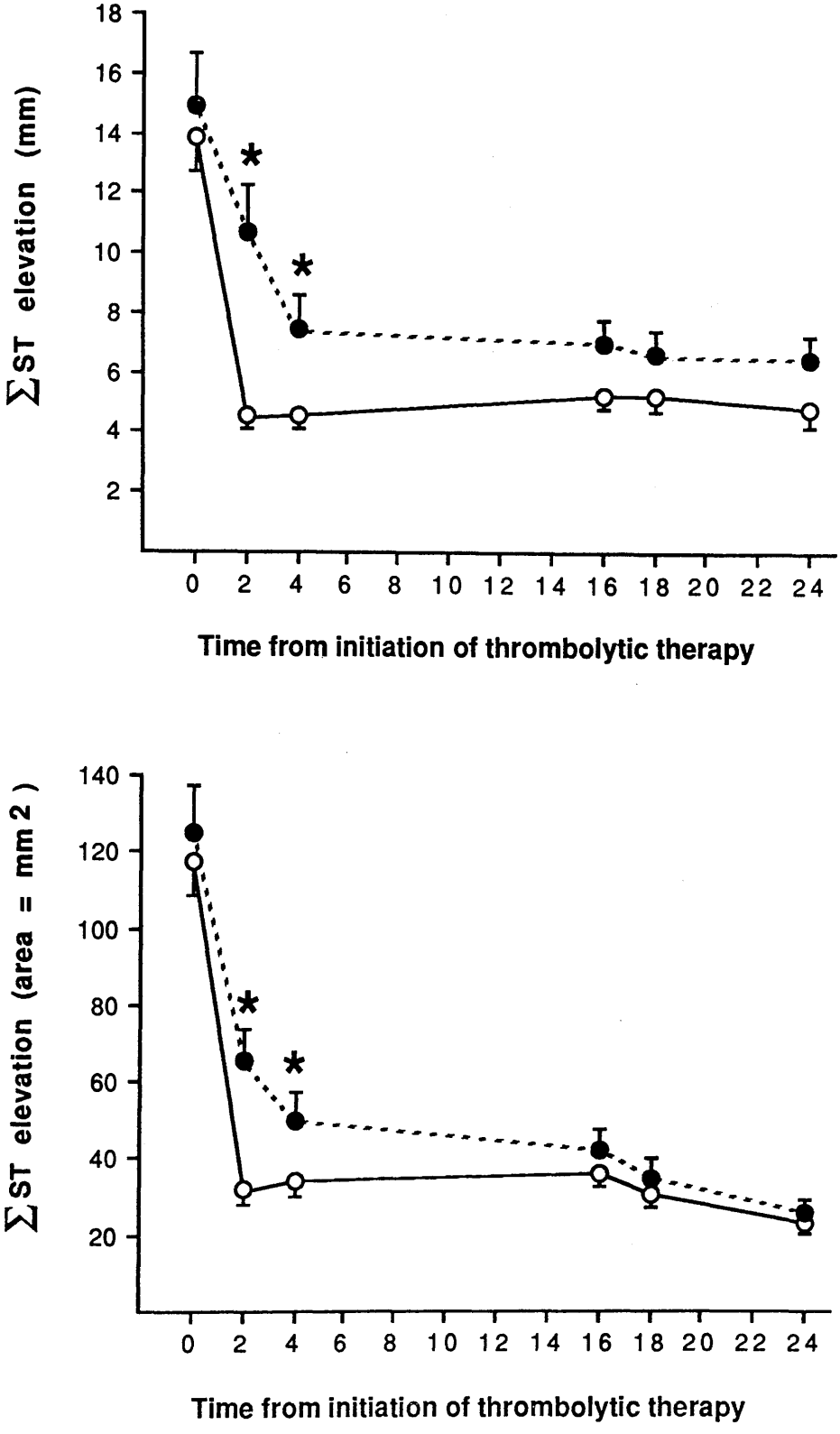
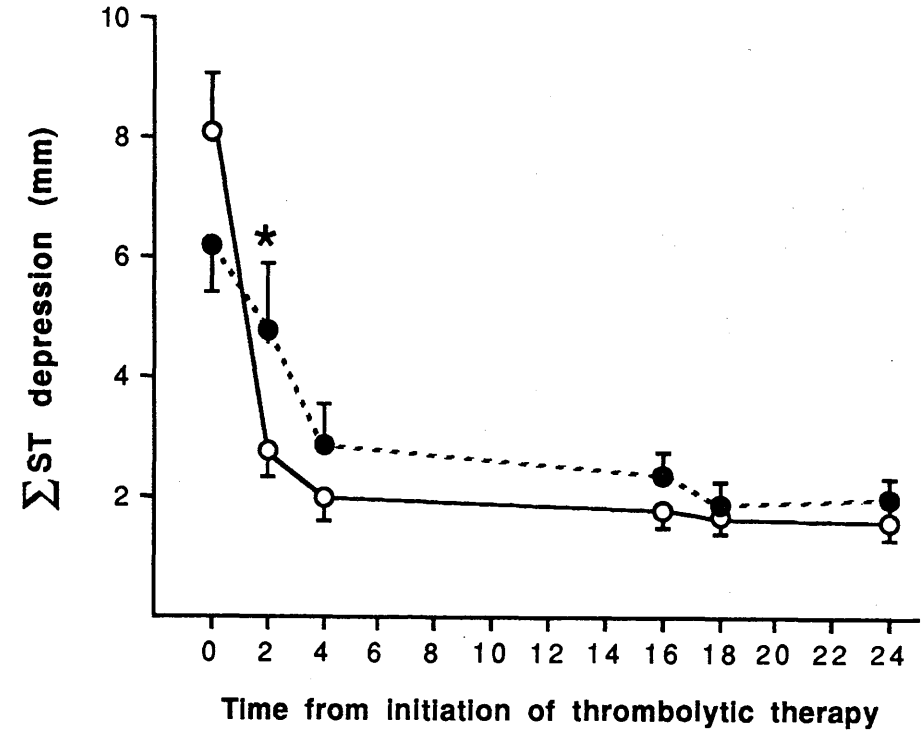


FIGURE 29: RESOLUTION OF ST SEGMENT ELEVATION OVER 24 HOURS. Both ∑ST height and ∑ST area are shown. Patients are divided into non reperfusions (●) and reperfusions (O) according to 90 minute angiography. Asterisks (*) denote significant differences between groups ($p<0.05$)



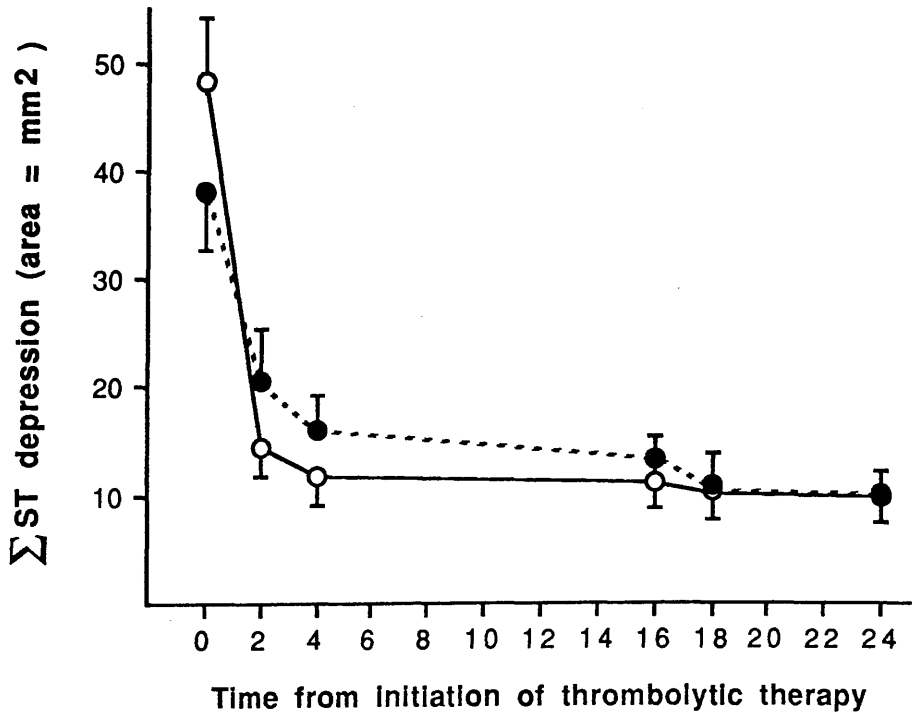


FIGURE 30: RESOLUTION OF ST SEGMENT DEPRESSION OVER 24 HOURS. Both ∑ST depth and ∑ST area are shown. Patients are divided into non reperfusions (●) and reperfusions (O) according to 90 minute angiography. Asterisks (*) denote significant differences between groups ($p<0.05$)

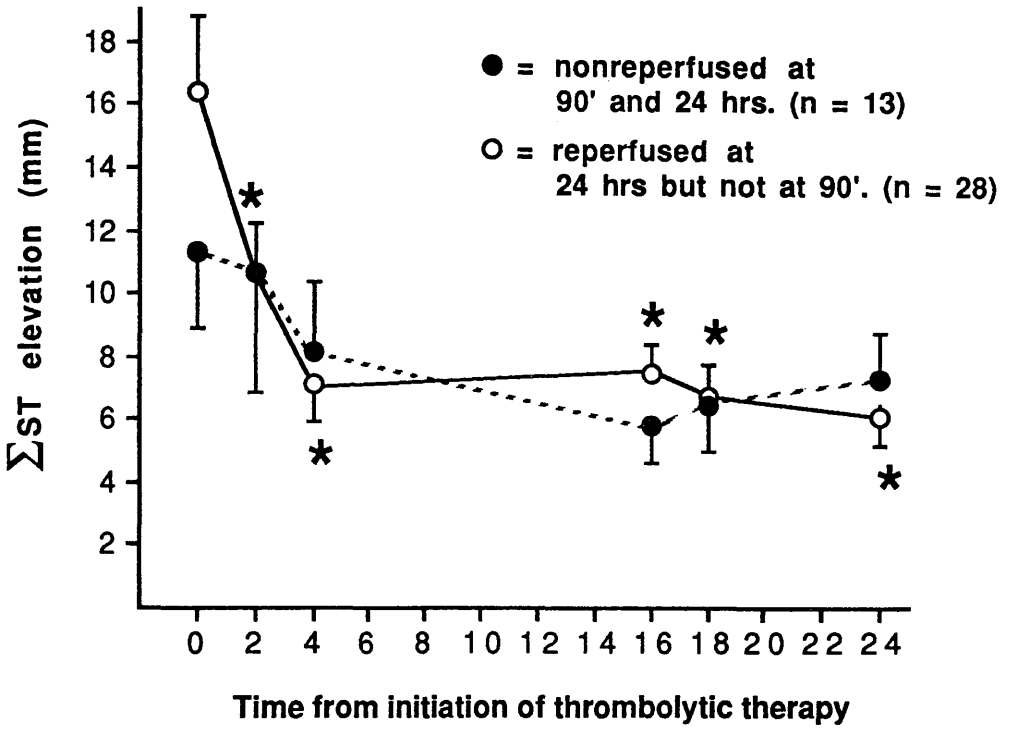


FIGURE 31: COMPARISON OF RESOLUTION IN ∑ST ELEVATION BETWEEN PATIENTS WITH PERSISTENTLY OCCLUDED VESSELS AT 24 HOURS AND PATIENTS WHO REPERFUSE LATE. Patients who reperfuse late (n=28; ○) have a higher baseline ∑ST elevation than non reperfusions (n=13; ●) $p<0.05$. In this figure the asterisks (*) denote significant differences from baseline within groups ($p<0.05$)

8.3.2. Fractional Change

Fractional Change (F.C.) values were calculated for each of 106 patients at each of the time points. Nineteen patients did not have a F.C. calculted, 12 of whom did not have a 90 minute angiogram to determine patency, 2 did not have an admission ECG and 5 had the 2 hour ECG missing. The two patients (58 and 80) with negative enzymes were excluded from analysis. Different ECG parameters were used to calculate the F.C, which are as follows: 1. using the single lead with maximal ST segment elevation; 2. $\sum$ST elevation in all leads; 3. $\sum$ST elevation in those leads showing elevation at presentation and 4. by following $\sum$ST elevation in leads dedicated to the infarct site (i.e. II, III, AVF for RCA occlusions, V_1-V_4 for LAD occlusions and I, II, III, AVL, AVF, V_5, V_6 for Cx occlusions). In addition the first three parameters were also used to calculate F.C. for ST segment depression.

The best time to calculate F.C. to maximise separation of the two groups (reperfusions and non reperfusions) was at two hours. Later time points had an unacceptably low specificity, and the examination of arbitrary cut-off points of F.C. values indicating reperfusion confirmed the previous finding that a F.C. value of $\geq$ 0.5 again maximised separation. These results are shown in Table 28 using the single lead with maximal ST segment elevation to calculate F.C.

Using a F.C. value calculated at 2 hours following intravenous therapy from a single lead with maximal ST segment elevation and a cut-off level of $\geq$ 0.5 gives a sensitivity of 81% and a specificity of 60%. Scatter diagrams of F.C. values using this technique and of F.C. values calculated from $\sum$ST elevation on all leads showing elevation at admission are shown in Figure 32. Table 29 compares sensitivity and specificity using the different ECG parameters for calculating F.C. and shows that following ST segment shift in a single lead with maximal elevation on admission gives a result more sensitive and specific than any other parameter. In particular, exploiting the resolution of ST segment depression whether in a single lead or across multiple leads does not improve the test, and is limited in that it can only be applied to patients who have reciprocal change present. Ten patients with LAD occlusion had to be excluded from this analysis as no ST depression was present in any lead.

The use of a F.C. calculated at 2 hours from a single lead is equally good at detecting patency irrespective of the site of infarct. From Figure 33 it can be seen that the specificity for detecting non reperfusions is slightly higher for RCA occlusions (67% vs 55.5% for LAD occlusions).

The degree of perfusion within groups on the TIMI scale (0-1 for non reperfusion and 2-3 for reperfusion) has no relation to the F.C. value (Figure 34). Although there is a larger number of non reperfused patients who have a TIMI grade of 0 (n=30) compared to those with a TIMI grade of 1 (n=10), the percentage of patients in both groups having a F.C. $\geq$ 0.5 is the same, and the specificity of the test does not change (60% for TIMI 0 or 1). Similarly, of the patients who reperfused a larger percentage had a grade 3 perfusion (n=45) compared with grade 2 perfusions (n=19). The sensitivity of a F.C. value $\geq$ 0.5 is 82% for TIMI grade 3 and 79% for TIMI grade 2. The percentage of patients in each group with a F.C. value $\geq$ 0.75 is not significantly different (32% TIMI 2 vs 44% TIMI 3, NS).

F.C. CUT OFF LIMIT*		Hours Post Treatment For Calculation Of F.C. 2	4	16	18	24
0.25	SENSITIVITY	91%	89%	89%	90%	93%
	SPECIFICITY	30%	24%	15%	5%	10%
0.5	SENSITIVITY	81%	77%	73%	82%	84%
	SPECIFICITY	60%	48%	27%	24%	23%
0.75	SENSITIVITY	41%	53%	31%	40%	40%
	SPECIFICITY	88%	71%	85%	70%	72%

* CUT OFF LIMIT = F.C. if x $\geq$ F.C. = Reperfusion
if x $<$ F.C. = Non reperfusion

TABLE 28: THE SENSITIVITY AND SPECIFICITY OF THE F.C. CALCULATED FROM A SINGLE LEAD SHOWING MAXIMAL ST ELEVATION TO DETECT REPERFUSION AND NON REPERFUSIONS AT DIFFERENT TIMES AND AT DIFFERENT PREDETERMINED CUT-OFF LEVELS.

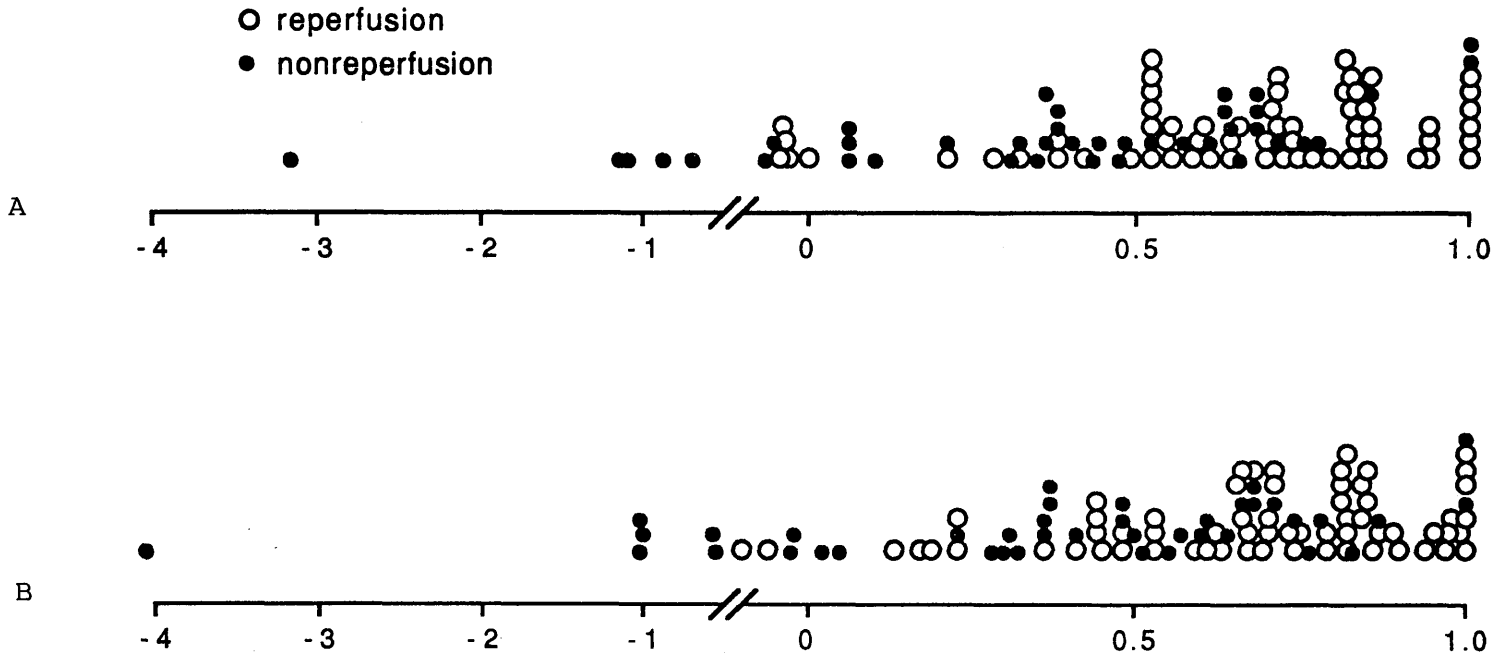


FIGURE 32: SCATTERGRAMS OF FRACTIONAL CHANGE VALUES AT 2 HOURS CALCULATED USING SINGLE LEAD WITH MAXIMAL SHIFT (A) AND USING $\sum$ST ELEVATION IN LEADS SHOWING ELEVATION ON ADMISSION (B)

Fractional Change At 2 hrs	Sensitivity	Specificity
F.C. (single lead maximal $\uparrow$)	81%	60%
F.C. ($\sum ST\uparrow$ - all leads)	73%	60%
F.C. ($\sum ST\uparrow$ - leads with $ST\uparrow$ on admission)	77%	55%
F.C. ($\sum ST\uparrow$ - in leads dedicated to infarct site)	77%	55%
F.C. (single lead maximal $\downarrow$)	76%	53%
F.C. ($\sum ST\downarrow$ - all leads)	69%	58%
F.C. ($\sum ST\downarrow$ - in leads with $ST\downarrow$ on admission)	74%	47%

TABLE 29 COMPARISON OF SENSITIVITIES AND SPECIFICITIES OF F.C.'S CALCULATED AT 2 HOURS USING DIFFERENT ECG PARAMETERS

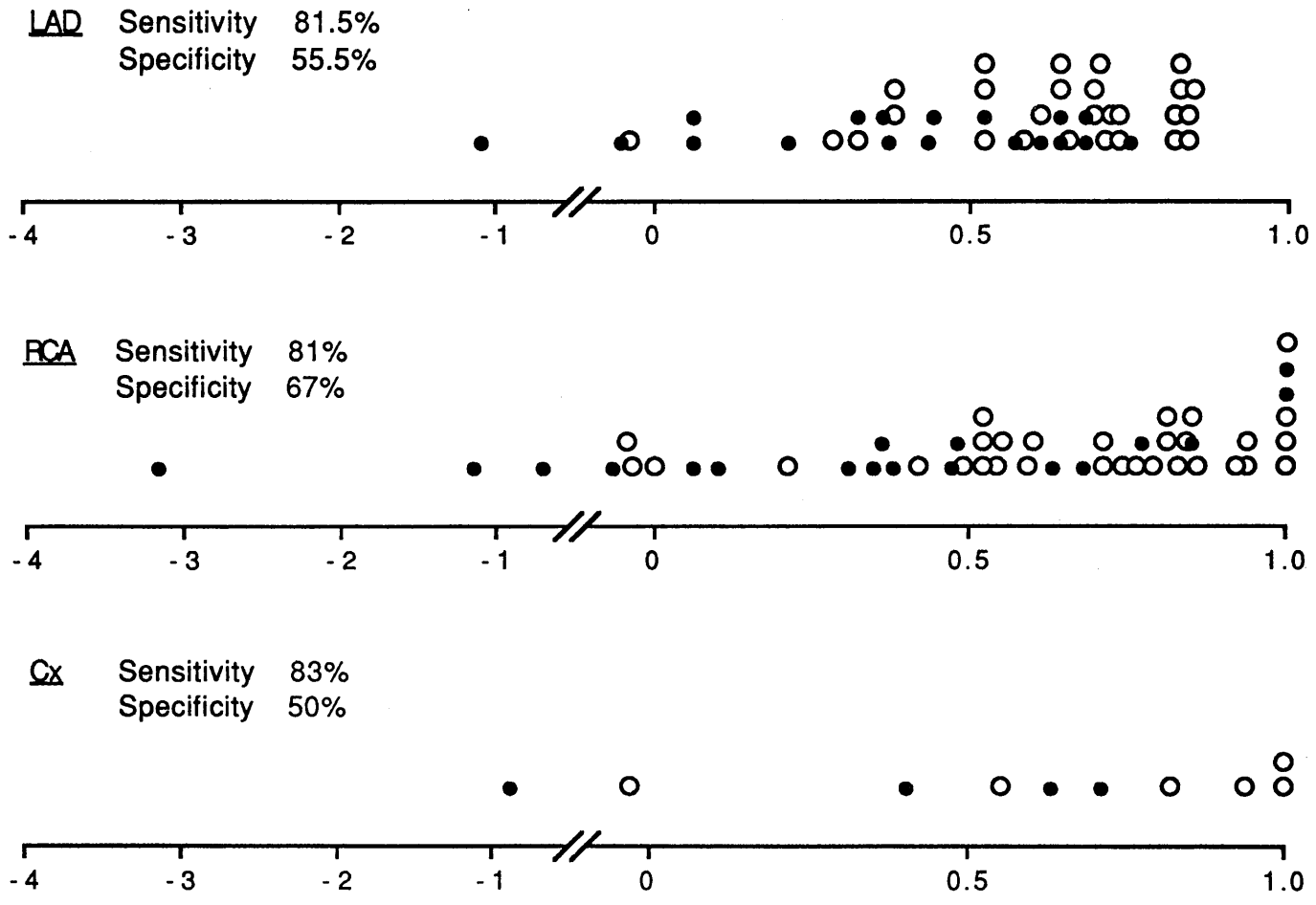


FIGURE 33: DISTRIBUTION OF F.C. VALUES (FROM SINGLE LEAD AT 2 HOURS POST THERAPY) AND SENSITIVITY AND SPECIFICITY OF A F.C. VALUE $\geq$ 0.5 TO DENOTE REPERFUSION DEPENDING ON THE INFARCT RELATED ARTERY

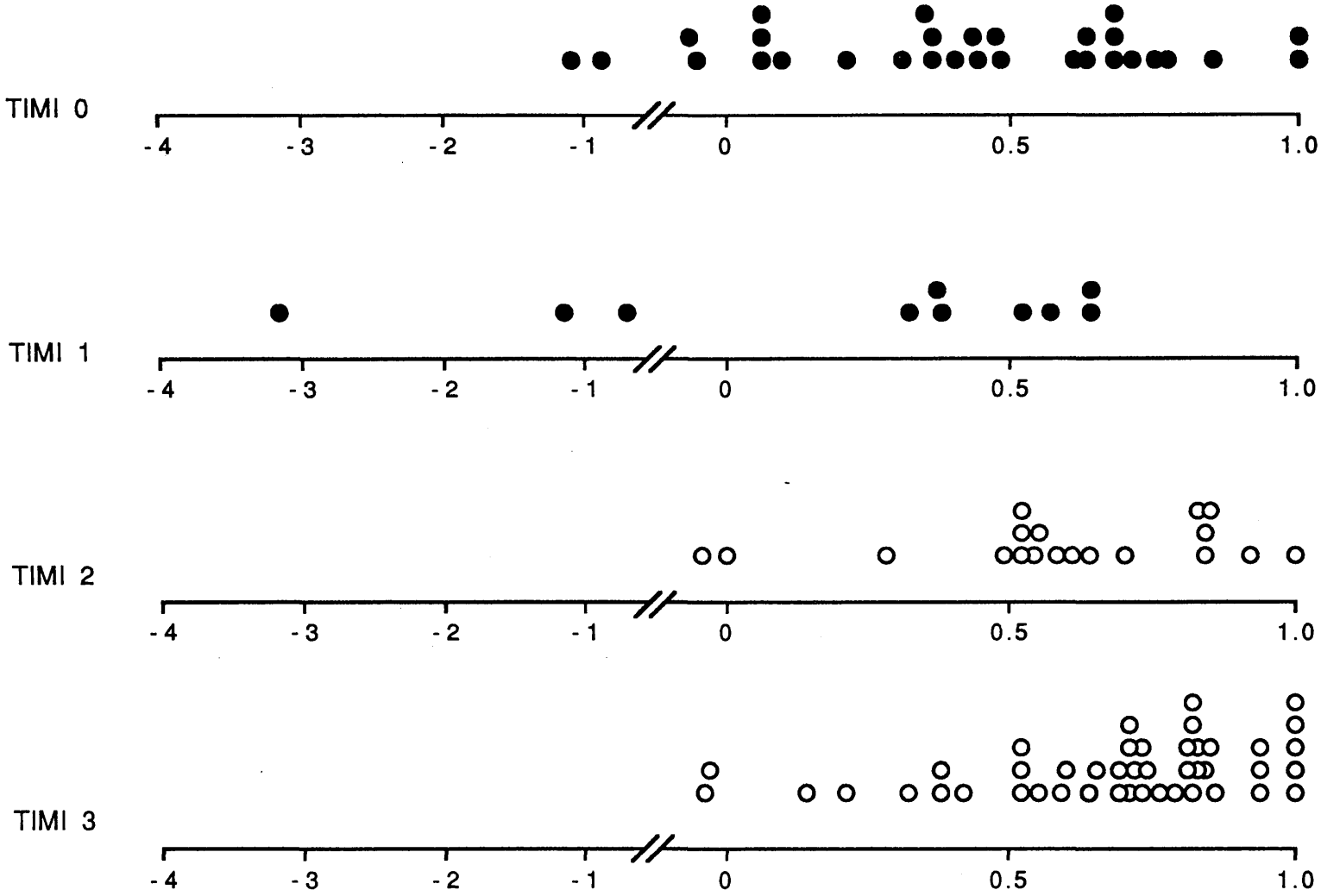


FIGURE 34: DISTRIBUTION OF F.C. VALUES (SINGLE LEAD CALCULATED AT 2 HOURS) RELATED TO TIMI GRADE OF REPERFUSION

8.3.3. Influence of Collateral Supply on Fractional Change

Fifteen patients were seen to have collateral supply to the distal part of the infarct related artery and 10 of those patients had not reperfused anterogradely at the time of the 90 minute angiogram. The extent of collateral supply and the F.C. values (single lead at 2 hours) are shown in Table 30. Three of 4 patients who all had a "falsely" high F.C. had good collateral supply (one grade 3, two grade 2) while the remaining patient had grade 1 collateral supply to a non dominant Cx artery. Of the 6 patients with low F.C. values, 3 had grade 1 collateral supply and 3 had grade 2. Although inconclusive with small numbers and depending on what is a fairly subjective assessment of collateral supply, satisfactory coronary flow via collaterals to the infarct territory may result in resolution of ST changes despite no anterograde flow. F.C. values $\geq$ 0.5 may reflect perfused myocardium and a value of $<$ 0.5 may be more specific than the 60% already reported in this chapter for non-perfusion of the infarct territory.

Patient No.	IRA	90' Angio TIMI Grade	F.C.(2 hrs)	Grade of Collaterals
1	RCA	0	0.68*	2
7	RCA	0	0.31	2
11	RCA	0	0.06	1
14	LAD	0	0.43	1
51	RCA	0	1.0*	3
59	RCA	1	-3.15	2
94	RCA	0	-0.26	2
117	Cx	0	0.63*	2
118	Cx	0	0.71*	1
120	LAD	0	0.21	1

* = Falsely high F.C. value at 2 hours

TABLE 30 DISTRIBUTION AND EXTENT OF COLLATERAL SUPPLY TO OCCLUDED INFARCT RELATED VESSELS AND FRACTIONAL CHANGE VALUES

8.3.4. **Evolution of electrocardiographic infarct pattern**

Figures 35 and 36 show the sequential changes taking place in the 12 lead ECG over a 24 hour period for patients with and without a patent artery as assessed at the 90 minute angiogram. The parameters studied are both for single R and Q wave amplitudes in the lead identified with maximal ST elevation on admission, and for $\sum$R and $\sum$Q wave amplitudes taken from all leads showing ST elevation on admission. Figure 35 shows that by following the Q wave in a single lead showing maximum injury pattern on admission there is a significant attenuation of Q wave amplitude in patients with a patent artery at 90 minutes. This attenuation in Q wave amplitude becomes apparent at 4 hours and the difference is maintained at all subsequent time intervals up to and including 24 hours, (mQ wave amplitude = 5.9$\pm$0.8 mm (reperfusion) vs 7.8$\pm$1.0 mm (non reperfusion) at 4 hours ($p<0.05$), and 6.4$\pm$0.7 mm vs 9.4$\pm$1.3 mm at 24 hours ($p<0.05$)). Exactly the same pattern is seen for $\sum$Q wave amplitude (m$\sum$Q=16.6$\pm$2 mm (reperfusion) vs 20.2$\pm$3.2 mm (non reperfusion) at 4 hours ($p<0.05$), and 18.9$\pm$2.1 mm vs 26.4$\pm$3.8 mm at 24 hours ($p<0.05$)) (Figure 35). By contrast although both groups (reperfusions and non reperfusions) show a significant reduction in R wave amplitude (both single R and $\sum$R) at all times from baseline, there is no difference between the two groups (e.g. mR wave amplitude = 5.7$\pm$0.51 mm (reperfusion) vs 4.8$\pm$0.58 mm (non reperfusion) on admission (NS) and 1.5$\pm$0.28 mm vs 1.2$\pm$0.32 mm at 24 hours

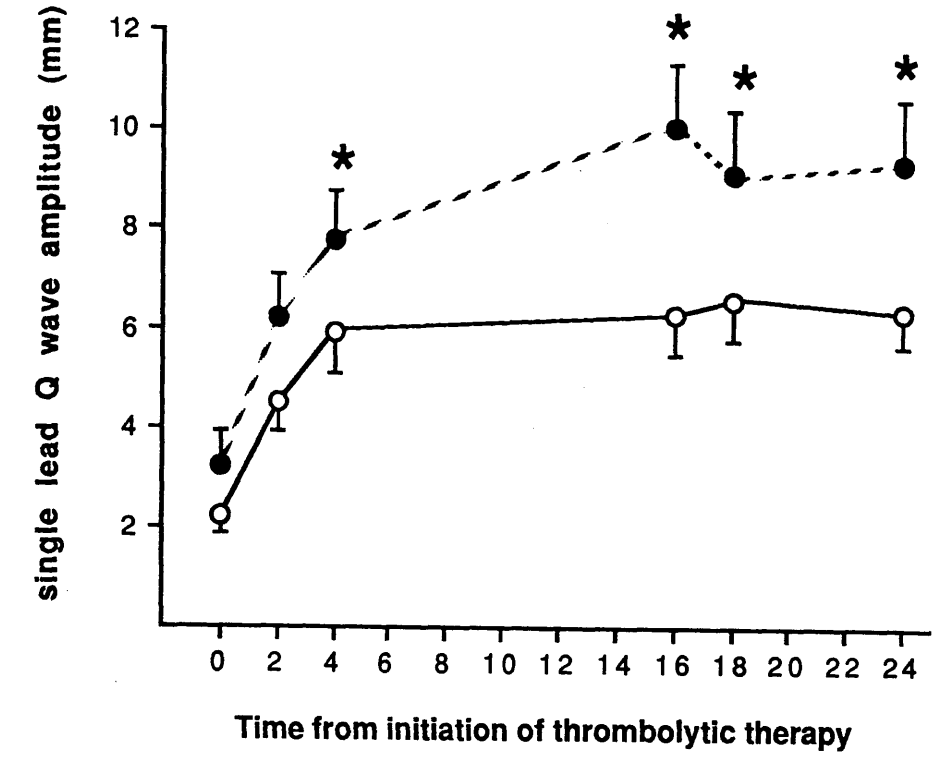
(NS)). This suggests that the presence of an early patent artery does not have any beneficial effect on R wave preservation.

Figures 37 and 38 show the same data sub-divided according to infarct related artery. Circumflex occlusions have been excluded from this analysis due to the small numbers involved. It can be seen that the majority of the difference in Q wave development between patients with and without a patent artery at 90 minutes (Figure 35) reflects the attenuation of Q wave development seen predominantly in LAD occlusions. Although patients with a RCA occlusion who do not reperfuse by 90 minutes have a tendency to develop larger Q waves than patients who reperfuse early, this difference is not statistically significant. This is true irrespective of whether examining a single lead with maximum injury pattern, or the $\sum$Q in all leads showing ST elevation on admission (Figure 37). Although there was no obvious difference in loss of R wave (single lead or $\sum$R) between patients with and without a patent artery (Figure 36) this is not true when the infarct related artery is identified separately. Figure 38 shows that patients with a LAD occlusion who reperfused by 90 minutes have less R wave loss at 16, 18 and 24 hours compared to patients with a non patent vessel at 90 minutes. This is not true of RCA occlusions. It can also be seen that the admission values for single lead

R wave amplitudes are greater for inferior infarcts (RCA occlusion) than for anterior infarctions (LAD occlusions) ($P<0.05$). This is due to the fact that the lead showing most injury pattern in anterior infarctions is either V2 or V3 (Figure 22) which naturally have small R wave amplitudes compared to lead II or lead III for inferior infarcts.

The presentation of this data has so far assumed an absolute reperfusion deadline at 90 minutes. As discussed in Section 8.3.1. the "non reperfusions" at 90 minutes represent a heterogenous group, the majority (28 of 41) of which have reperfused by 24 hours. Table 31 shows the mean values available at 24 hours for each of the ECG parameters; single Q, $\sum$Q, single R, $\sum$R, dependent on perfusion status cross-tabulated for both angiograms. Two of the subdivisions are very small; all time non reperfusions n=12, and reocclusions between 90 minutes and 24 hours n=3. Nevertheless there appears to be a trend for those patients who reperfused late to have the largest Q waves and smallest R waves. Figures 39 and 40 show the development of Q and R waves over 24 hours for those patients who never reperfuse, compared with those who reperfuse between 90 minutes and 24 hours. Surprisingly it is this latter group who show greater loss of R waves and more Q wave development. In addition, it appears that the group of patients in whom thrombolysis is unsuccessful show a tendency to have greater development of the

electrocardiographic infarct on admission (mean Q amplitude = 5.5±2.2 vs 2.3±0.5). This difference does not quite reach statistical significance when tested by ANOVA. However, the late reperfusers show a significant increase in Q wave amplitude from baseline by 2 hours (mQ amplitude 2.3±0.5 mm to 6.1±0.96 mm, $p<0.05$) and at all subsequent time points, whereas the patients with persistently occluded vessels, although showing a trend to further Q wave development over the 24 hour period (mQ amplitude on admission 5.5±2.2 mm to 9.0±2.9 mm at 24 hrs), this increase is not statistically significant from baseline. Figure 40 shows a trend for the late reperfusers to have a greater loss of R wave amplitude compared to those who do not reperfuse at all. The standard error bars however are wide and there is no significant difference between the two groups.



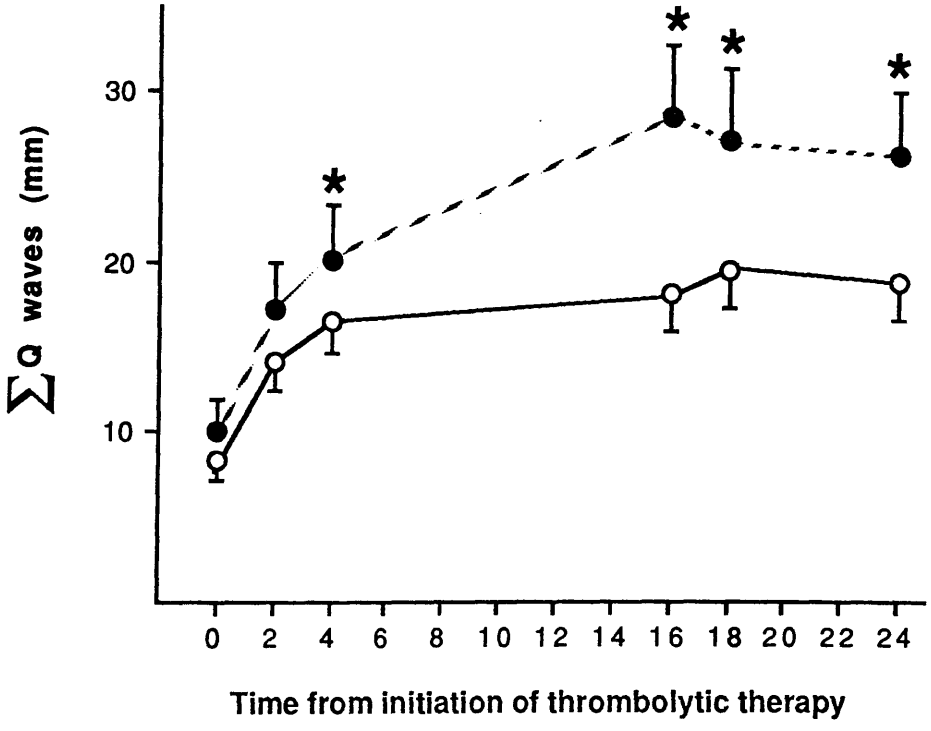


FIGURE 35: Q WAVE DEVELOPMENT OVER 24 HOURS BOTH FOR A SINGLE LEAD SHOWING MAXIMAL INJURY AND FOR $\sum$Q IN ALL LEADS SHOWING ST ELEVATION ON ADMISSION. Patients are divided into non reperfusions (●) and reperfusions (O) according to the 90 minute angiogram. Asterisks (*) denote significant differences between groups ($p < 0.05$)

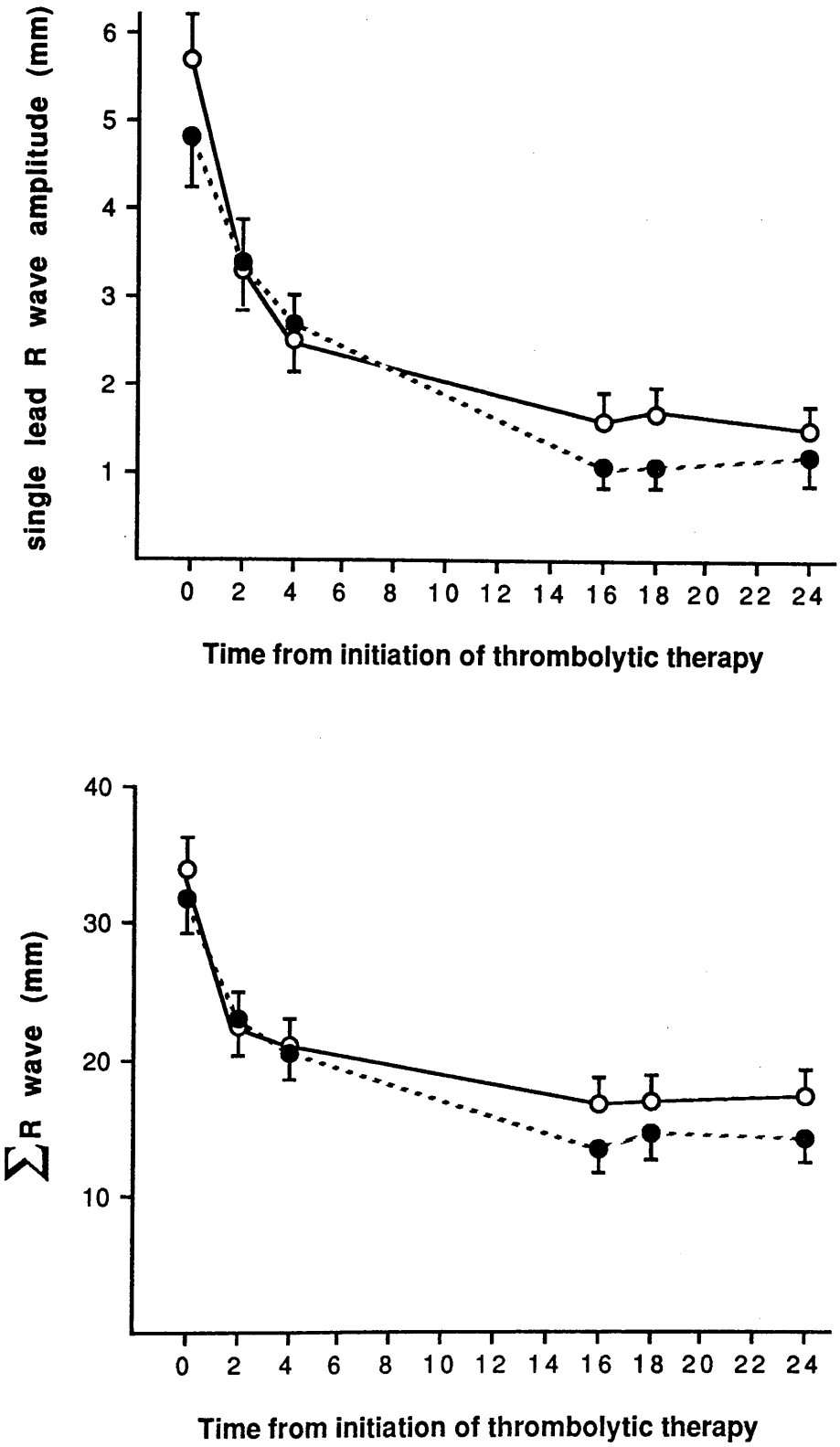


FIGURE 36: R WAVE LOSS OVER 24 HOURS BOTH FOR A SINGLE LEAD SHOWING MAXIMAL INJURY AND FOR $\sum$R IN ALL LEADS SHOWING ST ELEVATION ON ADMISSION.
Patients are divided into non reperfusions (●) and reperfusions (O) according to 90 minute angiography. There are no significant differences between groups.

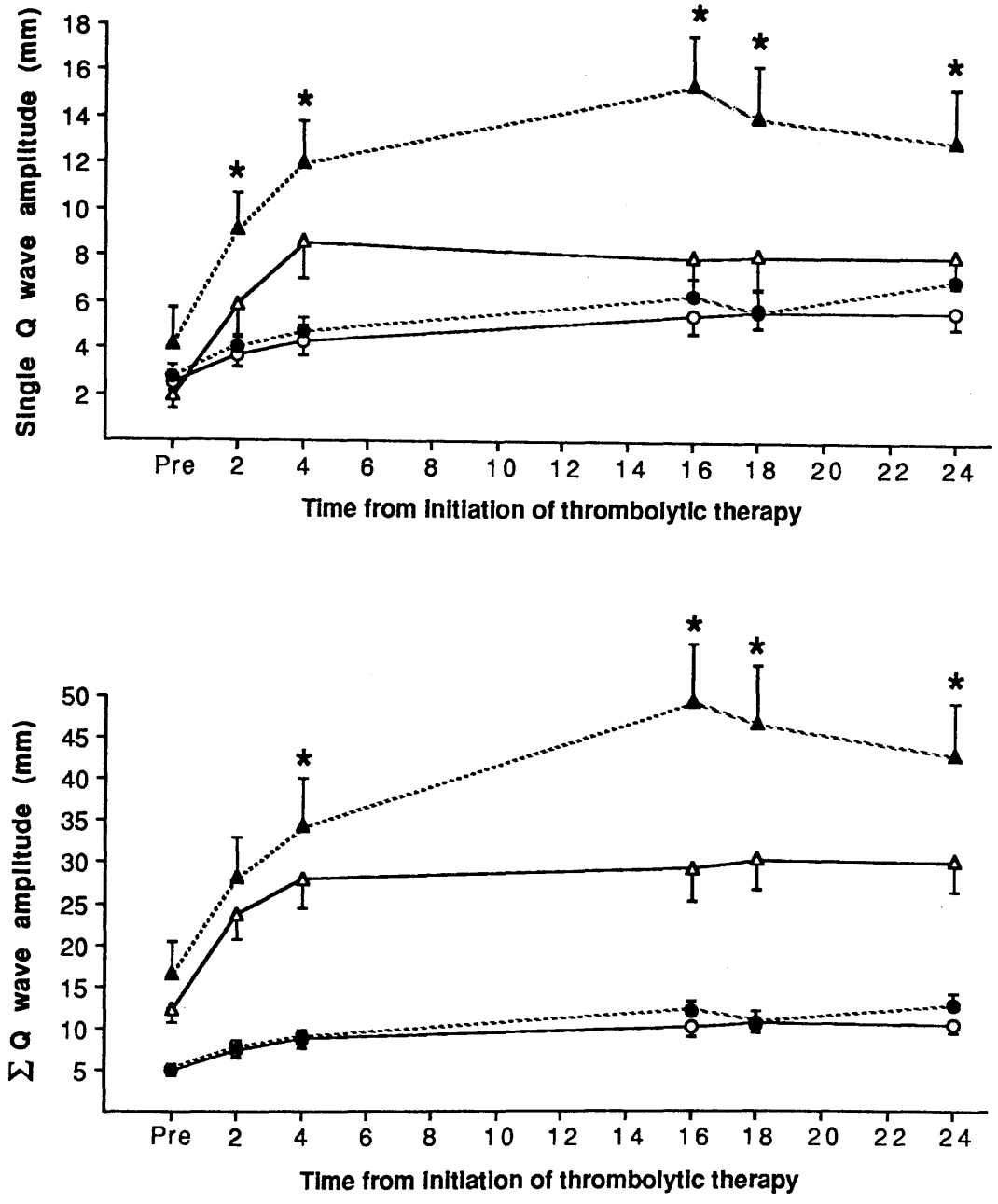


FIGURE 37: Q WAVE DEVELOPMENT OVER 24 HOURS ACCORDING TO INFARCT RELATED ARTERY. Patients are divided into LAD (△ and ▲) and RCA (○ and ●) occlusions and reperfusions (△ and ○) and non reperfusions (▲ and ●) according to 90 minute angiography. Asterisks (*) denote significant differences ($p<0.05$) between reperfusions (△) and non reperfusion (▲) for LAD infarctions

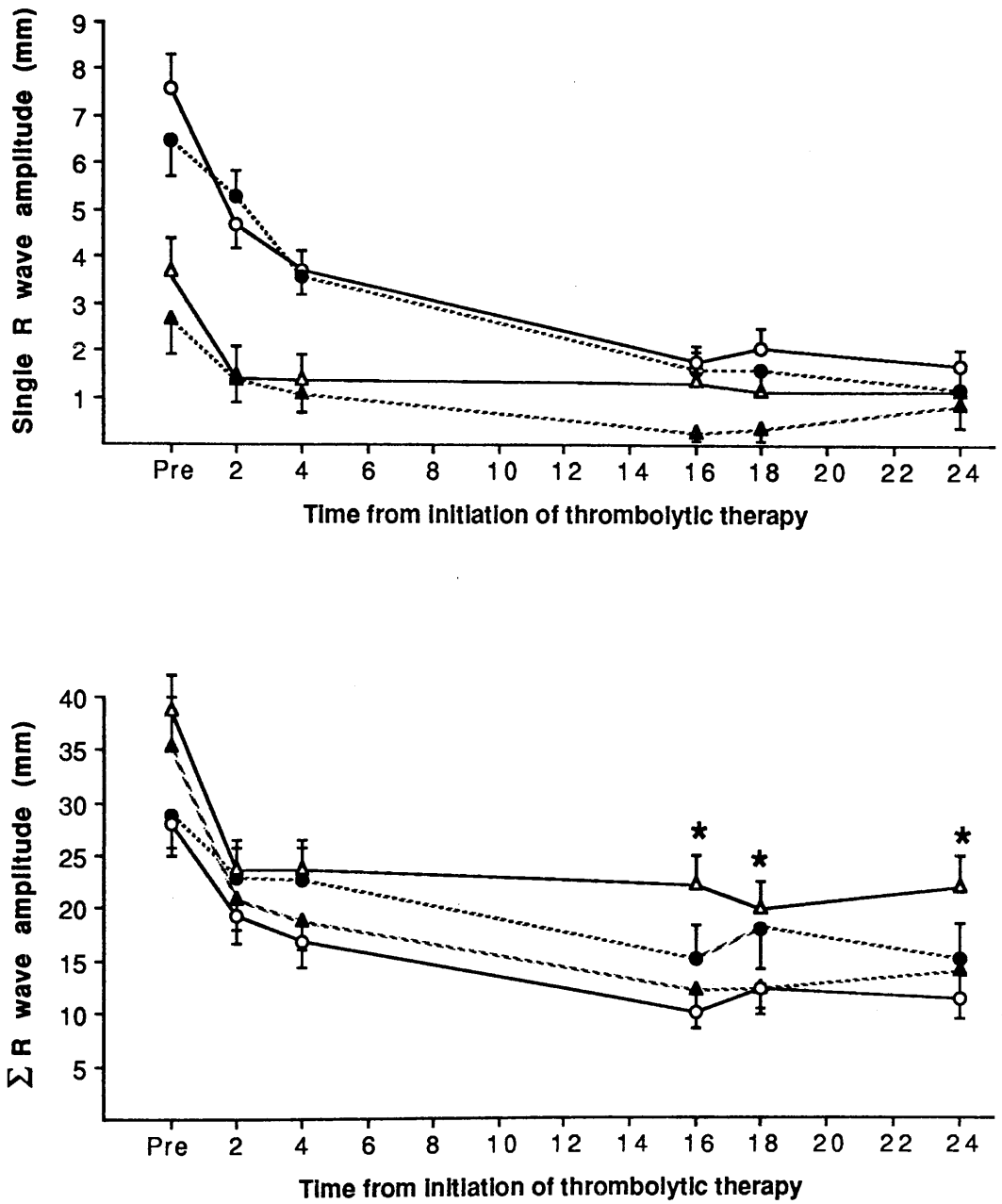


FIGURE 38: R WAVE LOSS OVER 24 HOURS ACCORDING TO INFARCT RELATED ARTERY. Patients are divided into LAD (△ and ▲) and RCA (○ and ●) occlusions and reperfusions (△ and ○) and non reperfusions (▲ and ●) according to 90 minute angiography. Asterisks (*) denote significant differences ($p<0.05$) between △ and ▲ .

ECG Parameter	90 Minute Angiogram	24 Hour Angiogram Non Reperfusion	Reperfusion
Total Numbers In each cell	Non reperfusion	12	25
	Reperfusion	3	65
Single Q	Non reperfusion	9.0±2.9	10.0±1.5
	Reperfusion	7.3±4.3	6.3±0.76
$\sum Q$	Non reperfusion	22.1±7.8	29.4±5.0
	Reperfusion	20.1±14.3	18.8±2.2
Single R	Non reperfusion	2.7±0.9	0.5±0.21
	Reperfusion	2.3±1.3	1.5±0.29
$\sum R$	Non reperfusion	14.8±4.6	13.6±1.9
	Reperfusion	12.5±1.6	17.8±2.0

TABLE 31: MEAN VALUES (±SE) AT 24 HOURS FOR SINGLE Q, $\sum Q$, SINGLE R, $\sum R$, RELATED TO PERFUSION STATUS CROSS-TABULATED FOR BOTH ANGIOGRAMS

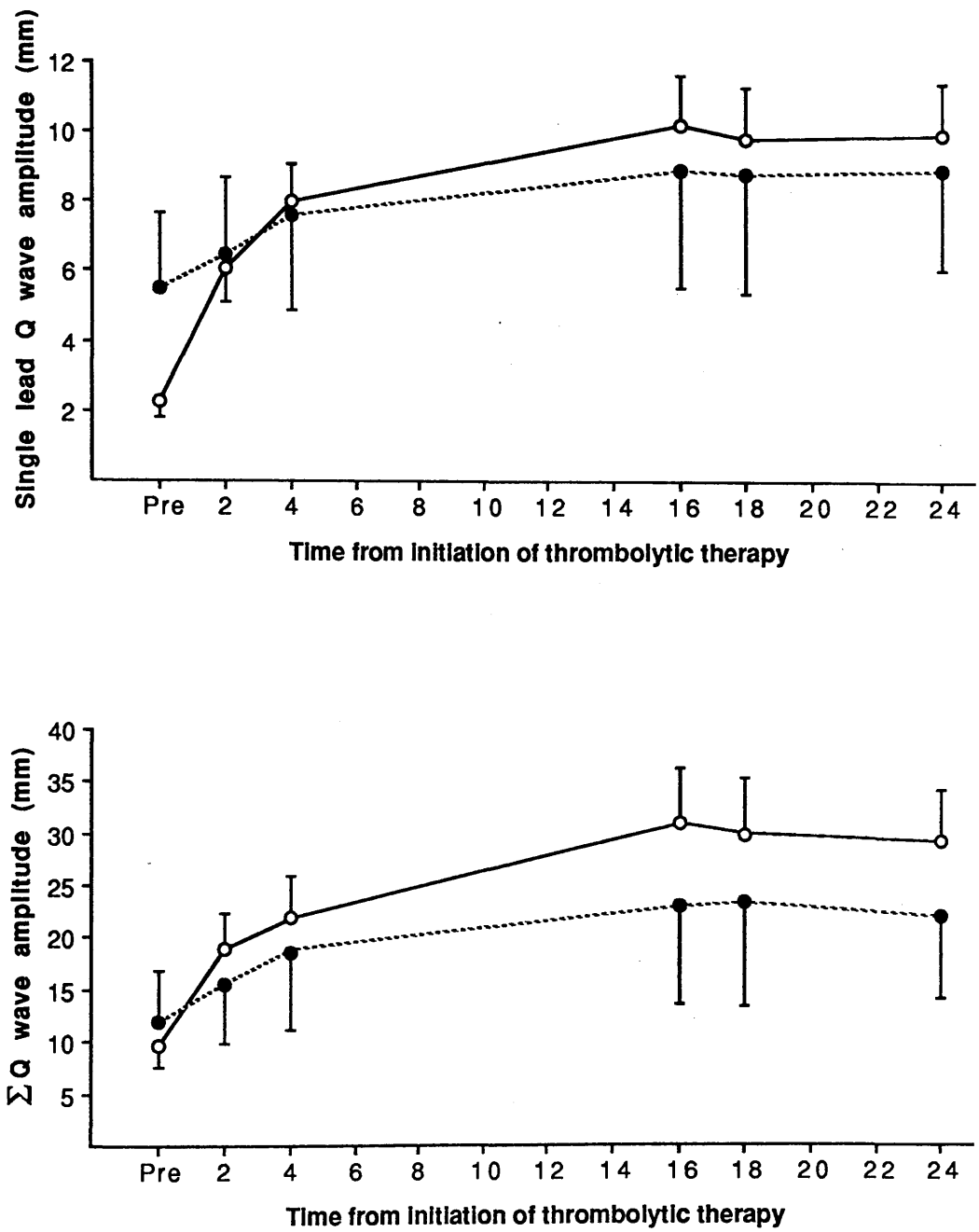


FIGURE 39: COMPARISON OF Q WAVE DEVELOPMENT BETWEEN PATIENTS WITH PERSISTENTLY OCCLUDED VESSELS (●) AT 24 HOURS AND PATIENTS WHO REPERFUSE LATE (○)

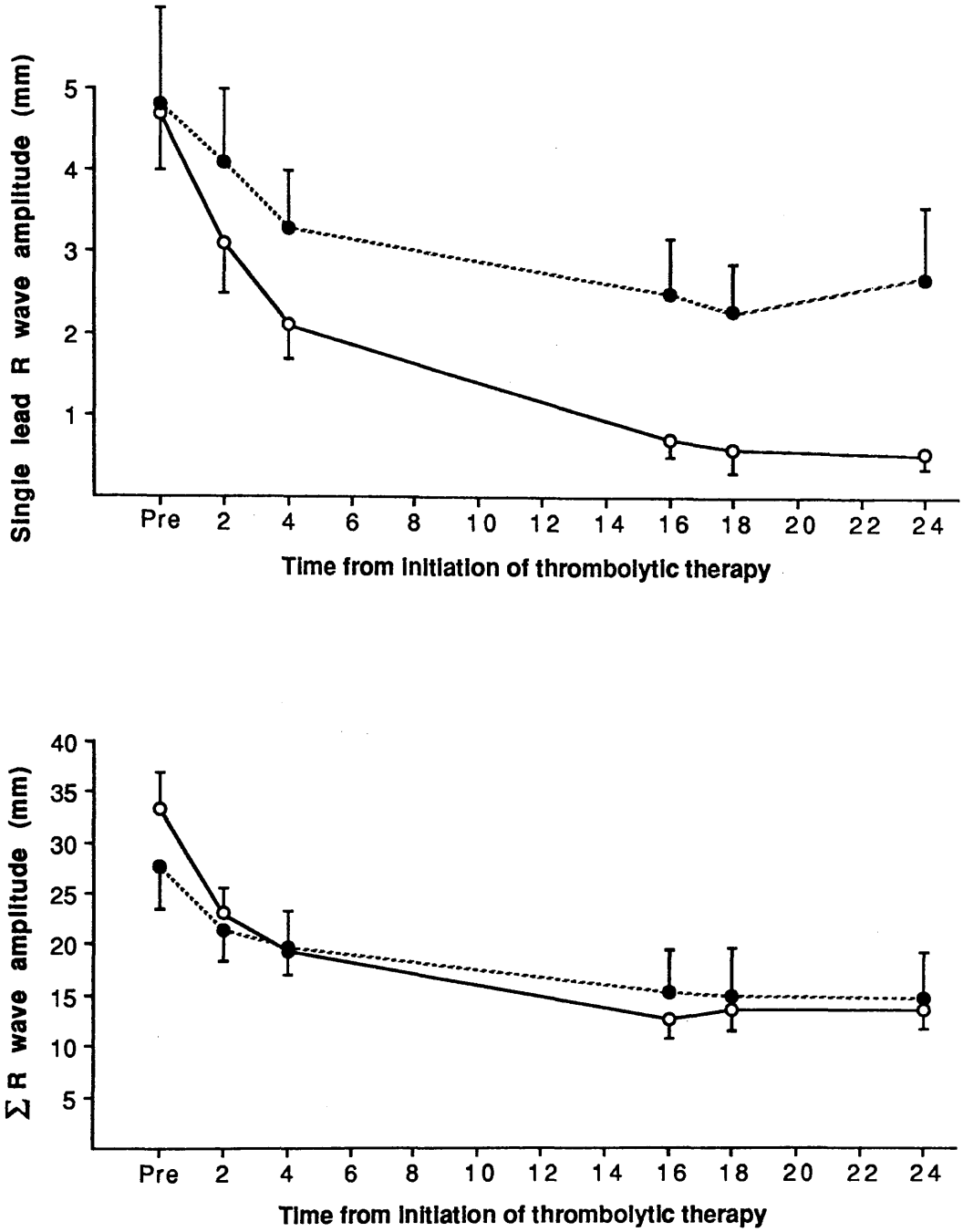


FIGURE 40: COMPARISON OF R WAVE LOSS BETWEEN PATIENTS WITH PERSISTENTLY OCCLUDED VESSELS (●) AT 24 HOURS AND PATIENTS WHO REPERFUSE LATE (○)

8.3.5. QRS Scores

Figure 41 shows the development of the simplified Selvester QRS score over 24 hours for patients with and without a patent artery at 90 minutes. Although both groups start with similar QRS scores on admission (mean QRS score = 2.4$\pm$0.33 (reperfusion), mean QRS score = 2.6$\pm$0.34 (non reperfusion) NS), patients who achieve a patent artery early (at or before 90 minutes) have significantly lower QRS scores than patients who have not reperfused by this time point. This difference in scores is apparent at 4 hours post treatment (mean QRS score 3.9$\pm$0.44 (reperfusion) vs mean QRS = 5.1$\pm$0.67 (non reperfusion) $p<0.05$), and is maintained at each subsequent time point up to 24 hours (mQRS = 4.9$\pm$0.47 (reperfusion) vs mQRS 6.3$\pm$0.65 (non reperfusion), $p<0.05$). Fourteen patients were noted to have sustained a previous infarct and their baseline scores were significantly higher than patients presenting with a first infarction (4.7$\pm$0.96 vs 2.5$\pm$0.23 respectively). Omitting these patients from the analysis does not affect the overall results. The mean QRS score at 24 hours for patients with no previous infarct and a patent artery at 90 minutes is 4.7$\pm$0.46 compared with a mean score of 6.4$\pm$0.7 for patients with a first infarct who are occluded at 90 minutes ($p<0.05$).

Table 32 shows mean QRS scores (± SE) at 24 hours for subgroups of patients according to patency of infarct related artery, both at 90 minutes and at 24 hours for all patients and after excluding those with previous infarction. The total number of patients with angiographic evidence of reocclusion between 90 minutes and 24 hours is very low (n=3). Subdivision of the databank into smaller groups really precludes meaningful statistical analysis - nevertheless it can be seen that rather than the group who never achieve a patent artery, it is the group that reperfuses late which has the tendency to the highest QRS scores (5.3±1.2 vs 6.6±0.87 respectively).

The above analysis has so far incorporated all infarctions irrespective of which artery was responsible. Previous work (Chapter 4) addressed QRS scores in anterior infarcts only. The QRS scores on admission for LAD and RCA occlusions are significantly different, mean QRS = 3.9±0.39 and 1.2±0.23 respectively ($p<0.05$). Figure 42 shows the development of the QRS score for LAD and RCA occlusion based on patency data at 90 minutes. It can be seen that the difference in the QRS score between reperfused and non reperfused groups shown in Figure 41 for all infarcts really reflects the marked attenuation in the QRS score seen in patients with LAD occlusion who reperfuse by 90 minutes. There is no significant difference in QRS scores between groups for RCA occlusion,

suggesting the use of the QRS score to show myocardial salvage following reperfusion is unhelpful in acute inferior myocardial infarction. Table 33 shows mean QRS scores at 24 hours related to perfusion data for both LAD and RCA occlusions for all patients presenting with a first infarction. The trend for patients who reperfuse late to have the highest QRS scores is again reflected here irrespective of which artery is involved.

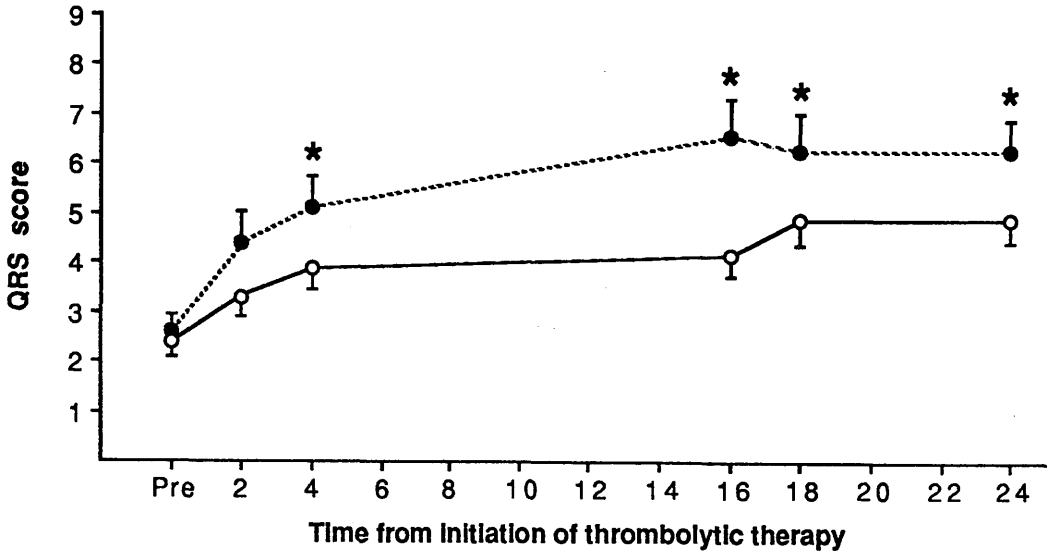


FIGURE 41: EVOLUTION OF SIMPLIFIED SELVESTER QRS SCORE OVER 24 HOURS FOR ALL PATIENTS ACCORDING TO VESSEL PATENCY AT 90 MINUTES. Patients who obtain a patent artery early (O) have lower QRS scores than those patients who remain occluded at 90 minutes (●). Asterisks (*) denote significant differences between groups

All patients

		24 Hour Angiogram	
		Non Reperfusion	Reperfusion
90 Minute Angiogram	Non Reperfusion	5.3±1.2 (n=12)	6.6±0.87 (n=25)
	Reperfusion	3.3±2.8 (n=3)	4.9±0.48 (n=65)

Omitting patients with previous M.I.

		24 Hour Angiogram	
		Non Reperfusion	Reperfusion
90 Minute Angiogram	Non Reperfusion	4.8±1.2 (n=11)	7.1±0.93 (n=22)
	Reperfusion	5.0±4.0 (n=2)	4.6±0.47 (n=61)

TABLE 32: MEAN QRS SCORE (± SE) AT 24 HOURS POST TREATMENT RELATED TO ANGIOGRAPHY BOTH AT 90 MINUTES AND AT 24 HOURS FOR ALL PATIENTS AND AFTER EXCLUDING THOSE WITH PREVIOUS INFARCTION

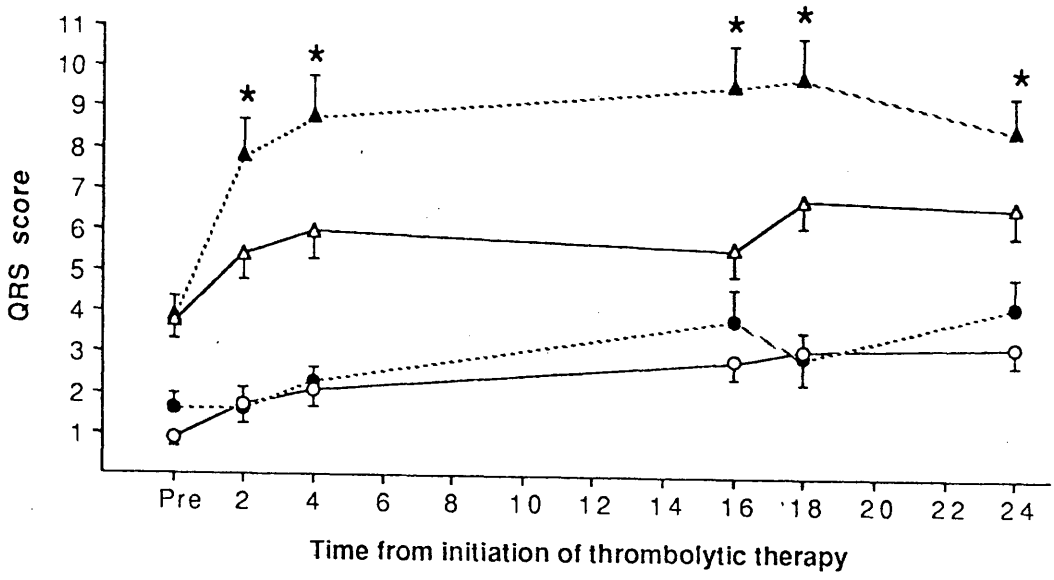


FIGURE 42: EVOLUTION OF SIMPLIFIED SELVESTER QRS SCORE OVER 24 HOURS ACCORDING TO PATENCY DATA AT 90 MINUTES AND TO INFARCT RELATED ARTERY. Patients are divided into LAD (Δ and ▲) and RCA (○ and ●) occlusions, reperfusions (Δ and ○) and non reperfusions (▲ and ●) according to 90 minute angiography. Asterisks (*) denote significant differences ($p<0.05$) between reperfusions (Δ) and non reperfusions (▲) for LAD infarctions. There is no significant difference between reperfusion (○) and non reperfusions (●) for RCA infarctions

LAD occlusion

90 Minute Angiogram	24 Hour Angiogram: Non Reperfusion	24 Hour Angiogram: Reperfusion
Non reperfusion	8.3±1.75 (n=4)	8.7±1.08 (n=12)
Reperfusion	9.0±0.0 (n=1)	6.7±0.82 (n=26)

RCA occlusion

90 Minute Angiogram	24 Hour Angiogram: Non Reperfusion	24 Hour Angiogram: Reperfusion
Non Reperfusion	3.6±1.3 (n=5)	4.6±1.1 (n=8)
Reperfusion	3.2±1.2 (n=6)	3.5±0.45 (n=37)

TABLE 33: MEAN QRS SCORES AT 24 HOURS FOR LAD AND RCA OCCLUSIONS RELATED TO PERFUSION STATUS CROSS TABULATED FOR BOTH ANGIOGRAMS

8.4 DISCUSSION

This chapter demonstrates the sequential electrocardiographic changes which take place in a large number of patients with acute myocardial infarction treated with thrombolytic therapy. No attempt has been made to differentiate those ECG changes occurring in either treatment group as morphologically both treatments behave the same with no difference in patency rates either at 90 minutes or at 24 hours. The important comparison is between reperfused and non reperfused cornary arteries, and also between anterior and inferior infarctions. Further division of these sub groups according to thrombolytic agent administered serves only to dilute the power of statistical comparison. The observational ECG data from this study has been examined to determine if practical information concerning reperfusion and myocardial salvage can be inferred.

Physicians treating patients with thrombolytic agents have long been aware of the phenomenon of rapid resolution of ST segment elevation reflecting reperfusion (Ganz et al., 1981). Quantification of those changes has been attempted, but some of the earlier studies compared treatment groups with placebo groups and did not separate the treatment groups into those with and without a patent artery (Anderson et al., 1983; Anderson et al., 1984). The results shown here confirm the very rapid drop in ST segments accompanying a patent artery at 90 minutes,

compared with non reperfused arteries, but show no difference in the ultimate level to which the ST segments fall by 24 hours. It appears that it is the rate of fall which discriminates patent from non patent vessels. Although the resolution of ST segment depression follows a similar pattern, there is not such a marked difference between groups. Calculating the F.C. or a proportional drop in ST segments from a single lead with maximal injury pattern on admission, and using a value $\geq$ 0.5 to denote a patent artery gave a test with a sensitivity of 81% and a specificity of 60%. This test calculated at 2 hours using a single lead with maximal ST elevation was the best indicator of a patent artery, and has the advantages of simplicity. It does however fall short of the sensitivities and specificities reported for the initial study in Chapter 3 (Table 8). The reasons for this may be severalfold; firstly there were only 3 non reperfusions in the test group of the initial study and miss-classification of one of those dropped the specificity to 67% from 100% in the training group. This present study represents a larger, and perhaps more realistic, number of non reperfusions; secondly with this current study the timing of the 90 minute angiogram was stringently adhered to, as was the timing of the ECGs. In the initial pilot study, the post treatment 12 lead ECG was performed at a mean time of 302$\pm$141 minutes and the angiogram for the intravenous anistreplase group performed between 90 and

180 minutes post treatment. This will lead to a greater number of patients being seen to have reperfused, and the later ECG recording will take into account some of the natural decline of ST elevation irrespective of that directly attributable to reperfusion. Clearly the 90 minute patency rate, despite being universally reported as a surrogate endpoint in multiple clinical trials, is not a morphologically sensible endpoint, as patients are still reperfusing after the angiogram has been completed. Of the group of patients designated "non reperfusion" at 90 minutes, 28 had a patent artery by 24 hours and only 13 were persistently occluded. In the so-called late reperfusions, 90% of the total fall in ST segments at 24 hours had occurred by 4 hours, compared with a very gradual decline in persistently occluded vessels. The specificity of the test may be increased if one assumes that a percentage of the "false high" F.C. values at 2 hours may represent a patent artery recanalised after the 90 minute angiogram. Also, this study has shown that in a small group of patients, collateral supply to the infarct territory via the contralateral artery may result in a F.C. value $\geq$ 0.5 despite the fact no anterograde perfusion can be seen, suggesting adequate myocardial perfusion. The F.C. test applied equally well to all infarct related arteries.

Subgroup analysis of late reperfusers and all time non reperfusers revealed that not only did the patients who

had unsuccessful thrombolysis have significantly less ST segment elevation on admission (Figure 31) but they also had a tendency to a greater Q wave amplitude in the lead with maximal ST elevation, although there was no significant difference in the $\sum$Q wave amplitudes across all leads. This suggests that it may be possible to select patients on admission who are unlikely to have a successful response to thrombolysis; those patients seem to have more established infarcts in electrocardiographic terms, especially in leads reflecting the epicentre of the infarct. Previous data has shown that patients with $\sum$ST elevation <1.2 m.V on admission show no beneficial effects from streptokinase on enzymatic infarct size, left ventricular function or mortality, but these results were not specifically related to the presence or absence of reperfusion (Vermeer et al., 1986). This cut-off value of 1.2 mV $\sum$ST elevation is strikingly similar to the mean value of the $\sum$ST elevation (11.3 mm or 1.13 mV) seen in patients who never reperfuse in this study. Similarly work by Bar et al. (1987) noted that there was no significant infarct limitation seen in patients with small amounts of ST elevation, but again the study did not directly relate this to perfusion status.

This study has confirmed the earlier work presented in Chapter 4, showing that myocardial salvage can be shown following early reperfusion in anterior infarction in

terms of reduced Q wave development, attenuation of R wave loss, and a reduced QRS score. This is not however the case for inferior myocardial infarctions - a feature which is obscured if looking only at the results in global terms (Figure 35 and 41). As discussed in Chapter 4, previously published work has failed to show a significant difference in QRS scores between reperfusions and non reperfusions (Mikell et al., 1986; Hackworthy et al., 1988) or that a difference only exists when patients treated very early (<1.5 hours) are compared with those treated later (Koren et al., 1985). These groups have not examined anterior and inferior infarctions separately, and the failure to do this may have masked any difference directly attributable to anterior infarctions. The inability of the QRS scores to reflect myocardial salvage in inferior infarctions appears not be a function of the smaller number of leads indicating inferior changes as the score is weighted towards these leads, but reflects no significant difference in the component parts of the score, i.e. Q wave amplitude, R wave amplitude, R/Q wave ratio etc. (Figures 37 and 38). Without a left ventricular ejection fraction it is difficult to know whether this reflects a real absence of myocardial salvage, or the inability of the 12 lead ECG to adequately reflect changes in the inferior surface of the heart. Certainly although the benefit in mortality is independent of site of infarction, some trials have been unable to show any improvement in left ventricular function in inferior infarction (Western

Washington Trial 1988, National Heart Foundation of Australia 1988).

Of particular interest is the observation that those patients who reperfuse late (>90 minutes) have a tendency to develop electrocardiographically bigger infarcts in terms of Q waves, loss of R wave amplitude and bigger QRS scores compared to those who reperfuse early and also to those who do not reperfuse at all. It is possible that these electrocardiographic indices may reflect an accelerated pattern of infarction, resulting from reperfusion injury.

Reperfusion injury is thought to occur when successful thrombolysis restores perfusion to myocardium which has been profoundly ischaemic, causing accelerated damage. Although much experimental animal and in vitro work has been performed to support this concept, the interaction between the area of infarcted myocardium, consisting of varying zones of profoundly ischaemic and necrotic tissue and the re-establishment of blood flow is very complex and a definitive in vivo study in the human has yet to be performed. In fairly gross pathological terms it is known that patients who have persistent coronary occlusions develop non haemorrhagic, pale infarcts in contrast to patients dying following documented reperfusion who have haemorrhagic infarcts. Multiple hypotheses have been

formed to explain reperfusion injury including alteration in microvascular permeability (Tilton et al., 1983), alphadrenergic stimulation (Sheridan et al., 1980) and free radical production (Burrell and Blake, 1989). Despite the molecular and biochemical level at which these interactions are occurring it may be that their effect could be picked up clinically using surface electrocardiography. Certainly the results presented in this chapter for the 12 lead ECG are an interesting and unexpected observation and merit further study, either using the 12 lead ECG or a multi-lead mapping study, which may better reflect changes occurring over various aspects of the infarction zone.

In conclusion, this chapter has presented the sequential ECG changes occurring in the first 24 hours after thrombolytic therapy for acute myocardial infarction and has related those changes to the clinical response following therapy. The data suggests that patients with a more established infarct pattern on admission are less likely to successfully reperfuse, that the rate of fall of ST segment elevation in the first 2 hours is a feature of reperfusion and has confirmed that the measurement of a F.C. value $\geq$ 0.5 hours following therapy in a single lead is a useful indicator of reperfusion, or perfusion, accepting the caveat that collateral supply from the contralateral artery may result in a high F.C. value despite no anterograde flow. This is true irrespective of

the infarct related artery. It is only patients with anterior infarction (LAD occlusion) who can be shown to have significant attenuation of electrocardiographic markers of necrosis following early lysis. There is no significant electrocardiographic evidence of infarct limitation for patients with inferior infarction (RCA occlusion). The observation that patients who reperfuse late tend to have more ECG evidence of infarction than patients with early reperfusion and also patients with persistent non reperfusion, has led to the hypothesis that this may represent reperfusion injury and requires further study in terms of confirmation of the result, and in following any possible resolution of ECG changes over a longer period than 24 hours.

CHAPTER 9

SUMMARY AND CONCLUSIONS

9.1 SUMMARY AND CONCLUSIONS

> **"It is remarkable that clinically useful ECG information keeps coming from well conducted studies related to major coronary occlusion even after 70 years of intense investigation"**
>
> (Bernard R. Chaitman, 1988)

Alhough the above quotation comes from an editorial commenting on a paper by Huey et al. (1988) which looks at circumflex occlusions, it is an appropriate statement with which to begin to justify and discuss the work of this thesis. The practice of thrombolysis has advanced dramatically over the last decade. It is now known beyond doubt that thrombolysis causes reperfusion, salvages myocardium causing increased ejection fraction and most importantly of all; saves lives. It is this last factor which has led to its widespread use in all areas of hospital practice. For every trial which reports a definitive result concerning some aspect of thrombolysis, another trial poses yet more unanswered questions; what is the absolute time limit for administration of therapy?; will adjuvant therapy prevent reperfusion damage?; what is the best way to prevent reocclusion? Many of these questions that remain to be answered deal with events happening at a molecular and cellular level. Even performing invasive coronary angiography in acute myocardial infarction and demonstrating a patent epicardial vessel is no guarantee of adequate tissue

perfusion - the so called "no-reflow" phenomenon (Kloner et al., 1974). Animal models and in vitro experiments while allowing detailed work have varying degrees of clinical relevance. Clinicians have for some time felt that surface electrocardiography is useful following intervention in acute myocardial infarction, but absolute quanitification of those changes which take place has not been performed. The advantages of electrocardiography are that it is available, reproducible, inexpensive and non invasive. Doctors are familiar with its interpretation and it is a technique which is constantly being used. If proven, application of simple measurements at specified times would provide a very useful clinical tool facilitating patient management, and may provide a non invasive means of following additional interventions.

This thesis has addressed several aspects of the 12 lead ECG in acute myocardial infarction, and will be summarised here not in the sequence of work presented chapter-by-chapter, but in terms of the chronological events occurring in acute myocardial infarction treated by thrombolysis, i.e. the presentation ECG and its relation to the infarct related artery, reperfusion and then myocardial salvage.

Performing coronary angiography within 90 minutes of starting thrombolytic therapy, as described for the anistreplase/streptokinase comparison study presented in Chapter 6, allowed a detailed correlation between the distribution of ST segment shift and the infarct related artery. Although a pre-selected group in that all patients had to meet the criteria of ST segment elevation ($\geq$1 mm in 2 limb leads or $\geq$2 mm in 2 precordial leads), many other studies relating infarct related artery to admission ECG changes depend on angiography performed at a considerable distance from the acute infarction. The results of the correlation confirmed the classical lead distribution in LAD and RCA occlusions on admission, and showed that ST segment elevation in I and AVL is a highly specific, but poorly sensitive, indicator of circumflex occlusion.

The importance of the presence of reciprocal change in acute myocardial infarction has been much debated. This work reports a higher incidence of reciprocal change in acute infarction than has previously been reported. This probably reflects the "younger" group of infarcts all presenting within 6 hours. It is clear from anatomical correlates that the presence of reciprocal change does not reflect coexisting arterial stenoses, but is an electrocardiographic mirror phenomenon.

There is no means of ageing the infarction in terms of degree of ST segment shift (elevation or depression). Infarcts presenting early do not necessarily have a greater degree of ST segment elevation. There is wide interindividual variability which presumably reflects the site of acute occlusion, whether the occlusion is total or sub total, the presence and distribution of collateral supply, the area of myocardium at jeopardy distal to the thrombus and the proximity of the infarct area to the surface electrodes. It does however appear that patients who have a more established infarct pattern on admission i.e. less ST segment elevation and a tendency to larger Q waves, are more likely not to respond to thrombolysis and to have a persistently occluded vessel at 24 hours. Work from this thesis and previously published work (Vermeer et al., 1986; Bar et al., 1987) support the view that if a patient presents with a myocardial infarction irrespective of time of onset of symptoms and has $\sum$ST elevation $<$ 1.2mV then the risk benefit ratio of treating with a thrombolytic agent increases. This sub group have not been shown to derive any benefit in terms of reperfusion, enzymatic infarct size, improvement in left ventricular function or a reduction in mortality.

Resolution of both ST segment elevation and depression has been mapped out for patients receiving thrombolysis. It is the rapid fall within the first 2-4 hours which differentiates patent from non patent arteries, although

the level to which both groups eventually fall at 24 hours is not significantly different. This more rapid rate of fall is more obvious for resolution of ST elevation than for ST depression. The initial pilot study reported in Chapter 3 which formulated the idea for calculating a Fractional Change value showed that a value of ≥ 0.5 was a sensitive and specific indicator of myocardial reperfusion. This study was performed in a smaller number of patients with few non reperfusions, and allowed a wider time window for the recording of the post-treatment ECG and also for angiography. When applied to the larger patient group randomised to anistreplase or streptokinase therapy, the same technique gave a sensitivity of 81% and a specificity of 60%. This may be a falsely low specificity for two reasons; one is that the Fractional Change is calculated from an ECG performed at 2 hours and the result related to angiographic patency which was determined 30 minutes earlier; it is clear that a lot of vessels continue to reperfuse after the 90 minute angiogram, with subsequent reduction of ST elevation, which would give rise to this apparently falsely high Fractional Change value. In addition effective collateral supply may have an effect on resolution of ST elevation and cause a high Fractional Change to result with no obvious anterograde flow.

The studies conducted in this thesis show that the sensitivity and specificity of the Fractional Change is not improved if calculated from multiple leads showing ST elevation. Taking the single lead with maximum injury pattern on admission gives a Fractional Change value more specific and sensitive than any other lead combination. The test is equally useful for LAD, RCA or Cx occlusions. The benefit of knowing whether the infarct related artery has reperfused or not depends on what the physician will do with the information. The benefits of aspirin as adjunctive medication by far outweigh the risks of its administration, the place of full body anticoagulation is not yet established but it is unlikely that one would want to subject a patient who has not reperfused to the risks of heparin and long-term warfarin. If a young patient is admitted with a large anteroseptal infarct, receives thrombolytic therapy and then progressively develops signs of cardiogenic shock, it may be that if his Fractional Change shows he has not reperfused, it would then be appropriate to consider further intervention in terms of angiography and intracoronary administration of a thrombolytic agent with mechanical perforation of the thrombus.

Electrocardiographic evidence of myocardial salvage was demonstrated in Chapter 4 in patients obtaining successful lysis of coronary thrombus, compared to a group of patients who received no medication other than simple

analgesia. This study confined itself to anterior infarctions and showed that although there was a significant reduction in the QRS score of the established infarct at 48 hours in the treated group compared to the control group, the reduction in this evolved score related to a jeopardy score on admission was not predictable on an individual basis. Chapter 8 showed that while this reduction in QRS score was maintained in anterior infarctions who reperfused compared to those who did not, a similar reduction in the final QRS score was not seen for successful inferior infarctions (RCA occlusion). Most previously reported studies using QRS scoring techniques have not separated out groups according to the anatomical site of the infarct, and as such may have masked any difference which did exist in anterior infarctions or incorrectly attributed a difference as being applicable to both RCA and LAD occlusions. The detailed electrocardiographic databank amassed for this later patient group presented in chapters 6-8, showed that the inability of the QRS score to show salvage in inferior infarction was not due to the smaller number of leads reflecting the inferior surface of the heart (II and AVF) compared to anterior infarctions, but was due to an inability of the component parts of the score (Q and R wave amplitudes) to show any difference depending on perfusion status even in leads reflecting the epicentre of the infarct.

The observation that patients who reperfused after 90 minutes tended to have bigger QRS scores, more Q wave development and more R wave loss was unexpected and of interest. Although primarily observational, it leads to the hypothesis that this is an electrocardiographic marker of reperfusion damage. Further study is required to verify these findings, and also to investigate if there is any recovery of the ECG pattern over several days - an electrocardiographic equivalent of myocardial stunning.

The major advantage in studying the group of patients recruited for the anistreplase/streptokinase comparison trial was being able to relate ECG changes to coronary anatomy defined by angiography performed acutely. This trial was set up to compare 30 I.U. anistreplase with 1.5 M. I.U. streptokinase in a double-blind randomised cross-over design using patency rates at 90 minutes and 24 hours as primary endpoints. The results show that there is no advantage of anistreplase over streptokinase in terms of coronary artery patency, which has been used here as a surrogate endpoint for coronary mortality. Justification for this relies on the fact that it is now ethically unacceptable to compare a new lytic agent with placebo. Comparison must be made with the standard therapy which is now generaly accepted as intravenous streptokinase. Comparative studies using mortality as an endpoint would need much bigger numbers than the 11,806 and 17,187 required for GISSI and ISIS 2 respectively. While these

proposed studies are underway in the form of GISSI 2 and ISIS 3, they take time to run and are expensive and costly to set up. The trial performed at Stobhill has refuted the claim that anistreplase is more effective than streptokinase in obtaining coronary patency, and by implication in reducing mortality. However, anistreplase has shown itself to be as effective as streptokinase and with the advantage of bolus administration, may yet find its niche in the thrombolytic field if out-of-hospital administration proves valuable.

In terms of further study - although the digitized database allowed a comprehensive collection of ECG parameters to be stored for multiple analyses, it still requires each 12 lead ECG to be manually digitized. Although the current system was well validated, an on-line computer system which would also signal average complexes from each lead of the 12 lead ECG would save a significant amount of time, and the signal averaging would reduce measurement error. A lot of the developmental work performed to start the digitized system, such as the set of rules for waveform definitions and the program to compute the QRS score would all be readily transferrable.

The work of this thesis has contributed to further understanding of the electrocardiographic changes which take place in acute myocardial infarction treated by thrombolysis, but there are so many questions still to be

answered that it is likely that Dr. Chaitman's quotation at the beginning of this chapter will be as true in a further 70 years time.

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APPENDIX I

PROTOCOL FOR ANISTREPLASE/STREPTOKINASE COMPARISON

1. **STUDY OBJECTIVES**

1.1. To measure and compare angiographically documented coronary artery patency at 90 mins. following intravenous APSAC 30 Units or i.v. streptokinase 1.5 million units.

1.2. To compare reocclusion rates at 24 hours after dosing.

1.3. To compare the safety of the different compounds with special reference to effects on blood pressure in the first 90 minutes after dosing.

2. **STUDY MEDICATION**

2.1. **Intravenous APSAC**

APSAC is the active site p-anisoylated derivative of the primary (human) lys-plasminogen-streptokinase complex prepared by immediate acylation of the serine residue in the active center of that complex as it is formed. The molecular weight is close to 131,000 Daltons.

APSAC is formulated in a mixture of clinical grade human albumin, D-mannitol and L-lysine. It is presented in vials, each containing 30 Units APSAC as a sterile, white lyophilized powder.

2.2. **Storage**

APSAC 30U vials have a shelf-life of 2 years when stored at or below 5 °C.

2.3. **Streptokinase**

Streptokinase is presented as a freeze-dried powder in vials containing 600,000 units of streptokinase. Streptokinase is stable for at least 3 years when stored at room temperature (<25 °C). Solutions prepared for infusion but left over or not used should be discarded.

3. **STUDY DESIGN**

A double blind, randomised, angiographically controlled study of intravenous APSAC or i.v. streptokinase in acute myocardial infarction with stratification according to infarct site.

3.1. **Number of patients**

A minimum of 80 patients will complete the study.

3.2. **Patient Entry**

Patients with clinical evidence of acute myocardial infarction who satisfy the inclusion/exclusion criteria will be eligible for randomisation.

3.3. **Stratification and Randomisation**

Patients will be stratified according to the site of infarction. Each stratum has been separately pre-randomised to receive APSAC 30 Units i.v. or streptokinase 1.5 million Units i.v.

3.4. **Coronary Angiography**

Angiography will be performed at 90 mins. and at 24 hrs after dosing.

3.5. **Blood pressure and heart rate monitoring**

Blood pressure and heart rate will be monitored immediately before drug and continuously throughout the 90 mins. post-treatment period. Blood pressure and heart rate will be recorded on the case report forms every 2 mins. until the end of the 90 min. angiogram.

3.6. **Primary Data End Points**

3.6.1. Angiographically documented patency (occlusion/perfusion grade 2,3) or occlusion (occlusion/perfusion grade 0.1) of the presumed infarct related vessel at 90 mins. after dosing.

3.6.2. Angiographically documented reocclusion (occlusion/perfusion grade 0,1) or sustained patency (occlusion/perfusion grade 2,3) at 24 hrs after dosing in those who had patent infarct related vessels at 90 mins.

4. **PATIENTS AND METHODS**

All patients with suspected acute myocardial infarction who satisfy the inclusion/exclusion criteria will be admitted.

5. **INCLUSION CRITERIA**

Patients admitted to hospital;

5.1. Aged 70 yrs or under.

5.2. With chest pain or other symptoms of acute myocardial infarction of at least 30 minutes

duration who can be treated within 6 hours of symptom onset.

5.3. With ECG evidence of ST segment elevation of at least 0.1mV in two or more standard leads and/or 0.2mV in two or more precordial leads.

5.4. In whom appropriate consent is obtained for participation in the study.

6. EXCLUSION CRITERIA

6.1. Patients with systolic blood pressure below 95 mmHg.

6.2. Patients on anticoagulant therapy.

6.3. Patients with a known history of haemorrhagic diatheses or significant recent bleeding from another site.

6.4. Patients with documented or suspected active peptic ulceration with 1 year.

6.5. Patients with a history of cerebrovascular accident.

6.6. Patients who have had surgery, major trauma or head injury within the previous 4 months.

6.7. Patients who have received streptokinase or APSAC therapy within the previous 6 months.

6.8. Patients with severe hypertension, blood pressure above 200/120 mmHg.

6.9. Patients who have received prolonged chest compression prior to randomisation.

6.10. Pregnant females or those in whom pregnancy cannot be ruled out. Females who are menstruating or who are of child bearing potential.

6.11. Patients with diabetic proliferative retinopathy.

6.12. Patients in whom coronary angiography is contra-indicated.

6.13. Patients who have had coronary angioplasty within 1 month of presentation or those with a history of CABG or prosthetic valve insertion.

6.14. Any condition requiring immediate surgical intervention.

6.15. Any clinical suspicion of dissecting aneurysm.

6.16. Transmural myocardial infarction within 3 months.

6.17. Patients with serious or life-threatening disease unrelated to the circulatory system.

7. STRATIFICATION AND RANDOMISATION

Patients will be stratified according to the site of infarction on the admission ECG. Those with anterior or lateral infarction will be assigned to group A and inferior or posterior infarction to group I. Each of the 2 groups (A and I) has a separate randomisation sequence for 30 Units APSAC or 1.5 million units of streptokinase. Consecutive numbers starting from 1 will be used within each group.

Two identification, self-adhesive labels will be detached from study drug pack, one to be placed in the record form and the other attached to a postcard which should be posted within 12 hours of patient entry. The label identifies the precise batch of study drug.

The double blind nature of the study will be ensured by a "double dummy" technique. Patients will receive "placebo APSAC" and "active streptokinase" or "active APSAC" and "placebo streptokinase".

8. **TREATMENT**

The treatment regimen will be as follows:
The vial labelled APSAC will be dissolved in 5 mls of water for injection or physiological saline to be administered intravenously over 5 minutes. To minimize foaming, the solution must be gently swirled AND NOT SHAKEN.

Two and one half of the three ampoules marked streptokinase will be dissolved in 500ml of 5% Dextrose to be infused over 60 minutes.

Injection and infusion will begin at the same time. Solutions must be administered immediately after reconstitution.

9. CORONARY ANGIOGRAPHY

9.1. Coronary angiography will be via a brachial or femoral artery approach. At lease three views (LCA) or two views (RCA) of the infarct related vessel will be taken during each procedure. One of these will be the optimal view for maximising the percent residual stenosis.

9.2. An angiogram will be performed at 90 minutes from the start of dosing. The catheter will then be withdrawn, but the sheath will be left in place for up to 48 hours.

Perfusion is defined as a grade 2 or 3 (occlusion/perfusion grade) at 90 minutes. Patients with grade 0-1 occlusion at 90 minutes will not require further angiographic study and will be given the benefit of the best available treatment at the discretion of the attending physician. They will be recorded as "persistent occlusions" for the purpose of the analysis.

9.3. Only patients with patency (occlusion/perfusion grade 2-3) at 90 minutes will be required to undergo coronary angiography at 24 hours after dosing, but patients with non-patent arteries at 90 minutes may undergo further angiography at the discretion of the physician in charge.

10. **BLOOD PRESSURE MONITORING**

Arterial pressure and heart rate will be recorded immediately before and continuously for 90 mins after dosing. Copies of all tracings will be reported in the relevant section of the case record form prior to their being placed in the inside cover.

11. **HEPARIN ADMINISTRATION**

Based on the result of the 90 minute post treatment angiogram, patients with Grade 0-1 occlusion may be given heparin and/or other therapy at the discretion of the attending physician. Patients with Grade 2-3 perfusion should receive heparin in a dose of 1000-1500 units per hour from between 4 and 6 hours after APSAC therapy or when the thrombin time has decreased to less than twice the control value.

Heparin treatment will be continued for 24 hours and further anticoagulation is at the physicians discretion.

12. **ECG RECORDINGS**

All patients will have single lead continuous ECG rhythm recordings for the first 24 hrs of the study. Rhythm disturbances will be reported in the appropriate section of the case report form.

Five 12 lead ECG's are required, these include one on admission, at 2, 4, 16, 18 and 24 hours. If the patients clinical condition changes substantially within the first 24 hours, further ECG's may be required.

13. CLINICAL ASSESSMENTS

13.1. Any symptoms thought to be associated with the procedure, the treatment or the disease will be noted.

13.2. Heart rate and blood pressure will be measured before dosing and continually for the first 90 mins. after dosing. There will be further non invasive measurements at 6, 12 and 24 hrs. after dosing or more frequently if indicated by a change in the patient's condition.

13.3. Temperature will be monitored at 6, 12 and 24 hours after dosing. Measurements will be taken more frequently if indicated by changes in the patient's condition.

14. LABORATORY OBSERVATIONS

Blood samples will be drawn to determine Hepatitis B status, cardiac enzyme concentrations, clinical chemistry, haematology.

14.1. Hepatitis B status

A blood sample will be taken before dosing and

tested for HBsAg.

14.2. **Cardiac Enzymes Concentrations**

Blood samples must be taken before dosing, at 90 mins. and 24 hrs after dosing for the estimation of CPK and routine cardiac enzymes.

14.3. **Clinical Chemistry and Haematology**

Blood samples will be taken before dosing, at 90 mins. and 24 hours after dosing for a routine screen.

14.4. **Urinalysis**

A urine sample will be collected at 24 hrs after dosing for the estimation of pH, blood, ketones, protein and bilirubin by means of "Dipstix".

15. **PRECAUTIONS**

15.1. **Ancillary medications**

No anti-platelet medication for 24 hours after thrombolytic therapy.

Additional drugs, such as analgesics, antiarrhythmics etc., should be administered in accordance with normal hospital practice.

15.2. **Dealing with excessive production of plasmin**

For the treatment of severe uncontrolled bleeding, it is suggested that the following steps be taken:

a) discontinue thrombolytic agent

b) application of local pressure where possible

c) reversal of the lytic state: Administer

TRANEXAMIC ACID in a standard dose of 500 mg intravenously over 2 minutes (other agents may be used). A further 500 mg tranexamic acid may be administered if the bleeding is not controlled after the replacement of clotting factors.

d) replace clotting factors with cryoprecipitate, fresh frozen plasma, or whole blood.

e) replace blood loss.

16. **STATISTICAL CONSIDERATION**

The major efficacy variables in this protocol will be patency at 90 minutes and reocclusion after patency.

The main objectives of this study are the measurements of patency and reocclusion after APSAC and streptokinase and the effect of these agents on blood pressure. Results will be compared using relevant statistical procedures.

Information regarding adverse reactions and abnormal laboratory tests will be presented in the form of listings and tabulations.

17. **DRUG ACCOUNTABILITY**

17.1 **On-site Storage and Distribution**

All investigational drug supplies will be stored in a refrigerator, maintained at 5 ^{o}C at the study

site. Shelf life for APSAC is 2 years. Access to the study medication must be limited to the principal investigator and other authorized members of his staff.

During periodic monitoring by Beecham staff, the drug supplies and case records will be reviewed for accuracy and completeness.

18. **INFORMED CONSENT AND PATIENT PRIVACY**

It is the investigator's responsibility that each subject or subject's legal representative signs an informed consent statement prior to participation in this study. An example of the patient information sheet and consent form are provided at the end of the protocol.

The patients will be informed of their rights to privacy but will be made aware that study data will be submitted to Beecham and to drug regulatory authorities for review and evaluation. They will also be informed that both Beecham and the regulatory authorities have the right to inspect the patient's medical records to verify the accuracy and completeness of the study records and results.

19. **REPORTING OF ADVERSE EVENTS**

The date, time of onset, duration and severity of any adverse reaction will be recorded. In the event of a persistent severe adverse event, e.g. hemiplegia resulting from CVA, the outcome should be determined at intervals up to 1 year.

PATIENT INFORMATION SHEET: THROMBOLYTIC THERAPY

A heart attack or a coronary thrombosis is the term used for a condition in which the flow of blood to the heart muscle is reduced to a degree that damage occurs. The reduction in blood flow is usually due to a blood clot or thrombus obstructing the arteries leading to the heart muscle. After a period of time, damage is irreversible and the course of the illness will follow the normal healing process. If a patient is admitted to hospital early enough, then treatment may be introduced which can dissolve the blood clot and can restore flow of blood to the area of muscle under threat of permanent damage.

The standard treatment for heart attack within the Coronary Care Unit of Stobhill Hospital is to give this therapy to dissolve the blood clot - that is thrombolytic treatment, to those patients admitted in the early stage of coronary thrombosis to obtain coronary artery flow, and to reduce the degree of damage. This form of treatment cannot be given to patients who have a predisposition to bleeding, such as those with stomach or duodenal ulcers, or to patients who have had strokes or operations in the recent past.

The standard drug available at present for thrombolytic therapy is called streptokinase, and at present we are conducting a study to compare the effects of this drug with a new drug of the same family called APSAC. This latter drug has been shown to be very successful in dissolving blood clots, and has been used in a widespread manner in mainland europe as well as in the U.K. In this study you will receive an infusion of either streptokinase or APSAC. This treatment is in addition to all normal forms of treatment. Although we are studying these drugs, their use will not prevent the introduction of any other treatment which is necessary for the underlying condition. To compare the effects of streptokinase and APSAC we are studying their effects on blood clotting, and therefore frequent blood sampling is taken from a small plastic tube inserted in your arm.

As a follow up to thrombolytic therapy to assess its success, and to determine if any other procedures or treatment should be given, an x-ray test, called a coronary angiogram, is often helpful, and we are performing this as part of the present study. This requires the insertion of a little plastic tube into an artery, and therefore signed consent is required before the performance of this test. The actual method of the test will be explained separately by the Doctor who will perform the procedure at the time. This investigation is not routinely performed in all centres, and is an additional procedure to the administration of therapy. Although we may use the information gained to help in your

management, the angiogram may not be of direct help in your individual case other than confirming your follow up treatment. After this x-ray test, a small tube will be left in your artery for approximately 24 hours, and our study requests that we perform a further angiogram at that time in the absence of any clinical contra-indications. This is an additional procedure, and would only be performed after further discussion and explanation.

There is no compulsion on you to enter the study, and you are free to withdraw from the study at any time without prejudice to your treatment and long-term follow up.

CONSENT FORM

I .....(full name and address) .....

.....

freely and voluntarily consent to take part in a clinical research study on **A Comparison of Streptokinase and APSAC in the Treatment of Acute Myocardial Infarction with coronary arteriogaphy,** which so far as is known should not carry any unusual risk.

I have read the accompanying information sheet. The nature and purpose of the study has been explained to me by Dr. .....

I have had the opportunity to ask any questions and I understand fully what is proposed.

I recognise that I may receive no benefit personally from the study. I accept that there may be other risks associated with the procedures which are not directly attributable to negligence on the part of those undertaking the procedures.

I understand that I am free to withdraw my consent at any time without prejudice to me or my medical care. I have been assured that any information obtained from me will not be disclosed to any other party in a manner which will reveal my identity.

Signature ..... Date .....

I confirm that I/Dr. .....have/has explained the nature and purpose of the clinical research study and the procedure in respect of which consent has been given by the above named.

APPENDIX II

PATIENT DETAILS FOR ST SEGMENT STUDY

	INITIALS	AGE	SEX	SITE OF M.I.	TREATMENT	REPERFUSION
1.	JW	64	M	ANTERIOR	i/c SK	YES
2.	JH	76	M	INFERIOR	i/c SK	YES
3.	FM	59	M	INFERIOR	i/c SK	NO
4.	MG	56	F	ANTERIOR	i/c SK	YES
5.	RC	50	M	ANTERIOR	i/c SK	YES
6.	TW	51	M	INFERIOR	i/c SK	NO
7.	JD	45	M	ANTERIOR	i/c SK	YES
8.	AE	58	M	ANTERIOR	i/c SK	YES
9.	WM	67	M	ANTERIOR	i/c SK	YES
10.	JL	68	M	INFERIOR	i/c SK	YES
11.	CR	62	M	INFERIOR	i/c SK	YES
12.	RW	61	M	INFERIOR	i/c SK	YES
13.	MD	66	F	INFERIOR	i/c SK	YES
14.	AC	45	M	INFERIOR	i/c SK	YES
15.	GMcH	59	M	ANTERIOR	i/c SK	YES
16.	EE	58	M	INFERIOR	i/c SK	YES
17.	AY	60	M	ANTERIOR	i/c SK	YES
18.	AH	75	F	INFERIOR	i/v APSAC	YES
19.	JB	68	M	ANTERIOR	i/v APSAC	YES
20.	AM	53	M	ANTERIOR	i/v APSAC	NOT KNOWN
21.	JC	62	M	ANTERIOR	i/v APSAC	YES
22.	DC	69	M	INFERIOR	i/v APSAC	YES
23.	CM	68	M	ANTERIOR	i/v APSAC	YES
24.	GS	49	M	INFERIOR	i/v APSAC	NO
25.	NB	64	M	ANTERIOR	i/v APSAC	YES
26.	WD	61	F	INFERIOR	i/v APSAC	YES
27.	JB	67	M	INFERIOR	i/v APSAC	YES
28.	CMcG	63	F	ANTERIOR	i/v APSAC	YES
29.	AD	67	F	INFERIOR	i/v APSAC	YES
30.	AR	39	M	INFERIOR	i/v APSAC	YES
31.	CM	59	F	ANTERIOR	i/v APSAC	YES
32.	WD	39	M	ANTERIOR	i/v APSAC	YES
33.	JN	69	M	INFERIOR	i/v APSAC	YES
34.	JP	45	M	ANTERIOR	i/v APSAC	YES
35.	AG	56	F	INFERIOR	i/v APSAC	YES
36.	SMcM	65	F	INFERIOR	i/v APSAC	YES
37.	EC	59	F	ANTERIOR	i/v APSAC	YES
38.	PL	46	M	INFERIOR	i/v APSAC	YES
39.	IK	56	M	INFERIOR	i/v APSAC	YES
40.	MT	51	M	INFERIOR	i/v APSAC	YES
41.	AM	58	M	ANTERIOR	i/v APSAC	NO
42.	RK	58	M	ANTERIOR	i/v APSAC	NO
43.	SM	48	F	ANTERIOR	i/v APSAC	NO
44.	RH	66	M	ANTERIOR	i/v APSAC	NO
45.	DH	49	M	ANTERIOR	i/v APSAC	NO

APPENDIX III

PATIENT DETAILS FOR ST/QRS STUDY

GROUP 1

	INITIALS	AGE	SEX	SITE OF M.I.
1.	EI	33	M	ANTERIOR
2.	WT	42	M	ANTERIOR
3.	CMcL	55	M	ANTERIOR
4.	WK	46	M	ANTERIOR
5.	AG	61	M	ANTERIOR
6.	TMcL	65	M	ANTERIOR
7.	MD	66	M	ANTERIOR
8.	AG	40	M	ANTERIOR
9.	HG	44	M	ANTERIOR
10.	AMcB	50	M	ANTERIOR
11.	MC	42	F	ANTERIOR
12.	GM	40	M	ANTERIOR
13.	DG	51	M	ANTERIOR
14.	WW	59	M	ANTERIOR
15.	JH	49	M	ANTERIOR
16.	AMcN	67	F	ANTERIOR
17.	JMcH	41	M	ANTERIOR
18.	JI	67	F	ANTERIOR
19.	WD	55	M	ANTERIOR
20.	GM	62	M	ANTERIOR
21.	TI	64	M	ANTERIOR
22.	FO'H	45	M	ANTERIOR
23.	HM	37	M	ANTERIOR
24.	AT	68	F	ANTERIOR
25.	CJ	56	M	ANTERIOR
26.	JC	65	F	ANTERIOR
27.	GW	66	M	ANTERIOR
28.	RB	69	M	ANTERIOR
29.	CS	58	M	ANTERIOR
30.	PMcM	51	M	ANTERIOR
31.	JT	76	F	ANTERIOR
32.	WS	65	M	ANTERIOR
33.	FE	71	M	ANTERIOR
34.	PC	62	M	ANTERIOR
35.	JR	60	M	ANTERIOR

GROUP 2

	INITIALS	AGE	SEX	SITE OF M.I.	TREATMENT	REPERFUSION
1.	WB	62	M	ANTERIOR	i/c SK	YES
2.	AC	53	M	ANTERIOR	i/c SK	YES
3.	CF	54	F	ANTERIOR	i/c SK	YES
4.	CMcC	70	F	ANTERIOR	i/c SK	YES
5.	JW	64	M	ANTERIOR	i/c SK	YES
6.	WK	53	M	ANTERIOR	i/c SK	NO
7.	MY	67	F	ANTERIOR	i/c SK	NO
8.	MG	56	F	ANTERIOR	i/c SK	YES
9.	RC	50	M	ANTERIOR	i/c SK	YES
10.	JD	45	M	ANTERIOR	i/c SK	YES
11.	AE	58	M	ANTERIOR	i/c SK	YES
12.	JA	55	M	ANTERIOR	i/c SK	YES
13.	AY	60	M	ANTERIOR	i/c SK	YES
14.	CF	52	F	ANTERIOR	i/V APSAC	YES
15.	DM	65	M	ANTERIOR	i/v APSAC	YES
16.	JD	48	F	ANTERIOR	i/v APSAC	YES
17.	LL	67	M	ANTERIOR	i/v APSAC	YES
18.	JH	45	M	ANTERIOR	i/v APSAC	YES
19.	JP	45	M	ANTERIOR	i/v APSAC	YES
20.	RK	58	M	ANTERIOR	i/v APSAC	YES
21.	EC	59	F	ANTERIOR	i/v APSAC	YES
22.	DJ	47	M	ANTERIOR	i/v APSAC	YES
23.	JC	64	M	ANTERIOR	i/v APSAC	YES
24.	JC	48	M	ANTERIOR	i/v APSAC	YES
25.	EM	69	F	ANTERIOR	i/v APSAC	YES
26.	JD	49	F	ANTERIOR	i/v APSAC	YES
27.	WM	72	M	ANTERIOR	i/v APSAC	YES
28.	JF	58	M	ANTERIOR	i/v APSAC	YES
29.	RMcC	62	M	ANTERIOR	i/v APSAC	YES
30.	WD	38	M	ANTERIOR	i/v APSAC	YES
31.	EAM	62	F	ANTERIOR	i/v APSAC	YES
32.	JG	60	M	ANTERIOR	i/v APSAC	YES
33.	DG	67	F	ANTERIOR	i/v APSAC	YES

GROUP 3

	INITIALS	AGE	SEX	SITE OF M.I.	TREATMENT	REPERFUSION
1.	JH	61	M	ANTERIOR	i/v APSAC	NO
2.	TMcQ	64	M	ANTERIOR	i/v APSAC	YES
3.	BR	49	M	ANTERIOR	i/v APSAC	YES
4.	JF	45	M	ANTERIOR	i/v SK	NO
5.	SA	47	M	ANTERIOR	i/v APSAC	YES
6.	KA	59	M	ANTERIOR	i/v SK	NO
7.	MK	52	F	ANTERIOR	i/v APSAC	YES
8.	WT	61	M	ANTERIOR	i/v SK	YES
9.	AB	48	M	ANTERIOR	i/v SK	NO
10.	PM	59	M	ANTERIOR	i/v SK	NO
11.	JG	48	M	ANTERIOR	i/v SK	YES
12.	AW	68	F	ANTERIOR	i/v SK	NO
13.	JS	53	M	ANTERIOR	i/v APSAC	NO
14.	JE	40	M	ANTERIOR	i/v APSAC	NO
15.	JC	31	M	ANTERIOR	i/v APSAC	YES
16.	JM	62	M	ANTERIOR	i/v APSAC	NO
17.	DC	46	M	ANTERIOR	i/v APSAC	YES
18.	JS	57	M	ANTERIOR	i/v SK	YES
19.	DMcC	59	F	ANTERIOR	i/v APSAC	YES
20.	JO	59	M	ANTERIOR	i/v SK	NO
21.	JB	55	M	ANTERIOR	i/v APSAC	YES
22.	RN	56	M	ANTERIOR	i/v APSAC	NO

APPENDIX IV

PROGRAM FOR QRS SCORE COMPUTATION

```
C# ECGSCR
      SUBROUTINE ECGSCR(QDUR,RDUR,S,RQ,RS,SCORE)
      DIMENSION QDUR(11),RDUR(11),S(11),RQ(11),RS(11)
C     WRITE(1,998) (QDUR(I),I=1,11)
C     WRITE(1,998) (RDUR(I),I=1,11)
C     WRITE(1,998) (S(I),I=1,11)
C     WRITE(1,998) (RQ(I),I=1,11)
C     WRITE(1,998) (RS(I),I=1,11)
  998 FORMAT(11F6.1)
      XL=0.0001
      SCORE=0
      IF(QDUR(1) .LT. 30.) GOTO 20
      SCORE=1.
      IF(RQ(1).LE. 1.0) SCORE=SCORE+1
   20 WRITE(1,999) SCORE
C  20 CONTINUE
      IF(QDUR(2) .GE. 30.) SCORE=SCORE+1
      IF(QDUR(2) .GE. 40.) SCORE=SCORE+1
   40 WRITE(1,999) SCORE
C  40 CONTINUE
      IF(QDUR(4) .LT. 30.) GOTO 50
      SCORE=SCORE+1
      IF(RQ(4) .LT. 1.0) SCORE=SCORE+1
   50 WRITE(1,999) SCORE
C  50 CONTINUE
      IF(QDUR(5) .LT. 30.) GOTO 60
      SCORE=SCORE+1
      QQ=QDUR(5)
      IF(QQ. GE. 50.) SCORE=SCORE+1
      IF(QQ .GE. 40.) SCORE=SCORE+1
      IF(RDUR(5).GE.XL) GOTO 55
      SCORE=SCORE+2
      GOTO 60
   55 IF(RQ(5) .LE. 2.) SCORE=SCORE+1
      IF(RQ(5) .LE. 1.) SCORE=SCORE+1
   60 WRITE(1,999) SCORE
C  60 CONTINUE
      IF(QDUR(6).GT. XL) SCORE=SCORE+1
  640 IF(RDUR(6).LT. 40.) GOTO 70
      SCORE=SCORE+1
      IF(RDUR(6).GT.50.) SCORE=SCORE+1
      IF(RS(6).GE.1.0 .OR. S(6).LE.XL) SCORE=SCORE+1
   70 WRITE(1,999) SCORE
C  70 CONTINUE
      IF (QDUR(7) .LE. XL .AND. RDUR(7) .GT. 20.) GOTO 760
      SCORE=SCORE+1
  760 IF(RDUR(7).GT.60.) SCORE=SCORE+1
  750 IF(RDUR(7).GE. 50.) SCORE=SCORE+1
      IF(RDUR(7).LT.50.) GOTO 80
      IF(RS(7) .GE. 1.5 .OR. S(7) .LT.XL) SCORE=SCORE+1
   80 WRITE(1,999) SCORE
C  80 CONTINUE
      IF(QDUR(8).GT.XL.OR.(RDUR(8).LE.30..AND.RDUR(8).GT.XL))
     +    SCORE=SCORE+1
   90 WRITE(1,999) SCORE
```

```
C   90 CONTINUE
       IF(QDUR(9).LE.20.) GOTO 920
       SCORE=SCORE+1
       IF(RDUR(9).GT.XL) GOTO 905
       SCORE=SCORE+2
       GOTO 100
  905  IF(S(9).LE.XL) GOTO 910
       IF(RQ(9).LE.1. .OR. RS(9).LE.1.) SCORE=SCORE+1
       IF(RQ(9).LE.0.5 .OR. RS(9).LE.0.5) SCORE=SCORE+1
       GOTO 100
  910  IF(RQ(9).LE.1.0) SCORE=SCORE+1
       IF(RQ(9).LE.0.5) SCORE=SCORE+1
       GOTO 100
  920  IF(RS(9).LE.1.0.AND.S(9).GE.XL) SCORE=SCORE+1
       IF(RS(9).LE.0.5.AND.S(9).GE.XL) SCORE=SCORE+1
  100  CONTINUE
       WRITE(1,999) SCORE
       IF(QDUR(10).LE.30.) GOTO 1030
       SCORE=SCORE+1
       IF(RDUR(10).GT.XL) GOTO 105
       SCORE=SCORE+2
       GOTO 110
  105  IF(S(10).LE.XL) GOTO 1020
       IF(RQ(10).LE.2.0 .OR. RS(10).LE.2.0) SCORE=SCORE+1
       IF(RQ(10).LE.1.0 .OR. RS(10).LE.1.0) SCORE=SCORE+1
       GOTO 110
 1020  IF(RQ(10).LE.2.0) SCORE=SCORE+1
       IF(RQ(10).LE.1.0) SCORE=SCORE+1
       GOTO 110
 1030  IF(RS(10).LE.2.0.AND.S(10).GE.XL) SCORE=SCORE+1
       IF(RS(10).LE.1.0.AND.S(10).GE.XL) SCORE=SCORE+1
  110  CONTINUE
       WRITE(1,999) SCORE
       IF(QDUR(11).LE.30.) GOTO 1130
       SCORE=SCORE+1
       IF(RDUR(11).GT.XL) GOTO 115
       SCORE=SCORE+2
       GOTO 120
  115  IF(S(11).LE.XL) GOTO 1120
       IF(RQ(11).LE.3.0 .OR. RS(11).LE.3.0) SCORE=SCORE+1
       IF(RQ(11).LE.1.0 .OR. RS(11).LE.1.0) SCORE=SCORE+1
       GOTO 120
 1120  IF(RQ(11).LE.3.0) SCORE=SCORE+1
       IF(RQ(11).LE.1.0) SCORE=SCORE+1
       GOTO 120
 1130  IF(RS(11).LE.3.0 .AND. S(11).GE.XL) SCORE=SCORE+1
       IF(RS(11).LE.1.0 .AND. S(11).GE.XL) SCORE=SCORE+1
  120  CONTINUE
       WRITE(1,999) SCORE
  999  FORMAT('SCORE = ',F6.3)
       RETURN
       END
```

APPENDIX V

ECG DATA FROM INTRA AND INTER-OBSERVER VARIATION STUDY

LIST OF PATIENTS USED IN INTER AND INTRA-OBSERVER VARIATION

Pt. No.	Initials	Age	Sex	ECG
1.	AS	64	F	Evolving acute inferior myocardial infarction
2.	PL	49	M	Within normal limits
3.	TMcK	23	M	Within normal limits
4.	WM	70	M	Hyperacute inferior myocardial infarction
5.	ML	49	M	Acute anterior myocardial infarction
6.	AMcM	55	F	Inferior myocardial infarction
7.	JM	52	M	Inferolateral ischaemia
8.	CT	62	M	Anterior myocardial infarction
9.	KH	50	M	Inferior myocardial infarction
10.	ES	45	F	Lateral ischaemia

APPENDIX VI

PATIENT DETAILS FROM ANISTREPLASE STREPTOKINASE COMPARISON TRIAL

No.	Initials	Age	Sex	IRA	Drug	Prev. M.I.
1.	JM	68	M	RCA	SK	No
2.	JMcG	66	M	RCA	SK	No
3.	DC	50	M	RCA	SK	No
4.	JC	51	M	LAD	SK	No
5.	NMcD	57	F	RCA	APSAC	No
6.	WN	42	M	RCA	APSAC	No
7.	JOC	42	M	RCA	APSAC	No
8.	WS	55	M	N/A	SK	No
9.	JH	61	M	LAD	APSAC	No
10.	CMcN	59	M	RCA	SK	Yes
11.	TR	67	M	RCA	SK	No
12.	PW	49	M	RCA	APSAC	No
13.	EMcI	60	M	LAD	SK	No
14.	IA	64	F	LAD	APSAC	Yes
15.	TMcQ	64	M	LAD	APSAC	No
16.	WW	55	M	RCA	APSAC	No
17.	RM	59	M	RCA	SK	No
18.	BR	49	M	LAD	APSAC	No
19.	MH	52	F	N/A	APSAC	Yes
20.	JF	45	M	LAD	SK	No
21.	SA	47	M	LAD	APSAC	No
22.	TG	45	M	RCA	SK	No
23.	RMcC	42	M	RCA	APSAC	No
24.	PK	44	M	RCA	SK	No
25.	DU	49	M	Cx	APSAC	No
26.	JH	45	M	RCA	SK	No
27.	WC	55	M	RCA	APSAC	No
28.	RR	55	M	RCA	APSAC	No
29.	KA	59	M	LAD	SK	No
30.	MK	52	F	LAD	APSAC	No
31.	GMcM	58	F	RCA	APSAC	No
32.	NG	58	F	RCA	SK	No
33.	WT	61	M	LAD	SK	No
34.	PD	50	M	LAD	SK	Yes
35.	AB	48	M	LAD	SK	No
36	WMcL	58	M	RCA	APSAC	No
37.	AP	68	M	RCA	SK	Yes
38.	WM	53	M	LAD	APSAC	No
39.	CM	55	M	RCA	APSAC	No
40.	EH	68	F	RCA	SK	Yes
41.	JC	65	M	LAD	APSAC	No
42.	WD	52	M	RCA	SK	No
43.	JA	52	F	RCA	SK	No
44.	SB	66	F	RCA	APSAC	No
45.	FC	44	M	LAD	APSAC	No
46.	JL	70	M	LAD	APSAC	No
47.	GC	47	M	LAD	SK	Yes
48.	RMcD	67	M	RCA	SK	No
49.	MH	64	F	Cx	APSAC	No
50.	RE	60	M	RCA	APSAC	No
51.	PL	58	M	RCA	APSAC	No
52.	JD	43	M	RCA	SK	No
53.	JF	68	M	LAD	APSAC	No

54.	MMcL	59	F	RCA	APSAC	No
55.	RD	40	M	RCA	SK	No
56.	JH	54	M	N/A	SK	Yes
57.	PM	59	M	LAD	SK	No
58.	JG	48	M	LAD	SK	No
59.	AF	44	M	RCA	SK	No
60.	SW	65	F	Cx	SK	Yes
61.	AW	68	F	LAD	SK	No
62.	MMcG	53	M	RCA	APSAC	No
63.	AO'N	58	F	Cx	APSAC	No
64.	EMcG	57	M	RCA	SK	No
65.	JB	67	M	LAD	APSAC	No
66.	WL	61	M	LAD	SK	Yes
67.	JS	53	M	LAD	APSAC	No
68.	JE	40	M	LAD	APSAC	No
69.	JC	31	M	Cx	APSAC	No
70.	AM	56	M	N/A	SK	No
71.	JM	62	M	LAD	APSAC	Yes
72.	WMcC	59	M	RCA	APSAC	No
73.	DC	46	M	LAD	APSAC	No
74.	JS	57	M	LAD	SK	No
75.	DMcC	59	F	LAD	APSAC	No
76.	WMcL	64	M	LAD	APSAC	No
77.	CA	65	F	RCA	SK	No
78.	ED	55	M	LAD	SK	No
79.	FH	54	M	RCA	APSAC	No
80.	WA	47	M	RCA	SK	No
81.	DP	56	M	Cx	SK	No
82.	WMcI	51	M	RCA	SK	No
83.	JO	59	M	LAD	SK	No
84.	NMcN	61	M	Cx	APSAC	No
85.	CG	60	F	RCA	APSAC	No
86.	WS	50	M	RCA	APSAC	No
87.	GH	67	M	LAD	SK	No
88.	RN	56	M	LAD	APSAC	No
89.	JB	55	M	LAD	APSAC	No
90.	GT	67	M	LAD	SK	No
91.	GR	51	M	Cx	APSAC	No
92.	RS	58	M	N/A	APSAC	No
93.	JN	64	M	RCA	SK	No
94.	WD	54	M	RCA	SK	No
95.	JH	55	M	LAD	SK	No
96.	JA	57	F	LAD	SK	No
97.	MD	59	F	LAD	APSAC	No
98.	NU	42	M	LAD	SK	No
99.	RK	41	M	LAD	SK	No
100.	TM	46	M	LAD	SK	Yes
101.	MM	62	F	LAD	APSAC	No
102.	JL	62	M	LAD	APSAC	No
103.	EH	45	M	RCA	APSAC	No
104.	HH	59	M	Cx	APSAC	No
105.	JW	56	M	RCA	APSAC	No
106.	EC	52	F	RCA	APSAC	No
107.	TS	54	M	LAD	SK	No
108.	JMcG	42	M	RCA	APSAC	No

109.	AB	47	F	RCA	SK	Yes
110.	MT	55	F	RCA	SK	No
111.	MS	55	F	LAD	SK	No
112.	RH	55	M	RCA	SK	No
113.	PM	52	M	Cx	SK	No
114.	AR	64	M	RCA	APSAC	No
115.	JJ	70	F	N/A	SK	No
116.	PR	61	M	N/A	APSAC	Yes
117.	DMcG	43	M	Cx	APSAC	No
118.	JS	61	M	Cx	APSAC	No
119.	PC	51	M	LAD	APSAC	No
120.	TJ	41	M	LAD	SK	No
121.	TM	63	M	RCA	APSAC	No
122.	CM	41	F	RCA	APSAC	No
123.	GMcD	65	M	LAD	SK	No
124.	CC	66	F	RCA	APSAC	No
125.	DC	65	M	LAD	SK	No
126.	RK	69	M	LAD	SK	No
127.	HT	67	M	LAD	SK	No
128.	RH	57	M	LAD	APSAC	No

APPENDIX VII

DEFINITION OF TIMI SCORES

DEFINITION OF TIMI SCORES
(Williams et al., 1986)

GRADE 0 (No reperfusion): There is no antegrade flow beyond the point of occlusion.

GRADE 1 (Penetration with minimal perfusion): The contrast material passes beyond the area of obstruction, but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for duration of the cine run.

GRADE 2 (Partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel, e.g. the opposite coronary artery or the coronary bed proximal to the obstruction.

GRADE 3 (Complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed as the same vessel or the opposite artery.

APPENDIX VIII

PUBLICATIONS AND PRESENTATIONS ARISING FROM WORK OF THESIS

PUBLICATIONS

1. Electrocardiographic prediction of coronary artery patency following thrombolytic therapy in acute myocardial infarction using the ST Segment as a non invasive marker.
   Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS.
   Br Heart J 1988;60:275-80.

2. Electrocardiographic evidence of myocardial salvage following thrombolysis in acute myocardial infarction.
   Hogg KJ, Lees KR, Hornung RS, Howie CA, Dunn FG, Hillis WS.
   Br Heart J 1989;61:489-95.

3. Angiographic patency study of anistreplase versus streptokinase in acute myocardial infarction.
   Hogg KJ, Gemmill JD, Burns JMA, Lifson WK, Rae AP, Dunn FG, Hillis WS.
   Lancet 1990;335:254-258.

PRESENTATIONS

1. ST Segment analysis as a non invasive predictive indicator of coronary artery reperfusion in acute myocardial infarction.
   Hogg KJ, Hornung RS, Hockings N, Dunn FG, Hillis WS.
   Scottish Society for Experimental Medicine: Dundee. May, 1985.
   (Abstract Scottish Medical Journal 1985;30:194).

2. ST Segment analysis as a non invasive predictive indicator of coronary artery reperfusion in acute myocardial infarction.
   Hogg KJ, Hornung RS, Hockings N, Dunn FG, Hillis WS.
   European Society of Cardiology.
   Brighton. September, 1985.
   Abstract European Heart Journal 1985;6 Suppl. 1 p.16).

3. Electrocardiographic evidence of myocardial salvage following thrombolysis in acute myocardial infarction.
   Hogg KJ, Lees KR, Hornung RS, Dunn FG, Hillis WS.
   Eighth International Congress on Fibrinolysis.
   Vienna. August 1986.
   (Abstract Fibrinolysis Volume 1, Suppl. 1, 1986).

4. Thrombolysis in acute myocardial infarction with APSAC, electrocardiographic evidence of reduction in infarct size.
Hogg KJ, Lees KR, Hornung RS, Dunn FG, Hillis WS.
X World Congress of Cardiology.
Washington. September 1986.
(Abstract Proceedings of X World Congress of Cardiology p.35).

5. Comparative effect of anistreplase and streptokinase on coronary artery patency in acute myocardial infarction.
Hogg KJ, Gemmill JD, Lifson WK, Burns JMA, Rae AP, Dunn FG, Hillis WS.
American Heart Association.
New Orleans. November 1989.
(Abstract Circulation 1989;80:Suppl. II:II-419.)

6. ECG correlates of early coronary artery patency and myocardial perfusion following thrombolysis.
Hogg KJ, McKenzie A, Howie CA, Gemmill JD, Rae AP, Dunn FG, Hillis WS.
British Cardiac Society.
Torquay. May 1990.