INTRINSIC SYMPATHOMIMETIC ACTIVITY AND BETA-ADRENOCEPTOR BLOCKADE : CLINICAL AND METABOLIC STUDIES IN ISCHAEMIC HEART DISEASE.

A THESIS SUBMITTED

BY

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ABBREVIATIONS.

Apo	-	Apolipoprotein.
bpm.	-	beats per minute.
B.P.	-	Blood pressure.
CAD.	-	Coronary Artery Disease.
CNS.	-	Central Nervous System.
CPT.	-	Cold Pressor Test.
ECG.	-	Electrocardiogram.
EF.	-	Ejection Fraction.
ERV.	-	Expiratory Reserve Volume.
FEV .	-	Forced Expiratory Volume in 1 second.
FVC.	-	Forced Vital Capacity.
HDL.	-	High Density Lipoprotein.
IA.	-	Intraarterial.
IC.	-	Inspiratory Capacity.
IDL.	-	Intermediate Density Lipoprotein.
IRV.	-	Inspiratory Reserve Volume.
ISA.	-	Intrinsic Sympathomimetic Activity.
LCAT.	-	Lecithin Cholesterol Acyl Transferase.
LDL.	-	Low Density Lipoprotein.
LV.	-	Left Ventricle.
MI.	-	Myocardial Infarction.
MSA.	-	Membrane Stabilising Activity.
NYHA.	-	New York Heart Association.
RNV.	-	Radionuclide Ventriculography.
SIHG.	-	Sustained Isometric Handgrip.
VLDL.	-	Very Low Density Lipoprotein.

ACKNOWLEDGEMENTS.

Colleagues who have collaborated in individual studies are acknowledged at the beginning of each section.

I am particularly indebted to Dr. David Ballantyne Consultant Physician and Cardiologist, Department of Clinical Medicine, The Victoria Infirmary, Glasgow, who acted as my supervisor. He provided constant encouragement and stimulation throughout the period of research and provided constructive advice during the preparation of this thesis.

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I also wish to thank the staff of the Department of Medical Illustration in the Victoria Infirmary who prepared the figures contained in this thesis and Mrs. Ann McLachlan for the considerable care and effort expended by her in the typing of the manuscript.

DECLARATION.

The conception, planning and institution of all the experiments in this thesis was entirely my own work. Recruitment and clinical evaluations of subjects including exercise electrocardiograms, for each of the studies was conducted by myself.

Several experiments required technical assistance from laboratory colleagues. The extent of my personal contribution in relation to this technical assistance can be outlined as follows:

1. HAEMATOLOGICAL AND BIOCHEMICAL INVESTIGATIONS.

All blood samples were taken by myself. Full blood counts, plasma beta blocker levels and lipoprotein analyses were performed by technical staff.

2. RESPIRATORY FUNCTION TESTS.

These tests were carried out entirely by myself.

3. RADIONUCLIDE VENTRICULOGRAPHY.

All radionuclide ventriculograms were performed by myself with some assistance from technical staff. The analysis of all the resulting images was carried out by myself.

4. AMBULATORY ELECTROCARDIOGRAPHY.

Ambulatory ECG monitors were applied to subjects by myself with technical assistance. All recordings were analysed by myself.

5. CARDIAC CATHETERISATIONS.

All cardiac catheterisations were carried out by myself with supervision from Dr. David Ballantyne.

6. STATISTICAL ANALYSES.

I personally carried out all the statistical tests, but I acknowledge the statistical advice of colleagues (see Acknowledgements).

ROBIN J. NORTHCOTE

SUMMARY.

Beta-adrenoceptor blockade has become an established method of treating both angina pectoris and hypertension. Among the beta-adrenoceptor antagonists available, are several with distinct pharmacological properties including cardioselectivity, membrane stabilising activity and intrinsic sympathomimetic or partial agonist activity. This thesis is concerned with the clinical evaluation of the latter property in the long-term treatment of chronic stable angina pectoris. Several reports have suggested that beta blockers with with this property confer certain advantages over pure beta blockers, but their long-term effects in chronic angina pectoris have not been clearly demonstrated.

There are five main objectives to this thesis:

1. To determine the effect of pure beta blockers on left ventricular function during long-term treatment of angina pectoris and the influence of ISA.

2. To assess the long-term effect of beta blockers and the influence of ISA on the plasma lipo-protein profile.

3. To establish the efficacy of beta blockers with ISA in suppressing symptomatic and asymptomatic episodes of myocardial ischaemia

in chronic stable effort angina pectoris, in comparison to a 'pure' beta blocker.

4. To determine the effect of pure beta blockade on respiratory function during long-term treatment of angina pectoris in comparison to a beta blocker with ISA.

5. To assess the value of radionuclide ventriculography in the detection of coronary artery disease in our laboratory and the role of cold pressor stress and isometric handgrip exercise. In these investigations, propranolol was used as a pure beta blocker, pindolol was used as a prototype of a beta blocker possessing ISA.

From the studies contained in this thesis I have obtained the following results and conclusions:

1. Despite the demonstration of improved or sustained left ventricular function obtained with beta blockers possessing ISA, after single dose oral or intravenous administration, I failed to find any advantages using pindolol in chronic stable angina pectoris, when compared to propranolol. This conclusion is derived from the results of serial radionuclide ventriculography carried out at intervals during the course of a year's treatment with

both drugs in a controlled study. Left ventricular function at rest failed to improve in those taking pindolol, but significantly improved in those taking propranolol. This observation held for those with subnormal basal left ventricular performance in whom one might expect a beta blocker with ISA to have the greatest effect. However the results of this thesis do not disprove the potential of drugs with ISA to protect or improve left ventricular performance in patients with severely compromised left ventricular function as this group was not included in my investigation. It is concluded that ISA is an unhelpful property in terms of left ventricular function during chronic therapy of stable angina pectoris, in patients with normal or moderately compromised left ventricular function. It should be pointed out that the beneficial changes in left ventricular function observed in those taking propranolol were within the variability (5%) of the technique used. This may be partially offset by the fact that the study was controlled, statistical analysis was by 2-way analysis of variance and the variability of the technique was calculated using results from normal volunteers who are known to have greater variability of left ventricular performance.

2. A review of the literature shows little consistency in the plasma lipoprotein changes

in response to beta blockers. The most frequent changes noted by other investigators have been an elevation of total triglyceride with pure beta blockers and a fall in total high density lipoprotein. In comparing the effect of pindolol and propranolol in patients with chronic stable angina pectoris I found no significant change in total triglycerides with either drug and observed small falls in total HDL with both drugs although this was only significant for propranolol. Conversely HDL_2, which has been shown to have a more strongly negative correlation with coronary artery disease rose with both drugs, but this was only significant in those treated with propranolol after 52 weeks treatment. For those with initially elevated total cholesterol, pindolol caused a significant reduction throughout treatment, but this did not occur with propranolol.

3. Although pindolol was associated with more symptomatic and asymptomatic episodes of ST-segment depression than propranolol there was no significant difference between the two drugs. Propranolol resulted in a significantly lower heart rate, but was associated with a significantly higher hourly frequency of ventricular premature contractions. Thus, no significant difference could be demonstrated

in the efficacy of both drugs in suppressing myocardial ischaemia, although there was a trend in favour of propranolol.

4. Patients taking propranolol developed significantly increased airways obstruction throughout treatment and although this also occurred with pindolol, it was significantly less than that experienced with propranolol. These results suggest that deteriorating respiratory function was maintained throughout treatment with propranolol, and pindolol conferred protection against this effect.

5. Radionuclide ventriculography is a reproducible technique in our laboratory with cold pressor stress and isometric handgrip exercise proving to be useful, easily applied and reproducible interventions when comparative assessments are being made within the individual. However, when used to enhance the ability of radionuclide ventriculography to detect coronary artery disease they were insufficiently sensitive, although may be of use when the subject is incapable of dynamic exercise.

Thus, the long-term effects of beta blockers with and without ISA in patients with chronic stable angina pectoris differ from those observed in short-term studies. Although ISA has been shown to be a useful property in

many respects, some of the anticipated advantages could not be demonstrated by these experiments.

SECTION 1. GENERAL INTRODUCTION

1.1. PLAN AND AIM OF THESIS.

The studies which form the basis of this thesis were performed over the course of two and a half years from May 1982 until October 1984, during the tenure of my post of Research Fellow inCardiology at the Victoria Infirmary, Glasgow.

The main object has been to establish the clinical importance of intrinsic sympathomimetic activity possessed by beta blockers during the treatment of chronic stable angina pectoris. Despite their widespread use, the long-term clinical effects of beta blockers with and without ISA are poorly documented. Thus, I have investigated the influence of beta blockers with and without this property on left ventricular performance, plasma lipoproteins, symptomatic and asymptomatic myocardial ischaemia, respiratory function and adverse effects. In addition, the experiments involved presented an opportunity to evaluate the role of radionuclide ventriculography in the detection of coronary artery disease, and an assessment of cold pressor stress and isometric hand-grip exercise used in conjunction with this technique.

This thesis consists of eight sections of which Section 1 is the introduction. Sections 2-7 comprise the investigations conducted by the author and Section 8 contains the final commentary and references. Where necessary each section has been divided into subsections covering particular topics or experiments. Each table or

figure is described by a section number and a number corresponding to it's appearance in that section.

In the first section I have developed the concept of beta-adrenoceptor blockade and intrinsic sympathomimetic activity. In this introduction I have attempted to describe the current understanding of ISA and the known clinical effects and adverse reactions of beta blockers with this property in as brief a review as is commensurate with an understanding of the main topics of this thesis. This section lays the foundation for the following experiments and attempts to pinpoint important gaps in our knowledge of the clinical effects of these agents.

Section 2 describes briefly how patients with chronic stable angina were recruited for the experiments to follow and includes an assessment of patient compliance with the beta blockers used in each experiment and their adverse reactions.

Sections 3 and 4 contain the results of investigations using radionuclide ventriculography to determine left ventricular function. Section 3 investigates the role of ISA in the long-term treatment of chronic stable angina with beta blockers and Section 4 evaluates the reproducibility of radionuclide ventriculography in our laboratory and its use in the detection of coronary artery disease. In addition, the cardiovascular effects and application of cold pressor stress and isometric handgrip exercise are explored. All of the measurements of heart

rate and blood pressure in this thesis necessitated the use of a semi-automatic recorder, and the Hitachi HME-20 pulse and blood pressure monitor was chosen for this purpose and it's evaluation is contained in Section 4.

Section 5 contains the results from a long-term investigation into the effects of pure beta blockers and one with ISA on plasma lipoproteins and contains an extensive review of the current literature.

The study contained in Section 6 was designed to evaluate the effect of beta blockers with and without ISA on the frequency of symptomatic and asymptomatic myocardial ischaemia in chronic stable angina pectoris and their effect on heart rate and rhythm. This was carried out using ambulatory ECG recorders designed for the purpose. One of the long established concerns when using beta blockers is their effect on respiratory function. There is considerable evidence of increased airway narrowing following their administration. In Section 7, this is investigated with particular reference to the possible influence of ISA which may aleviate this effect.

In the final section (Section 8), I have attempted to construct a concise resume of my findings and place them in perspective to previous knowledge.

1.2. INTRODUCTION.

Beta-adrenoceptor blockade has become one of the mainstays in the therapy of ischaemic heart disease and hypertension in the last 15 years, and established use has clarified the efficacy and adverse effects of beta blockers. Despite this a number of misunderstandings regarding their properties have developed. Beta-adrenoceptor blockers or beta blockers can be classified according to their lipid solubility, cardioselectivity, possession of membrane stabilising activity (MSA) or intrinsic sympathomimetic activity (ISA) sometimes referred to as partial agonist activity. This thesis concerns this latter property and its possible clinical effects.

Several beta-adrenoceptors currently available exhibit ISA. These include pindolol, oxprenolol, acebutalol and alprenolol. As pindolol exerts the most potent "ISA effect", most of the current literature concerning ISA refers to this drug. In this introduction I have reviewed the current knowledge of beta blockade and ISA with special reference to pindolol.

The first beta blocker to be investigated in man - dichloroisoprenoline - was found to produce cardiac stimulation (1) causing a marked tachycardia (2). This effect was initially attributed, to stimulation of beta-adrenoceptors and was termed ISA (3). Although this

early beta blocker was unsuitable for clinical use, beta blockers with less potent ISA were later introduced which did produce effective beta blockade, such as pindolol and oxprenolol (4).

The importance of ISA is controversial and has resulted in considerable debate in recent years (5,6). There is no contention regarding the pharmacological definition or physiological potential of this property - but it is still not universally accepted as being of clinical value. However, the theoretical possibilities are now supported by evidence suggesting that ISA may have important therapeutic implications.

Although it is possible that ISA could diminish the clinical efficacy of beta blockade (7), pindolol appears to be as effective as beta blockers without ISA in the treatment of angina (4,8,9), hypertension (4,10) and arrhythmias (11-13) and may be of particular use in patients with compromised myocardial function (8,14).

1.3. PURE BETA ADRENOCEPTOR BLOCKADE.

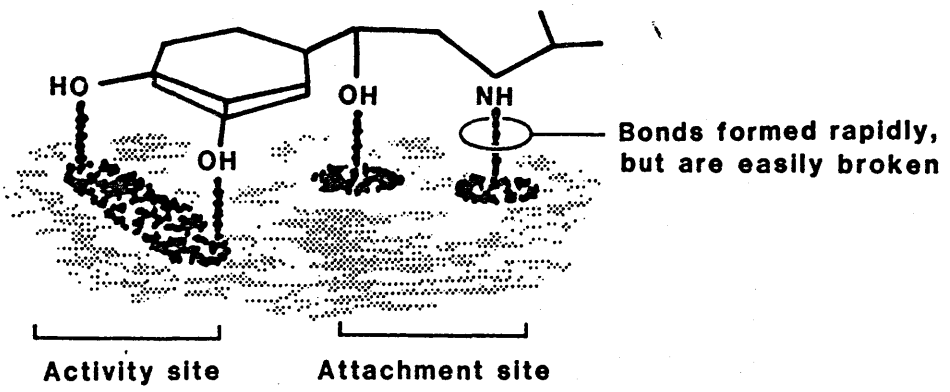
The sympathetic nervous system and circulating catecholamines exert their effects through receptors on the effector cell surface. These receptors can be divided into alpha-adrenoceptors and beta-adrenoceptors. Stimulation of alpha-adrenoceptors in the cardiovascular system leads to vasoconstriction, whereas stimulation of the beta receptors results in an increase in heart rate, atrio-ventricular conduction, myocardial contractility and peripheral vascular dilatation. Beta-adrenoceptor blockers were developed with the intention of attenuating the direct effects of sympathetic stimulation on the heart, particularly in the patient with ischaemic heart disease.

What is beta-adrenoceptor blockade? The beta-adrenoceptor is a localised region of the cell membrane which is sensitive to the effects of catecholamines. This region has the ability to combine reversibly with extracellular catecholamines. Such a reaction triggers a complex series of intracellular events resulting in the characteristic response of the parent cell. The receptor region is accepted as being part of a macro-molecular complex which is able to interact specifically with catecholamines, or their analogues, to effect a response.

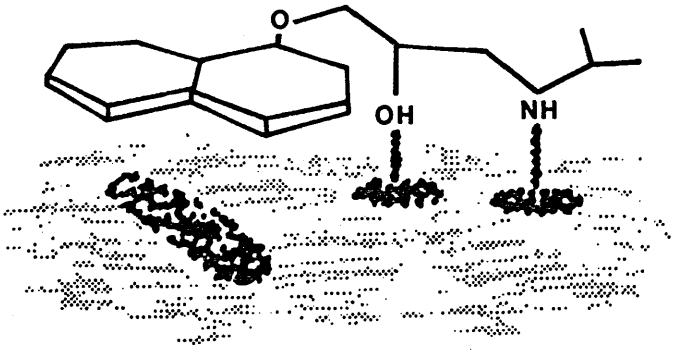
The molecular structure of Isoprenaline allows for its attachment at all major sites of a beta-adrenoceptor effecting maximum stimulation of the parent cell. Three components of the Isoprenaline molecule (Figure 1.1a) are important for its combination with the receptor (15). Modification of one of these sites of attachment results in a structure which is not optimal for occupation of the receptor, and thus activation of the receptor is slow and inefficient - in addition, the access of endogenous catecholamines is prevented, and therefore the beta-adrenoceptor has been blocked (competitive antagonism). Such an effect is schematically represented in Figure 1.1b which shows the combination of propranolol with the beta-adrenoceptor. Thus, beta blockers can be defined as chemical substances which specifically and competitively block the effects of catecholamines, and are structural modifications of the beta-adrenoceptor stimulant, isoprenaline. A pure beta blocker, like Propranolol, posesses an isoprenaline like side chain with an alternative aromatic nucleus (Figure 1.1b), and will compete with the endogenous agonist for the receptor site.

Beta-adrenoceptors occur in blood vessels, the heart, brain, kidneys, parts of the eye, lungs, uterus and insulin secreting cells of the pancreas and can be divided into $Beta_1$ or $Beta_2$ receptors according to the proposal by Lands in 1967 (16). The distribution of beta adrenoceptors is represented in Table 1.1. Although the heart contains predominantly $Beta_1$ receptors, it also contains some $Beta_2$ adrenoceptors. Therefore selectivity is not absolute.

ISOPRENALINE



PROPRANOLOL



PINDOLOL

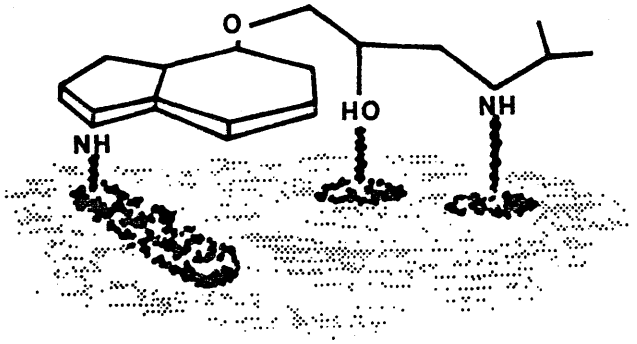


FIGURE 1.1

Schematic representation of the major points of attachment for a pure agonist (a. Isoprenaline), a pure antagnoist (b. Propranolol) and a partial agonist (c. Pindolol), to a beta-adrenoceptor site on a cell membrane. Such a combination of receptor and agonist/antagonist is said to take place in 'stereo-specific fashion'.

TABLE 1.1 CLASSIFICATION OF TISSUE BETA ADRENOCEPTOR

TISSUE	PREDOMINANT
Heart	B_1
Lung	B_2
Peripheral Blood Vessel	B_2
Central Nervous System	B_1B_2
Uterus	B_2
Metabolic Receptors	B_2

Some beta blockers have been developed which have a relative affinity for $Beta_1$ receptors more than $Beta_2$ receptors and these beta blockers have been termed CARDIOSELECTIVE. However, there is considerable evidence that the cardioselectivity of drugs such as practolol, atenolol or metoprolol is only a relative phenomena and may be lost or diminished with increasing dosage.(17)

1.4. BETA ADRENOCEPTOR BLOCKERS WITH INTRINSIC SYMPATHOMIMETIC ACTIVITY.

Beta blockers can be classified according to three main pharmacological properties, one of these; cardio-selectivity, has already been discussed. The other properties are membrane stabilising action and intrinsic sympathomimetic activity. ISA beta blockers have a molecular structure similar to Isoprenaline, but not entirely optimal for full stimulation (Figure 1.1c). Nevertheless, partial stimulation does occur simultaneously with beta blockade, as endogenous catecholamines are denied access to the receptor sites. ISA beta blockers therefore act as competitive antagonists in the same manner as other beta blockers (18), but are capable of sub-optimal stimulation of the receptors (Figure 1.2). (15) The potential for partial stimulation can be altered by restructuring the molecular configuration of the antagonist. Dichloroisoprenaline, the first beta blocker developed, had potent ISA and tended to increase resting heart rate and was not suitable for clinical use. (2) Of the beta blockers with ISA currently available pindolol has the most potent ISA, but does not have the pharmacological potency of adrenalin or isoprenaline. (7,15) Pindolol has up to 50% of the agonist activity of isoprenaline in laboratory animals, but this is probably an exagerated response when compared to humans. The relative ISA of the commercially available beta blockers is shown in Table 1.2. It may be expected that any benefits which the property

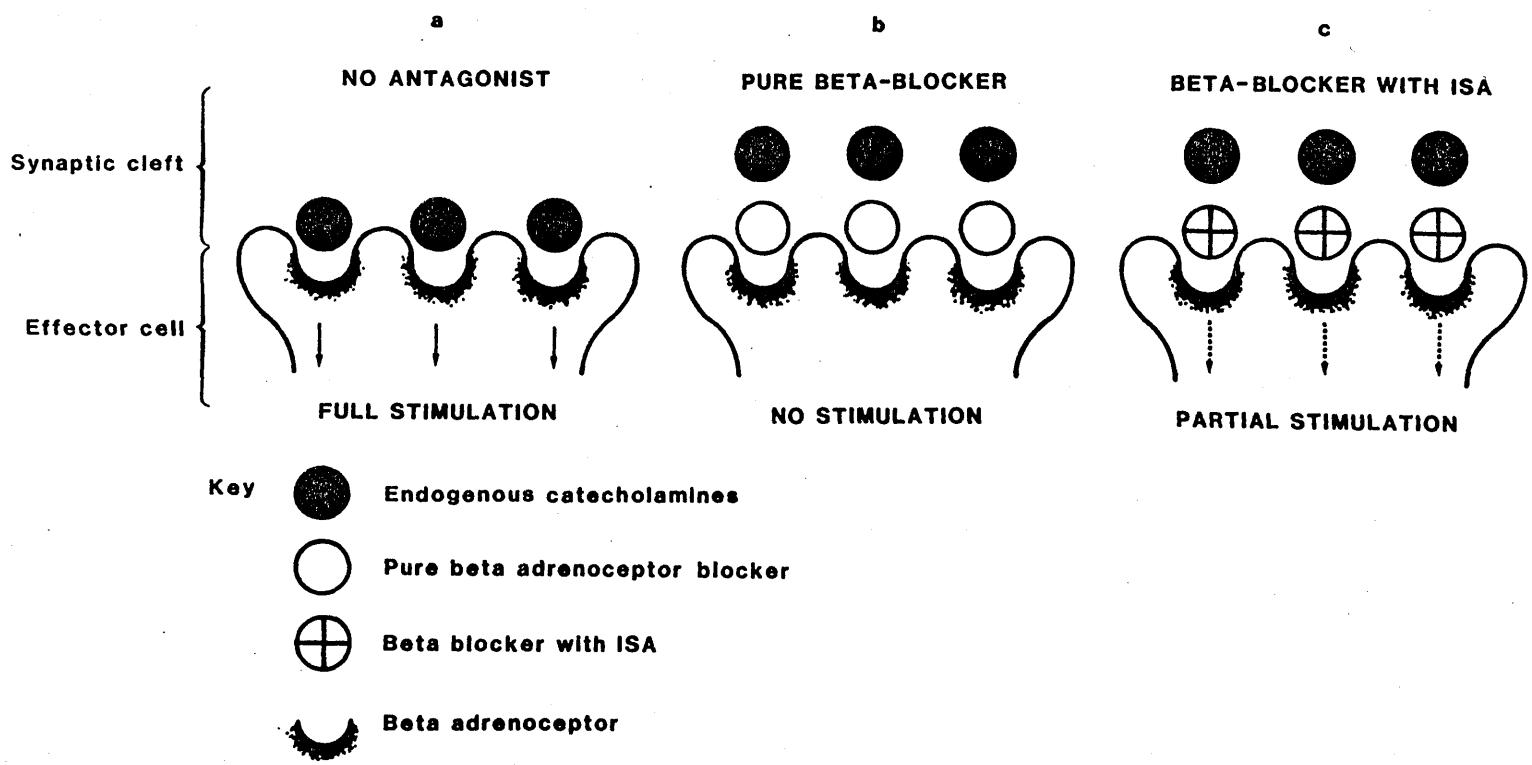


FIGURE 1.2

Schematic representation of beta-adrenoceptor interaction with a. endogenous catecholamines; b. a pure beta blocker and c. a beta blocker with ISA.

TABLE 1.2 RELATIVE DEGREE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY OF SEVERAL FREQUENTLY USED BETA ADRENOCEPTOR BLOCKING DRUGS.

DRUG	RELATIVE DEGREE OF ISA
Pindolol	++
Oxprenolol	+
Alprenolol	+
Acebutalol	+
Practolol	+
Propranolol	0
Timolol	0
Metoprolol	0
Atenolol	0
Nadolol	0
Sotalol	0
Labetalol	0

may acrue should be demonstrable with pindolol rather than those with weaker ISA.

The ISA of pindolol has been appreciated for many years and was investigated by Hill and Turner in 1969 who reported that in a dosage producing the same reduction in exercise induced tachycardia pindolol reduced heart rate to a lesser extent than did propranolol. (19) The degree of ISA in the individual beta blocker can be demonstrated in animals depleted of endogenous catecholamines by syrosingopine and adrenalectomy to abolish sympathetic activity. (20) In this situation, administration of propranolol will not affect heart rate as no endogenous catecholamines are present which can be "blocked". Pindolol, however, increases resting heart rate because of its partial agonist effect. (21) Such demonstration of ISA in man is not possible, although in the intact human, Hill (19) and Svendson (22) have demonstrated a smaller reduction in resting heart rate compared with other beta blockers.

It has been argued that ISA reduces or dilutes the beta blocking capability of a drug, but this is not correct. As these drugs also act as beta blockers they can be expected to protect the heart from the deleterious effects of excessive adrenergic stimulation during exercise or emotional stress by decreasing myocardial oxygen requirements at any given level of activity. (4) They will also block catecholamine induced increments in heart rate and the velocity and extent of myocardial

contraction. However, because of ISA the drugs' effect is most evident at times of low sympathetic drive eg. at rest or during sleep, whereas during periods of high sympathetic drive eg. during exercise or emotional stress, the effect of ISA is more difficult to discern. The inotropic action of these drugs is so weak that the nett result in man is to prevent the extreme effects of beta blockade, rather than to produce positive inotropic effects.

Theoretically, beta blockers with ISA would be expected to cause a smaller negative chronotropic and inotropic effect and reduce the tendency of the beta blocker to induce peripheral vasoconstriction and bronchoconstriction. However, beta blockers with ISA have different quantitative influences in different organs - the effects being greater in vascular smooth muscle than in cardiac or bronchial muscle. This may be due to variations in the number of beta-adrenoceptors available for stimulation or distribution of beta-adrenoceptor subtypes in different tissues. In addition, because of constantly varying sympathetic activity it is extremely difficult to measure the effects of ISA in man. Thus, although the theoretical advantages or influences of ISA can be readily demonstrated in isolated tissues, or in the experimental animal, the clinical influence in man is a subject of debate. (5,6)

Possible Advantages of ISA Beta Blockers are:

1. Stimulation of the sinus node and atrio-ventricular conduction during periods of low sympathetic activity, thereby reducing the liklihood of bradycardia and heart block during beta blockade, especially in the elderly.

2. Direct stimulation of contractile elements of the myocardium, and reduction in cardiac afterload because of vasodilation - resulting in a lesser reduction in myocardial contractility induced by beta blockade especially in the compromised heart.

3. Stimulation of $Beta_2$ bronchodilator receptors - offsetting some of the bronchoconstrictor effects of beta blockade.

4. Less tendency to develop peripheral vascular constriction through unopposed $Alpha_1$ stimulation by partial stimulation of the $Beta_2$ vasodilating adrenoceptors.

The overall effect is a probable increase in exercise capacity during beta blockade with a drug possessing ISA.

Membrane Stabilising Activity.

Although MSA is not a property covered in detail in this Thesis it is appropriate to distinguish this property from ISA. MSA will decrease the rate of rise and magnitude of the cardiac intracellular action potential and will prolong the refractory period of the myocardial cells. (23) Although both propranolol and pindolol (with ISA) exert weak MSA (24,25), this property is only apparent at doses far in excess of those necessary for beta blockade (26,27) and is probably of no therapeutic relevance.

1.5. PINDOLOL: PHARMACODYNAMICS AND PHARMACOKINETICS.

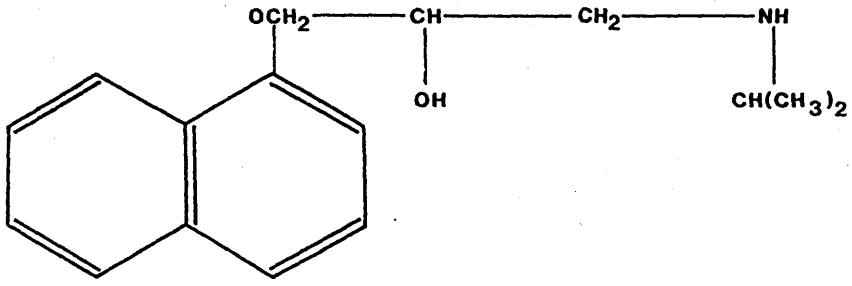
Structure.

Pindolol's molecular structure differs from propranolol by the substitution of an indole for a benzene ring in the aromatic nucleus of the molecule (Figure 1.3), which is capable of reacting with the beta receptor, unlike the benzene ring which is biologically inert.

Pharmacokinetics.

Pindolol is rapidly and almost completely absorbed (95%) after oral ingestion and absorption is not influenced by the presence of food. (28,29) The drug is detectable in plasma within 30 minutes following ingestion, and peak levels are recorded between 1-2 hours post ingestion. (28,29) First pass metabolism by the liver is low with an oral bio-availability of approximately 90%. (28,29) An increase in oral daily dosage of pindolol results in a proportional increase in concentration of the drug within the body (linear pharmacokinetics). (28,29) Although oral bioavailability is good, plasma drug concentrations may vary by as much as four fold after a single oral dose. (28-30) However, after multiple doses this falls to two fold. (29) The cause for this is not known although it has been suggested that it may be due to interindividual differences in the volume of distribution of the drug. Pindolol is only 40% bound to plasma proteins which is

PROPANOLOL



PINDOLOL

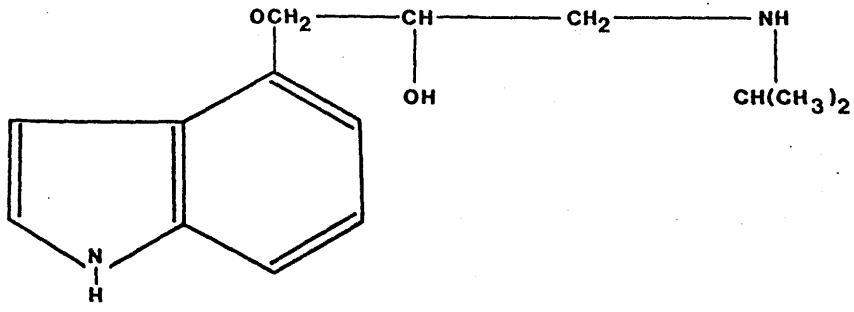


FIGURE 1.3

Molecular structure of a beta blocker with ISA (Pindolol) and without ISA (Propranolol). Note difference in aromatic nucleus of the molecules.

NB. Structural name of Pindolol = 1-(1H-indol-4-yloxy)-3-((1-methylethyl)amino)-2-propanol.

less than with other beta blockers (28) and this may account for a relatively high level of beta blockade at comparatively low total plasma concentrations. It's volume of distribution in healthy subjects is about 2 litres per kilogram of body weight. (28) An identical drug concentration does not guarantee an identical beta blocker response in different individuals. However, if the interindividual plasma drug concentration is the same, differences in degree of beta blockade will vary by only 2-3 fold. Thus, like all beta blockers, plasma levels offer little as regards a therapeutic guide although they can be useful when assessing patient compliance. (7) Plasma concentrations required to produce therapeutic beta blockade vary substantially between individuals (30) and therefore manipulation of the dose may be necessary for optimal beta blockade, although this need not present a greater problem with pindolol because of it's relatively low first pass hepatic metabolism when compared to other beta blockers (28,31), and consequent good bioavailability.

The drug is relatively lipophilic and as such, is able to cross the blood brain barrier and enter the central nervous system. It also crosses the placenta and is excreted in human milk.

Following oral administration the plasma concentration of pindolol declines monoexponentially in the normal subject, with a plasma half-life of 3-4 hours (29), although this can increase to about 7 hours in the elderly patient. (29) Despite a relatively short half-life

(similar to other beta blockers), the beta blocking effect persists for up to 9 hours, which can be demonstrated by a prevention of exercise induced tachycardia until this time. Approximately 60% of an oral dose is ultimately metabolised by the liver, with the remainder being eliminated unchanged in the urine. (28,29)

Dosage.

Previous work has confirmed adequate beta blockade with 15 mgs. pindolol per day - no haemodynamic benefit being observed with higher doses. (32) This implies that Pindolol is more potent per mg. than propranolol (by as much as 6-8 times) and this can be confirmed by comparing the ability of both drugs to inhibit isoprenaline induced tachycardia. (7) This difference in potency cannot be explained by differences in the side chain of the molecular structure - this being identical to propranolol (Figure 1.3), and is more likely to be the consequence of a lower percentage of the drug bound to plasma proteins (33) and superior bioavailability.

Unlike the relative cardioselectvity of alternative beta blockers such as atenolol or metoprolol, which is attenuated at high therapeutic doses (7,34,35), the ISA is not lost when higher doses are administered. (36) However, this activity occurs with low doses and has a flat dose response curve confirmed by studying the effect of the drug on resting heart rate throughout a wide range of therapeutic doses. (36,37) In common with other beta

blockers drug tolerance does not appear to develop with longterm use, this applying to both the beta blocking and ISA effect. (10,38)

Thus the pharmacodynamics and pharmacokinetics of pindolol are favourable in comparison to other beta blockers although it would appear that pindolol requires to be administered in a twice or thrice daily dose which may detract from it's patient acceptability in comparison to other beta blockers such as atenolol which can be given in a single daily dose.

1.6. CONFIRMING THE PRESENCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY.

Animal Studies.

Qualitative and quantitative demonstration of ISA can be performed in the animal model in whom the effect of reflex sympathetic nervous stimulation and the effects of endogenous catecholamines are abolished. This can be achieved by adrenalectomy, vagotomy and pretreatment with reserpine or syringoserpine. (20,39) In this situation there is an increase in heart rate when a beta blocker with ISA is administered, but no change when a pure beta blocker is given (40) (Figure 1.4). As the increase in heart rate observed with the ISA blocker can be antagonised by propranolol, such an effect must be mediated through beta receptor stimulation. A similar change is observed in the contractile force of isolated strips of heart muscle (4), demonstrating a positive inotropic effect. Although these changes are observed in this artificial setting, it may not be appropriate to extrapolate to the intact organism.

Human Studies.

The demonstration of ISA in man is necessarily indirect. The effect of pindolol on heart rate in man has been shown to be dependant on the initial level of sympathetic activity. (41) For example, in a study examining the effect of pindolol on heart rate,

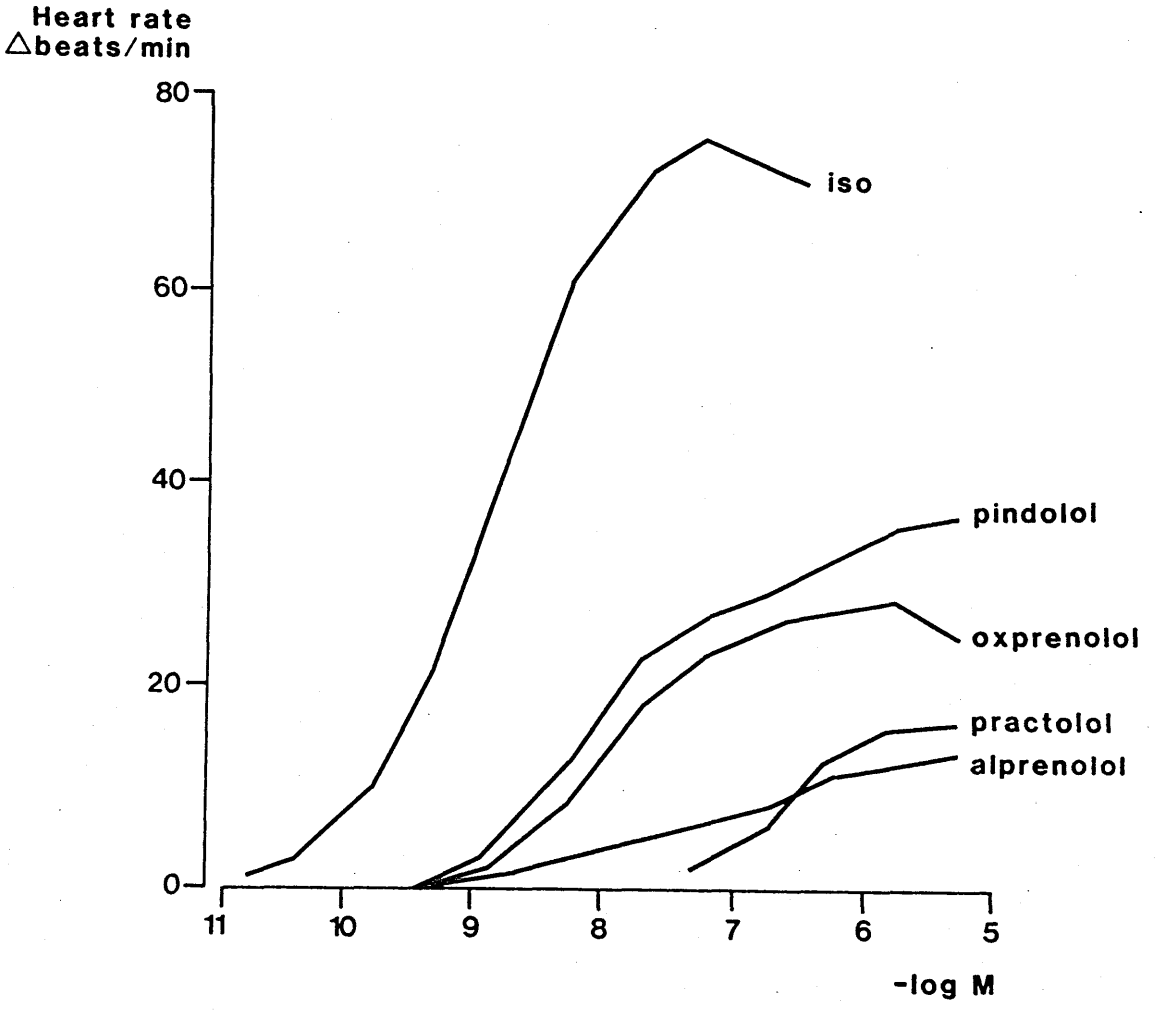


FIGURE 1.4

Positive chronotropic effect of 4 beta blocking drugs with partial agonist activity in the isolated right atrium of the cat.
(Reprinted from Kaumann and Blinks (40).)

iso = isoprenaline.

in 7,000 hypertensives, (42) the subjects who exhibited initial resting heart rates of over 90 beats per minute (bpm) responded with a significant reduction in heart rate when given pindolol. However, those with heart rates in the region of 70-90 bpm had little change in heart rate and those with rates less than 70 bpm responded with an increase in heart rate. Overall, drugs possessing ISA cause a smaller reduction in resting heart rate than beta blockers without ISA (8,10,43), however, tachycardia induced by exercise (8,10), or Isoprenaline, is attenuated to a similar extent by all beta blockers. Thus, the greatest influence of ISA occurs when sympathetic tone is low, and will therefore be appreciated only in resting subjects. This effectively alters the circadian rhythm of heart rate, such that profound reduction in heart rate during sleep is countered by ISA while peaks during exercise or emotional stress (high sympathetic tone) are attenuated (44) (Figure 1.5). The effect of ISA will predominate over the beta blocking effect at times of low sympathetic activity and visa versa when sympathetic activity is high.

Thus, although beta blockers with ISA can be shown indirectly to influence changes in heart rate in a unique way when compared to other beta blockers, the clinical relevance is debatable and will now be discussed.

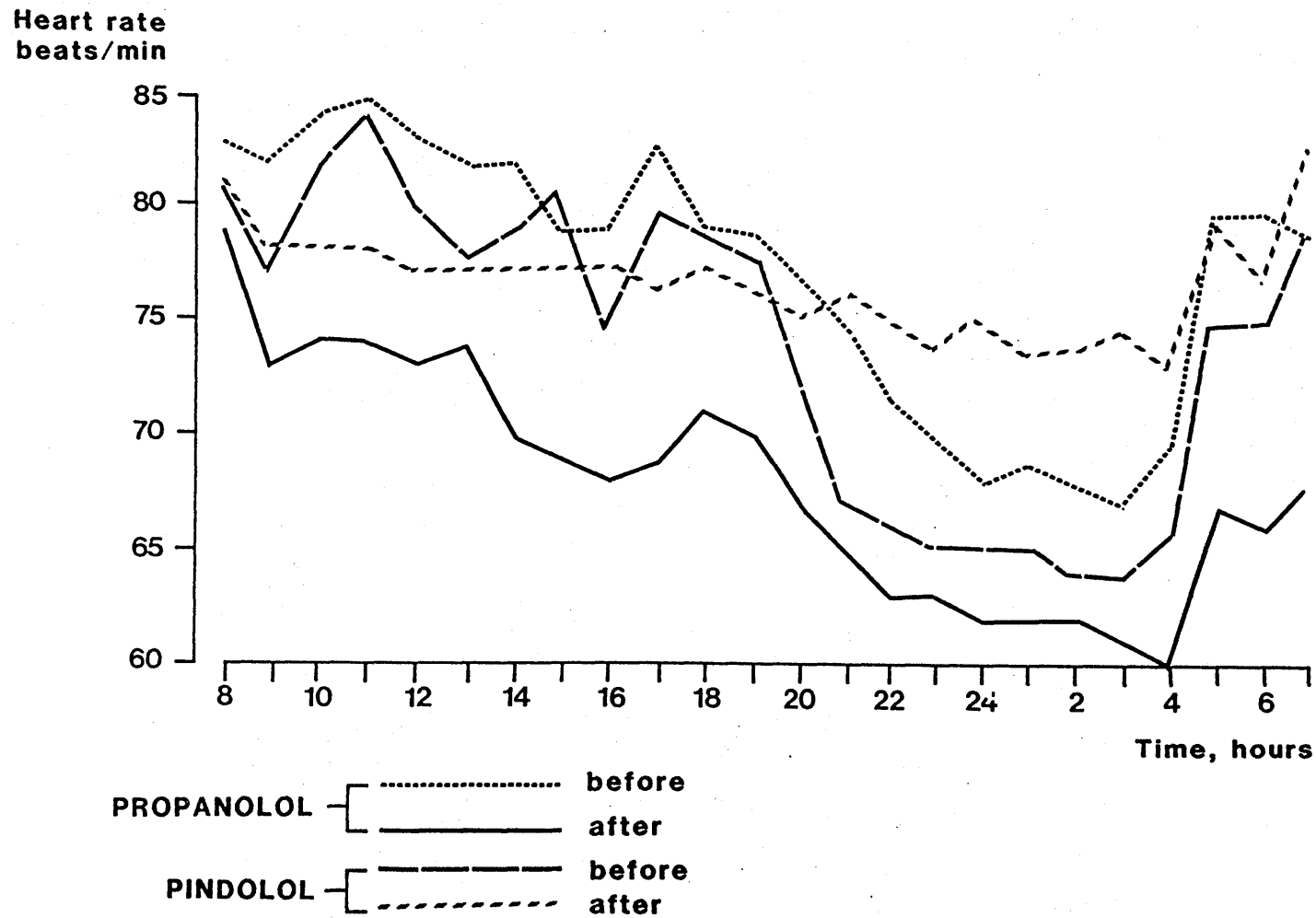


FIGURE 1.5

Influence of propranolol and pindolol on 24 hour ambulatory heart rate in 7 patients with coronary heart disease and 3 with hypertension. (Reprinted from Fitscha et al (44).)

1.7. HAEMODYNAMIC EFFECTS OF BETA BLOCKERS - WITH AND WITHOUT ISA.

The effect of beta blockers on cardiovascular haemodynamics has been investigated in a number of situations.

Beta blockers are known to diminish heart rate and to reduce the positive inotropic effects of sympathetic activity, this leads to a reduction in left ventricular contractility and consequently a fall in cardiac output. These effects are aggravated by an increase in left ventricular afterload which is caused by blockade of the peripheral vasodilator $beta_2$ receptors with resultant vasoconstriction and indirect reflex vasoconstriction secondary to the reduction in left ventricular contractility.

Theoretically it would be expected that a beta blocker possessing significant ISA would offset these effects by providing direct positive inotropic stimulation, causing a smaller reduction in heart rate and by stimulating peripheral vasodilator $Beta_2$ receptors thereby reducing the rise in left ventricular afterload caused by pure beta blockade.

In a comparison of pindolol, atenolol and propranolol on haemodynamics of dogs, Clark (45), administered each drug followed by a dose of isoprenaline,

to assess the degree of beta blockade. The beta blockers lacking ISA produced significant reductions in cardiac output whereas pindolol produced small increases. Changes in total peripheral resistance occuring in response to each drug were inversely proportional to the changes in cardiac output, since blood pressure remained constant. These results have been confirmed in healthy human volunteers and in patients with ischaemic heart disease.(22)

Using intravenous administration in patients with ischaemic heart disease, Svendson (46) found that the reduction in cardiac output was attenuated by beta blockers with ISA. For example, cardiac output was reduced by 26-28% by propanolol and atenolol, 12-17% by practolol (moderate ISA) and was not altered by pindolol. In another short-term intravenous study the effects of four beta blockers were compared in subjects with severe coronary artery disease - all four drugs caused a reduction in cardiac output, but oxprenolol and practolol (with ISA) produced significantly less depression than propranolol or metoprolol. However, in a longer term study over 7 weeks comparing oxprenolol and propranolol in hypertensive subjects, Franciosa (47) could not demonstrate any significant difference in haemodynamic parameters between both drugs. It may be that if a drug with a greater potency of ISA were used in long-term studies a more attractive haemodynamic profile would be found when compared with beta blockers without ISA. In this respect, Man in't Veld et al (48,49), investigated the effects of chronic oral therapy with pindolol in patients severely

disabled by orthostatic hypotension and confirmed that heart rate, stroke volume, cardiac output and mean arterial pressure were increased by pindolol.

Systemic vascular resistance has been shown to fall to a greater extent after treatment with oxprenolol or pindolol (with ISA) when compared to propranolol in numerous studies in patients with CAD (50,51) and hypertension. (52) In general, beta blockers without ISA cause an increase in systemic vascular resistance by direct blockade of vasodilator $Beta_2$ receptors in arteriolar vessels, together with an indirect reflex vasoconstriction mediated through $Alpha_1$ adrenoceptors resulting from a reduction in left ventricular contractility. Systemic vascular resistance falls when a beta blocker with ISA is given because vasodilation occurs due to stimulation of the $Beta_2$ vasodilator receptors.

Therefore, beta blockers with ISA may have value in minimising the haemodynamic disturbance associated with blockade of cardiovascular sympathetic drive.

Left Ventricular Function and Beta Blockade.

In addition to the probable haemodynamic benefits of a beta blocker with ISA, myocardial contractility has also been assessed. It has been suggested that left ventricular contractility in animals and humans may be impaired to a lesser extent with beta blockers possessing ISA. (51,53,54) However, it would be misleading to suggest

that beta blockers with ISA cannot compromise left ventricular function, as it has been shown that cardiac contractility can fall with pindolol.

Different methods of investigating left ventricular performance have been used in the assessment of pindolol on these parameters, including thermodilution (46,55), dye dilution (56), measurements of systolic time intervals (57), echocardiographic techniques (58) and more recently measurement of left ventricular ejection fraction and other parameters of left ventricular contractility by radionuclide methods. (59,60) These latter methods tend to be more reliable and reproducible than the previous techniques. In general, but not consistently, these studies suggest that the depressant effect of pindolol on left ventricular performance is less than that of propranolol. However, one factor shared by most studies on myocardial performance is that only relatively short treatment periods were used. Thus, we still do not have information regarding the long-term effects of pure beta blockers or those with ISA on left ventricular function. As most patients with ischaemic heart disease or hypertension are treated with beta blockers on a long-term basis, it is important to determine the effect on left ventricular performance over an extended period of treatment. Perhaps this may reflect some further advantage of ISA.

The choice of patient in whom the drug is studied is also important as this can alter interpretation of the results. For example, in patients with normal or near

normal left ventricular function, some studies have shown that oral administration of propranolol does not significantly influence resting global or segmental left ventricular function using radionuclide techniques. (61-63) In a separate study of patients with moderate to marked left ventrcular dysfuntion, a significant reduction in left ventricular ejection fraction was observed in a group treated with a pure beta blocker. (64) This would imply that if ISA has any beneficial effect on left ventricular performance, it would be most evident in patients with impaired left ventricular function before commencing therapy.

Pure beta blockers cause a reduction in the heart's pump capability secondary to a reduction in the myocardial force of contraction and an excessively slow heart rate. In the healthy heart, stroke volume is more dependant on sympathetic drive than contractility. In the failing heart, stroke volume is more dependent on contractility and pump function may only be adequate in the presence of compensating sympathetic excitation. Pure beta blockers will suppress this excitation and may precipitate myocardial insufficiency. To compound the situation, in addition to contractility, the increase in heart rate required to compensate for the reduction in stroke volume is also inhibited, and pure beta blockers will block peripheral vasodilator Beta $_2$ receptors causing a tendency to vasoconstriction and an increase in systemic vascular resistance. It is probable that in the failing heart, a beta blocker with ISA would be less likely to cause these effects.

1.8. CLINICAL APPLICATIONS OF BETA BLOCKERS WITH ISA.

Ischaemic Heart Disease.

Beta blockers are one of the major drug groups used in the medical management of angina pectoris. The rationale behind their use lies in their ability to reduce myocardial oxygen demand. The major determinants of myocardial oxygen demand are heart rate, systolic blood pressure, myocardial contractility, the duration of left ventricular emptying or ejection, and ventricular size. In the normal individual oxygen demand rises during exercise due to an increase in heart rate, blood pressure and contractility. Subsequently the oxygen supply is able to increase as there is an increase in perfusion pressure in the coronary arteries. However, if there is compromised flow in the large coronary arteries due to atheromatous plaques or coronary artery spasm then perfusion pressure falls and oxygen supply declines, resulting in myocardial ischaemia. Since a beta blocker can attenuate the heart rate, blood pressure and contractility response to exercise or emotional stress then they are capable of maintaining myocardial oxygen demand within the limits allowed by the diseased supply vessels.

Since beta blockers with ISA will only reduce heart rate at times of increased oxygen demand (42,43) it could be argued that subjects with rest or nocturnal angina would not be suited to these drugs and would

benefit more from a pure beta blocker. One recent report from Quyyumi et al (65) compared the effect of pindolol and atenolol in fifteen subjects with effort and nocturnal angina on symptoms and ambulatory S-T segment responses. This was a short-term study, but confirmed that heart rate, frequency of angina and the frequency and magnitude of episodes of S-T depression were reduced significantly more by atenolol than by pindolol. The suggestion is that a reduction in resting heart rate is especially important when treating rest angina and ISA may be a deleterious property in patients with severe angina. Thus, in certain patients with angina at rest the ISA effect may occasionally inhibit the achievement of bradycardia sufficiently slow to lessen the risk of developing ischaemia. However, it is unusual to use a beta blocker alone for rest angina, so it is difficult to place this suggestion into clinical perspective.

In contrast to the above study, several authors have failed to show any significant antianginal differences between various beta blockers with different pharmacological properties. When administered on a short or long-term basis to patients with stable, exertional angina pectoris (9,66-69) (distinct from severe or rest angina pectoris) most beta blockers are equally effective in reducing the frequency of anginal episodes and glyceryl trinitrate consumption.

For subjects with exercise induced angina, this would appear to be a consequence of the ability of beta

blockers with ISA to be equally effective in blocking exercise induced tachycardia as discussed earlier. (43)

One would expect that exercise tolerance would be improved equally by pure beta blockade and beta blockers with ISA, and this has been confirmed in one study of 52 patients with angina pectoris comparing pindolol and propranolol. (8) Single dose studies using small doses of pindolol (2-5 mg) in patients with angina have demonstrated increases of 35-45% in work capacity until onset of symptoms as measured by bicycle ergometry. (70,71) To compound this issue however, it must be appreciated that pure beta blockade can diminish exercise capacity (72) in normal individuals and although overall exercise tolerance is improved by pure beta blockers in angina pectoris this is attenuated by other influences of the drug. In hypertensive patients, Franciosa (73) has found less depression of exercise tolerance with beta blockers with ISA. Thus, exercise tolerance may be enhanced by a beta blocker with ISA - although this has not yet been clearly demonstrated in patients with CAD.

In summary the available evidence suggests that patients with effort angina will benefit equally from treatment with beta blockers with or without ISA in terms of decreasing symptoms. Because of other beneficial effects already discussed in this section, however, a beta blocker with ISA may be the drug of choice for mild to moderate angina pectoris. However, in patients with angina at rest, pure beta blockers, by lowering resting

heart rate appear to have a distinct advantage over beta blockers with ISA when used as monotherapy. (65) In terms of antianginal efficacy only, no advantage has been demonstrated for beta blockers with ISA.

Hypertension.

Beta blockers with ISA are effective antihypertensives. The efficacy of pindolol in hypertension has been established in numerous placebo controlled trials (10), and the blood pressure lowering effect is quantitatively similar to propranolol, thiazides, and methyldopa. (10) Systolic and diastolic blood pressure is reduced by approximately 15% with postural hypotension a very rare complication. (10) The maximal hypotensive effect occurs in the first week of treatment with a dose of 15-20 mg/day. (10) However, one of the drawbacks to treatment has been a greater frequency of central nervous system side effects compared to propranolol. This aspect shall be discussed in Section 1.10.

The mechanism by which beta blockers lower blood pressure is a matter for conjecture. One possibility is that cardiac output falls (74), however, as pindolol causes a smaller reduction in cardiac output that pure beta blockers, the antihypertensive effect of pindolol may result from a reduction in peripheral vascular resistence (46), as a result of stimulation of peripheral vasodilating $beta_2$ receptors. (75)

Thus, reports indicate that beta blockers with ISA are effective antihypertensives. However, there are reports of a paradoxical rise in blood pressure in response to large doses of beta blockers. The first reports attributed this phenomenon to a beta blocker with ISA leading to a suggestion that all beta blockers with ISA had the unique action of causing a rise in blood pressure. However, this anomalous reaction has now been described with pure beta blockers also. (76)

Use of Beta Blockers with ISA as Antiarrhythmic Drugs.

Beta blockers with ISA have antiarrhythmic properties similar to pure beta blockers. This results from the ability of a beta blocker to antagonise the effects of catecholamines on cardiac automaticity. (74) Intrinsic sympathomimetic activity does not seem to negate this effect as pindolol has been shown to be as effective as propranolol in the treatment of supraventricular tachyarrhythmias (11,12) and useful for the treatment of ventricular tachyarrhythmias.(13)

1.9. EFFECT OF BETA BLOCKERS ON PLASMA LIPOPROTEINS.

Although changes in the lipoprotein profile induced by a beta blocker could be designated an adverse effect, I shall discuss this aspect separately because some of the effects induced by beta blockers with ISA may be advantageous, and a major part of this thesis deals exclusively with these changes.

Inevitably treatment of ischaemic heart disease or hypertension with beta blockers is a long-term prospect, and it has been appreciated for some time that such treatment may result in an adverse effect on the lipoprotein profile - thus reducing the benefit of beta blockade.

The literature concerning the effect of beta blockers and lipids is conflicting and no consistent differences have been found which suggest that ISA or cardioselectivity may profer an advantage. As with studies concerning left ventricular function and haemodynamics, there are very few investigations examining the effect of chronic therapy. Since these drugs are usually prescribed on a long-term basis clinical trials over a longer period of time are required.

In an early study, Tanaka (77) administered Propranolol to ten patients over an eight week period and found an increase in very low density lipoprotein (VLDL) triglyceride and reduction in low density lipopotein (LDL)

- triglyceride and high density lipoprotein (HDL) cholesterol. Of four other, more recent medium-term studies (78-81) studying the effect of propranolol on lipids, two (79,81) showed a significant elevation of serum triglyceride and none showed any change in cholesterol. In two of these studies (81,82), HDL was significantly reduced. Thus, medium term studies are conflicting and there are no long-term studies in the literature involving propranolol to provide further information. Only one long-term study of a pure beta blocker exists, in which Lehtonen, (82) using sotalol, found increased levels of total triglyceride, cholesterol, VLDL and LDL with a reduction in HDL cholesterol.

Of several studies (83-85) involving cardio-selective beta blockers approximately half of the studies show an elevation of triglycerides. None show any change in cholesterol and the few investigators who have measured HDL and it's subfractions have shown either no change or a reduction. (83,85) Therefore cardioselectivity does not seem to alter the response of plasma lipids to beta blockade.

Studies involving beta blockers with ISA (86-88) again show conflicting results. Serum total cholesterol was found to rise in only one (87), and triglycerides do not seem to change significantly. HDL either maintains its pretreatment level or rises. This latter effect is in distinction to the fall which occurs with pure beta blockers. (80-82,85) Since an increase in LDL and a

reduction in HDL are associated with an increased risk of CAD (89,90) - beta blockers with ISA may offer an advantage over other beta blockers in terms of plasma lipoprotein metabolism in long-term therapy. However, no consistent effect can be seen on reviewing the literature (91), and further long-term studies are required to confirm the influence of ISA on plasma lipoproteins.

1.10. ADVERSE EFFECTS OF BETA BLOCKADE - INFLUENCE OF ISA.

Like all beta blockers, those with ISA are associated with a number of adverse or unwanted effects. These adverse effects are similar to other beta blockers and seem to be related to the beta blocking activity of the drugs. (92,93) The adverse effects are generally not dose related, will occur relatively early after administration and are invariably mild. The reported adverse effects experienced with pindolol are summarised in Table 1.3. (42,94,95) In terms of frequency, dizziness and dyspepsia are the most commonly reported adverse effects. It is noteworthy that dyspnoea or wheeze occur in a very small proportion. Whether compounds with ISA behave as pure beta blockers in terms of adverse effects, or confer some clinical benefit shall now be discussed.

Heart Rate and Cardiac Conduction.

Pure beta blockers can be associated with severe symptomatic bradycardia. For example, both propranolol and atenolol slow the sinus rate, prolong sino-atrial and atrio-ventricular nodal conduction time and prolong the effective refractory period of the atrio-ventricular node. (96) In a study using beta blockers in mild to moderate hypertensives, McNeil and Lewis (43) found that a heart rate of less that 55 beats per minute was present in 17% and 31% of subjects being treated with metoprolol and atenolol respectively. In contrast, only 0.03% of subjects

TABLE 1.3 REPORTED ADVERSE EFFECTS OF ORAL PINDOLOL THERAPY.

BODY SYSTEM	ADVERSE EFFECTS	FREQUENCY (% OF PATIENTS) Golightly LK (94) (1982) n = 1,379	Rosenthal et al (42) n = 7,062	Crowder and Cameron (95) n = 8,989
CARDIOVASCULAR SYSTEM	Palpitations	6(0.4)	-	50(0.6)
CENTRAL NERVOUS SYSTEM	Fatigue, Lassitude	66(4.8)	213(3.0)	426(4.7)
	Vivid Dreams	86(6.2))	246(3.5)	-
	Insomnia, Sleep Disturbance.	44(3.2))		155(1.7)
	Dizziness	43(3.1)	547(8.1)	810(9.0)
	Depression	21(1.5)	-	68(0.8)
	Headache	24(1.7)	348(4.9)	317(3.5)
	Nervousness, Irritability	11(0.8)	-	-
	Hallucinations	4(0.3)	-	-
	Lightheadedness	-	-	220(2.4)
GASTROINTESTINAL SYSTEM	Dyspepsia	28(2.0)	529(7.5)	678(7.5)
	Dry Mouth or Nose	19(1.4)	15(0.2)	45(0.5)
	Diarrhoea (loose Stools)	6(0.4)	-	67(0.7)
GENITOURINARY SYSTEM	Impotence) Decreased Libido)	11(0.8)	2(0.03)	-
MUSCULOSKELETAL SYSTEM	Muscle or Leg Cramps	37(2.7)	-	182(2.0)
	Cold Extremities	11(0.8)	-	71(0.8)
	Tremor	7(0.5)	68(1.0)	60(0.7)
PULMONARY	Dyspnoea/Wheezing	12(0.9)	55(0.8)	-

treated with a beta blocker with ISA (pindolol) developed this level of bradycardia. As with other beta blockers pindolol may increase the degree of atrio-ventricular block and can cause atrio-ventricular dissociation in patients with heart block, but this is to a lesser extent than with pure beta blockers. (97)

Despite this difference, it is not clear whether protection from severe bradycardia in the majority of patients offers any advantage and may detract from the benefit of beta blockade in a patient with severe or rest angina pectoris.

Myocardial Contractility.

Beta blockers are capable of precipitating congestive cardiac failure in susceptible individuals. Patients with a poor cardiac reserve may rely on a high level of sympathetic tone to maintain cardiac output - if this is removed by effective beta blockade then myocardial insufficiency may result. A beta blocker with ISA is less likely to remove sympathetic stimulation to the same extent and may protect against the development of congestive cardiac failure. However, pindolol does not provide absolute protection in this respect (98), and has been associated with heart failure with severe acute pulmonary oedema on initiation of therapy. (99) In addition, in two large studies of patients with hypertension treated with either propranolol (pure beta blocker) or oxprenolol with moderate ISA, the incidence of heart failure was shown to

be low and similar for both drugs. (100,101)

Thus, although a number of studies have demonstrated protection of myocardial contractility with beta blockers possessing ISA (46-49,51,53,54,), those examining the symptomatic occurrence of congestive cardiac failure have been unable to demonstrate a clear advantage of beta blockers with ISA over pure beta blockers.

Withdrawal Phenomena.

Although not strictly an adverse effect, withdrawal of a beta blocker can result in clinical deterioration, and it is possible that ISA may influence such phenomenon.

In the setting of angina pectoris, if a pure beta blocker is withdrawn abruptly there can be a resurgence of symptoms and occasionally precipitation of myocardial infarction, cardiac arrhythmias or sudden death. (102) This phenomenon usually occurs 1-21 days after discontinuing the drug (103,104) and the cause is unknown. Heart rate rises for several days after withdrawal (105), and it has been suggested that an overshoot of catecholamines may be responsible. Such phenomena may not be apparent on withdrawal from treatment of a beta blocker with ISA (103,104), but it is still the general recommendation that withdrawal is carried out gradually.

There are few clinical situations where withdrawal of a beta blocker need be abrupt, suggesting that any

possible benefit of beta blockers with ISA in this context may not be clinically useful. In the Coronary Care situation folowing myocardial infarction beta blockers occasionally have to be withdrawn because of hypotension or congestive cardiac failure. Abrupt withdrawal of a pure beta blocker at this time may increase the possibility of cardiac arrhythmia or infarct extension whereas an "ISA blocker" may be less likely to do so, but this remains to be proven.

Peripheral Circulatory Effects.

The contractile state of the peripheral arteriolar vessels is the result of two competing influences. Sympathetic stimulation of $Beta_2$ adrenoceptors results in vasodilation, whereas, stimulation of $Alpha_1$ adrenoceptors results in vasoconstriction. Thus, if stimulation of $Beta_2$ receptors is antagonised, an unopposed arteriolar constriction occurs, and this can result in symptoms of cold extremeties or aggravation of Raynaud's Phenomenon and intermittent claudication. These latter adverse effects are amongst the most frequently reported with pure beta blockers (106) - primarily due to diminished peripheral vascular blood flow mediated by vasoconstriction and perhaps contributed to by a reduction in cardiac output. One would expect that partial stimulation using a beta blocker with ISA of the peripheral $Beta_2$ receptor would offset this adverse effect, by diminishing systemic arteriolar resistance and increasing organ blood flow. However, this hypothesis has been difficult to prove.

Likewise $Beta_1$ selective (cardioselective) beta blockers would be expected to result in less vasoconstriction than a pure beta blocker.

According to various sources, the incidence of cold extremeties varies from 10-60% of patients on propranolol, 21% with metoprolol, 19% with atenolol, but only 10% with pindolol. (76) Quantitative measurements of peripheral blood flow are difficult to make and so one cannot draw absolute conclusions from the results of such studies. However, oxprenolol (with moderate degree of ISA) has been shown to have less effect on forearm blood flow and skin temperature than propranolol (107), and pindolol has been shown to reduce the resistance in the femoral vascular bed of dogs (15) and to reduce the systemic vascular resistance of hypertensive patients. (46,92) From a symptomatic viewpoint Marshall et al (108) have indicated that cold extremeties and Raynaud's Phenomenon are less common with cardioselective beta blockers than those with ISA.

Thus, there may be an advantage in using beta blockers with ISA in subjects with peripheral vascular disease or Raynaud's Phenomenon to prevent a deterioration in symptoms.

Respiratory Effects.

Beta-adrenoceptors in the lung are predominantly $Beta_2$ receptors, sympathetic stimulation of these receptors effecting bronchodilatation. By preventing stimulation of

these receptors, pure beta blockers can precipitate bronchoconstriction and this was confirmed with propranolol shortly after its introduction when administered to asthmatics. There is evidence suggesting that a cardio-selective ($Beta_1$) beta blocker or one with ISA offsets this disadvantage. However, it should be appreciated that even these drugs can precipitate bronchospasm in individual cases, especially asthmatics. (109,110) Most studies which have assessed respiratory function during beta blocker therapy have shown a benefit with cardioselective drugs or those with ISA as opposed to pure beta blockers (11,111,112) which invariably induce bronchospasm in susceptible individuals. Although some patients with bronchospastic disorders tolerate pindolol reasonably well (11,113,114), the opposite is also true and the use of all beta blockers in patients with chronic obstructive airways disease or overt asthma is not recommended. There is no evidence in the literature suggesting that ISA is superior to cardio-selectivity in this respect.

Central Nervous System.

From Table 1.3 it can be seen that central nervous system adverse effects are among the most common reported with pindolol. As pindolol is considered to have intermediate lipid solubility (or lipophilicity) in comparison with other beta blockers (115), it is capable of crossing the blood-brain barrier (116) and exerting CNS side effects as enumerated in Table 1.3, and changes from normal, in the electro-encephalogram. (117) In comparison

with metoprolol and atenolol, abnormally vivid dreaming and insomnia is reported twice as often in patients taking pindolol. (112) In three studies (112,118,119) CNS adverse effects were more severe and frequent with pindolol compared to other beta-blockers and occurred in 20% of pindolol recipients.

Thus, there is a clear disadvantage with beta blockers possessing ISA in terms of central nervous system adverse effects.

Carbohydrate Metabolism.

Impaired glucose metabolism (120), hypoglycaemia (121) and reduced insulin secretion (122) have all been reported with beta blocker therapy. It is not clear at present whether the possession of ISA alters these responses. It has been suggested that the serum insulin response to a glucose load is inhibited by propranolol and metoprolol, but not by pindolol (123), but whether ISA is an important determinant of carbohydrate metabolism, especially in diabetics, is uncertain.

Summary.

In terms of adverse effects there are numerous theoretical benefits in using a beta blocker with ISA. It would appear that myocardial performance, respiratory function and peripheral circulation are maintained, but it is still not clear whether patients with myocardial

dysfunction, conduction disorders, bronchospastic disease, or peripheral vascular disease derive benefit. In the context of cardiac failure, heart block or bronchial asthma there is currently a dearth of information to suggest that beta blockers with ISA are safer than pure beta blockers.

1.11. RECENT DEVELOPMENTS.

At present attempts are being made to exploit the pharmacological property of ISA in terms of a positive inotropic agent in the treatment of heart failure (124), and a new group of drugs, including prenalterol, dobutamine and ICI-118587 are currently being used or are under investigation. These compounds are structurally similar to beta blockers and possess 20-60% of the inotropic effect of isoprenaline. In high dosage, however, their beta blocking effect becomes more prominent and prevents further stimulation of the heart.

Assuming an oral preparation of these drugs can be formulated, they may prove useful in the long-term management of myocardial insufficiency.

1.12. SUMMARY.

Beta blockers with ISA offer an alternative treatment with possible clinical benefit, which may have no significant disadvantages over pure beta blockers. However, the distinction of clinical benefit is not clear cut between drugs with and without ISA. Beta blockers with ISA seem to confer some protection against myocardial insufficiency, broncho-spastic disorders, reduction in peripheral blood flow and conduction disturbances, and may possibly present a more favourable lipoprotein profile. The disadvantages appear to occur in it's use in severe or rest angina, where a significant fall in resting heart rate is not always observed. However, to date, there is a dearth of information concerning the long-term use of beta blockers with and without ISA in chronic stable angina - the clinical condition along with hypertension, which accounts for the largest treatment group. Hard information is lacking in terms of difference with pure beta blockers on myocardial and respiratory performance, lipoprotein profiles and assessment of the degree and frequency of myocardial ischaemia.

Numerous published clinical reports may be collated to produce many interpretations of the clinical relevance of ISA in ischaemic heart disease, but further long-term study of the above parameters in chronic stable angina are required before firm conclusions can be drawn.

SECTION 2.

PATIENTS, COMPLIANCE AND ADVERSE EFFECTS.

2.1. Patient Recruitment.

2.2. Drug Compliance.

2.3. Adverse Effects.

2.1. PATIENT RECRUITMENT.

The majority of investigations reported in this thesis were performed on subjects with chronic stable angina pectoris. Eighty consecutive male patients attending a Cardiology Clinic were invited to participate in these experiments on the basis of the following criteria:

1. Patient history of chronic stable, effort angina pectoris (New York Heart Association Class II or III), either previously untreated or inadequately controlled on current therapy. No patient suffered pain at rest.

2. A positive exercise electrocardiogram using a modified Bruce Protocol (125), defined as ST-segment depression of >1 mm. for 0.08 seconds after the J point, developing in a previously normal lead and persisting for at least three complexes in conjunction with anginal chest pain. Patients who showed some ST segment depression before exercise were included only if the ST segment depression became deeper by by >1 mm. during exercise and if a previously normal lead showed ST depression.

3. Absence of clinical history or findings suggesting chronic obstructive airways disease, valvular or congenital heart disease,

cardiomyopathy, renal impairment, diabetes mellitus, unstable angina or myocardial infarction in the year prior to recruitment.

Patients were fully informed of the nature of the investigations and gave their written consent.

Using these selection criteria 40 male subjects were recruited and after baseline evaluation were randomised to treatment with either propranolol or pindolol. All patients were followed for 3-6 months before entry to the study to ensure their condition was stable. Two weeks before entry into the study a second exercise electrocardiography was performed to establish stability. These results are summarised in Table 2.1a. Apart from Glyceryl Trinitrate and longer acting nitrates or a beta blocker no other medication was consummed in this "run in" period. One month before entry into the study the longer acting nitrate or beta blocker was gradually withdrawn and for two weeks before entry only sublingual Glyceryl Trinitrate was allowed. Each patient was given written instructions to take either propranolol 40 mg. t.i.d. or pindolol 2.5 mg. t.i.d. for two weeks, then to double the dose of each. This dose was maintained for a further 50 weeks. Treatment was single-blind. Propranolol and Pindolol were supplied by I.C.I. Pharmaceuticals and Sandoz Pharmaceuticals Ltd., respectively. The tablets were reduced to powder form and placed in opaque, two-piece hard gelatin capsules. All analyses were performed without knowledge of the patient's treatment. After 52 weeks treatment with each

drug, the first nine patients completing the protocol in the propranolol group and first eight in the pindolol group were entered into a study using a double-blind crossover technique, to investigate the effect of these beta blockers on heart rate, arrhythmias and myocardial ischaemia. The physical and clinical characteristics of the two treatment groups is shown in full in Table 2.1b and c, and the study design represented in Figure 2.1. The randomisation resulted in even matching in terms of age, body mass, resting heart rate and blood pressure, severity and duration of symptoms and results of exercise electrocardiography. In Section 5, 13 subjects with mild to moderate hypertension were recruited in order to study the effect of sotalol hydrochloride on plasma lipoproteins and in Section 4 a group of 16 normal volunteers were recruited in order to perform an evaluation of radionuclide ventriculography in terms of reproducibility and in the detection of coronary artery disease. Thirty-four additional patients with chronic stable angina were recruited to investigate the reproducibility of radionuclide ventriculography and the usefullness of the cold pressor test (CPT) and sustained isometric handgrip (SIHG) exercise (Section 4).

Full details of the patient cohort used in each investigation is given in the respective section.

TABLE 2.1a. SYMPTOMATIC DETAILS OF PATIENT POPULATION WITH RESULTS OF FIRST AND SECOND EXERCISE ELECTROCARDIOGRAPHY - PINDOLOL.

n	Functional Class NYHA (1-4)	Duration of Symptoms (min)	Frequency of Pain (attacks/day)	Exercise Electrocardiogram					
				Maximum HR (bpm)		Exercise Time (minutes)		Maximum ST Depression (mm)	
				1	2	1	2	1	2
1	2	12	1	160	166	15	18	2	2
2	2	11	1	150	160	12.5	15	2	2
3	2	24	2	160	160	14	12.5	3	2
4	2	49	1	172	158	15.5	12	2	2
5	3	24	2	122	138	6	7.5	1	1
6	3	9	1	120	120	9	7.5	1	1
7	2	12	1	110	100	10	12	1	1
8	2	12	1	98	115	9	10	2	2
9	3	36	2	100	128	6	9.5	3	2
10	2	8	1	160	170	14	16.5	2	2
11	2	24	2	100	95	7	6	2	2
12	2	36	1	142	150	12	12	2	2
13	2	7	1	168	148	14.5	13	2	2
14	3	96	2	118	125	7.5	6	3	2
15	2	24	2	160	170	15	15	2	2
16	2	48	1	140	155	12	14	2	2
17	2	8	1	160	160	14	13	2	2
18	2	18	2	150	160	10	12	2	2
19	3	2	3	130	120	9	8	2	2
Mean ± S.D.	NA	24 ± 22.1	1.5 ± 0.61	138 ± 24.8	144 ± 21.7	11 ± 3.2	12 ± 3.5	NA	NA
				p = NS		p = NS			

TABLE 2.1b. Cont'd. SYMPTOMATIC DETAILS OF PATIENT POPULATION WITH RESULTS OF FIRST AND SECOND EXERCISE ELECTROCARDIOGRAPH PROPRANOLOL.

n	Functional Class NYHA (1-4)	Duration of Symptoms (min)	Frequency of Pain (attacks/day)	Exercise Electrocardiogram					
				Maximum HR (bpm)		Exercise Time (minutes)		Maximum ST Depression (mm)	
				1	2	1	2	1	2
20	3	9	2	100	95	9	6	1	2
21	2	6	1	125	145	13.5	15	2	2
22	3	10	1	118	130	6	8.5	3	2
23	3	48	4	115	120	6	6	3	2
24	2	6	1	170	162	15.5	16	2	2
25	2	12	1	210	180	18	16.5	2	2
26	3	5	3	110	130	5	7	1	1
27	2	60	1	130	115	10	8.5	1	1
28	3	14	2	125	115	12	12	2	2
29	3	18	2	120	120	9	10	1	1
30	3	6	3	125	140	6	9	1	1
31	3	5	2	110	130	9	9	1	1
32	2	2	1	180	160	17	14.5	2	2
33	2	3	2	120	140	6	8	2	2
34	2	12	1	128	135	14.5	12	2	3
35	3	48	4	138	120	9	7.5	3	2
36	3	6	2	120	148	10.5	12	3	2
37	2	60	1	195	180	18	15.5	2	1
38	2	6	2	160	155	12	10	3	3
39	2	4	2	110	130	8	11.5	3	2
40	2	12	3	155	140	10	10	2	2
Mean ± S.D.	NA	17 ± 19.1	1.9 ± 0.97	136 ± 30.2	138 ± 21.4	11 ± 4.1	11 ± 3.3	NA	NA
				p = NS		p = NS			

Table 2.1b GROUP AND INDIVIDUAL, PHYSICAL AND CLINICAL CHARACTERISTICS OF PATIENTS TREATED WITH PROPRANOLOL.

n	Age (yrs.)	Previous MI.	Height (m)	Weight (Kg)	Quetelet Index ($Kg/cm^2 x10^3$)	Smoking (no./day)	Resting HR	Resting BP
1	57	-	1.676	76.2	2.71	-	51	115/84
2	53	-	1.791	79.4	2.47	10-15	78	135/78
3	57	YES	1.702	67.1	2.32	-	73	184/103
4	51	YES	1.778	72.2	2.28	Ex-smoker	67	120/76
5	53	YES	1.803	75.3	2.32	-	79	111/77
6	54	YES	1.829	79.8	2.39	10-15	70	146/81
7	47	-	1.727	69.8	2.34	Ex-smoker	62	96/53
8	59	-	1.727	65.3	2.19	20	86	119/67
9	41	YES	1.676	74.8	2.61	Ex-smoker	62	109/79
10	64	-	1.791	80.7	2.52	Ex-smoker	61	171/89
11	45	-	1.803	110.7	3.40	4	63	109/84
12	52	-	1.727	75.3	2.52	-	62	149/39
13	46	-	1.626	58.5	2.21	20	80	121/86
14	58	-	1.803	72.6	2.23	-	87	159/85
15	55	-	1.791	81.6	2.55	-	71	207/103
16	59	YES	1.600	69.4	2.71	5	62	107/74
17	50	-	1.676	69.8	2.49	20	67	118/65
18	54	-	1.714	69.4	2.36	20-30	70	116/79
19	44	-	1.727	88.0	2.95	Ex-smoker	75	139/94
20	60	-	1.702	72.6	2.51	-	71	134/79
21	49	-	1.778	68.0	2.51	-	88	138/84
Mean or Total	52.7 ± 5.9	6 or 28.5%	1.73 ± 0.063	75.1 ± 10.42	2.49 ± 0.288	S 38% Ex-S 24%	70.7± 10.28	133±28.8 / 79±15.0

ABBREVIATIONS: MI = Myocardial Infarction; BP = Resting Blood Pressure (mmHg.); HR = Heart Rate (bpm.); S = Current Smokers; Ex-S = Ex-smokers.

Table 2.1c GROUP AND INDIVIDUAL, PHYSICAL AND CLINICAL CHARACTERISTICS OF PATIENTS TREATED WITH PINDOLOL.

n	Age (yrs.)	Previous MI.	Height (m)	Weight (Kg)	Quetelet Index ($Kg/cm^2 x10^3$)	Smoking (no./day)	Resting HR	Resting BP
22	48	-	1.753	70.3	2.29	Ex-smoker	68	148/58
23	49	-	1.727	67.1	2.25	7-8	59	121/76
24	45	-	1.880	69.8	1.98	Ex-smoker	61	118/81
25	68	-	1.829	73.5	2.20	-	76	125/64
26	58	-	1.727	74.4	2.49	-	70	145/85
27	67	-	1.727	69.8	2.34	Ex-smoker	67	136/79
28	39	YES	1.842	72,6	2.14	5-10	70	100/76
29	64	-	1.753	80.7	2.63	10	66	120/70
30	62	YES	1.600	59.9	2.34	Ex-smoker	73	139/73
31	38	YES	1.778	92.1	2.91	10	75	135/91
32	48	YES	1.676	73.0	2.60	Ex-smoker	59	118/83
33	56	YES	1.867	89.8	2.58	Ex-smoker	63	131/77
34	64	-	1.740	72.6	2.40	Ex-smoker	70	134/68
35	62	-	1.676	62.1	2.21	-	56	137/31
36	44	-	1.778	84.8	2.68	Ex-smoker	86	124/66
37	60	-	1.702	76.2	2.63	2	76	176/93
38	41	-	1.714	61.2	2.08	5	68	101/60
39	55	-	1.778	88.9	2.81	-	48	108/69
40	60	-	1.702	89.6	3.09	20	73	120/78
Mean or Total	54.1 ± 9.76	6 or 31.5%	1.74 ± 0.070	75.2 ± 9.96	2.45 ± 0.297	S 37% Ex-S 42%	67.6± 8.64	128±17.7 / 72±13.9

ABBREVIATIONS: As For Table 2.1a.

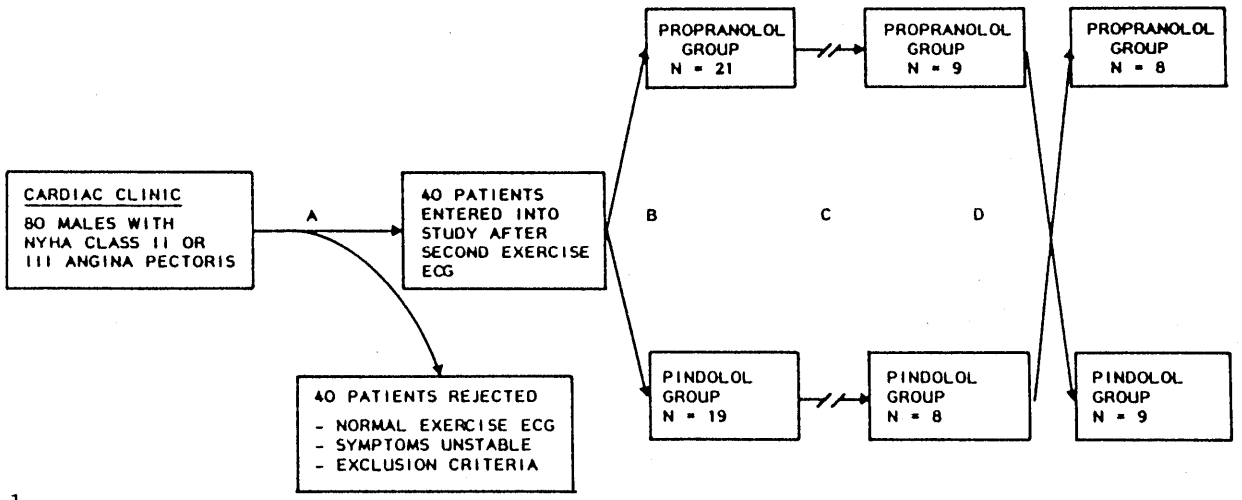


FIGURE 2.1.

Flow diagram showing study design and patient selection.

A. Eighty male patients recruited from a Cardiac Clinic with classical symptoms of angina pectoris. Exercise ECG performed and patients followed for 3-6 months before entry to the study. Forty patients were rejected either at the first exercise ECG or in the 3-6 months run in period because of failure to meet entry criteria.

B. Patients randomised to treatment with propranolol or pindolol.

C. One year study period during which patients were seen five times for investigations (see text).

D. On completion of one year, the first 9 patients in the propranolol group and 8 in the pindolol group, completing the study were recruited into a study to investigate the effects of these beta blockers on ambulatory heart rate, arrhythmias and ST segments. This part of the study had a double blind crossover design. (see Section 6).

2.2. DRUG COMPLIANCE.

> "Keep watch also on the fault of patients which often make them lie about the taking of things prescribed."
>
> Hippocrates.

The problem of adherance or compliance with prescribed medication has long been recognised as a potential reason for lack of therapeutic effect. Non-compliance with short-term regimens has been as high as 92% (126), although this was recorded in children. Thus, non-compliance may influence the interpretation of the results of clnical investigations (127), and it is appropriate to consider this aspect in any study dependant on patient compliance with prescribed treatment. Few, if any, studies which have examined the role of beta blockers in the treatment of hypertension or angina pectoris, have given consideration to compliance. In addition to failure to take prescribed medication, non-compliance may include the failure of patients to attend clinics or for investigations. The phenomenon of patients missing appointments or dropping out of studies, has been extensively studied. Caldwell et al (128) reported a 74% withdrawal rate in a 5 year period of chronic hypertensive patients attending an outpatient clinic while Stumler et al (129) found that 19.8% of a patient cohort was lost to follow up within 12 months of commencement of anti-hypertensive treatment. In terms of ingestion of prescribed medication, McKenney et al (130) observed that

only 16-25% of a group of hypertensives took 90-110% of their medication. Sackett (131) reported that only 48-62% of a study group are complaint with at least 80% of their medication while Marshall and Barritt (132) found that 72% of hypertensives were compliant with once a day medication, but only 64% on a twice daily regime.

Methods of assessing Compliance.

Several methods of assessing compliance have been devised. One method is the patient interview, asking he/she to estimate the number or percentage of tablets taken or missed out. This method has been shown to be relatively unreliable (133), but may provide some useful information, as about half of noncompliant patients will admit that they are ommitting at least some of their medication. (134,135)

Pill counts can be performed by asking the patient to return any unused tablets at each clinic visit. Thus calculating the number of pills consummed. A compliance value can then be determined for each patient from the following formula:

$$\text{Compliance (\%)} = \frac{\text{No. of prescribed tabs. taken by patient}}{\text{No. of tablets prescribed}} \times \frac{100}{1}$$

However, the results of pill counts must be interpreted with caution. It has been noted that some patients will dispose of medication that they have not

taken to give the impression that they have complied with treatment (136), and one study showed a 36% discrepancy between pill counts and physiological measurements used to determine consumption of antacids by subjects with peptic ulceration. (137)

Analysis of body fluids is commonly considered to be the most reliable method for assessing complaince. (138) However, such a random analysis provides an "all or none" result which may lead to an underestimation of non-compliance.

During the course of the investigations reported in this theses, compliance was assessed by patient interview, pill count and plasma beta blocker levels determined by a fluorimetric method described elsewhere. (139) Patients were asked if at least 90% of prescribed tablets had been consummed since the previous visit and if any had been ommitted. Drugs were packaged in such a way that there was an excess for each period between assessment visits. Pill count was thus performed at the 26 and 52 week visits following commencement of treatment. In addition 10 mls. of blood was taken from the sample required for other purposes (Section 5), for beta blocker estimation at each visit. Thus, patients were unaware that their compliance was being checked in this way.

Results.

Only one patient defaulted from some attendances after the 12 weeks visit. All patients reported that at least 90% of tablets had been consummed at the prescribed treatment times. Only 7 patients admitted occasional ommission of single doses usually because of employment restrictions. Two patients were found, from the pill count, (both taking pindolol) to habitually take more than the prescribed dose of drugs. Excluding these subjects, the remaining 38 individuals had a mean compliance of 91 ± 8% and 87 ± 5% at 26 and 52 weeks respectively. There was no significant difference between compliance estimated by pill count at these time, between those taking propranolol and pindolol.

The results of beta blocker assay at each interval of treatment are shown in Table 2.2. There was no significant variation in the levels of beta blocker in either group although the levels increased after 2 weeks therapy, which coincides with the doubling in dose of each beta blocker. The lower levels of beta blocker found in those taking pindolol reflect the lower oral dose required for therapeutic benefit compared to propranolol.

Comment.

There is no ideal way of assessing drug compliance, but the accepted techniques used in these patients indicated acceptable adherance to prescribed treatment.

TABLE 2.2 PLASMA BETA BLOCKER LEVELS THROUGHOUT 1 YEARS TREATMENT WITH PROPRANOLOL (n = 21) AND PINDOLOL (n = 19) (ng/ml.) RESULTS EXPRESSED AS MEAN ± SD.

	BASAL	2	6	12	26	52
PROPRANOLOL GROUP	n.d.	15.4 ± 11.52	16.1 ± 12.95	17.2 ± 12.34	14.3 ± 9.88	14.8 ± 11.51
PINDOLOL GROUP	n.d.	29.8 ± 26.86	33.7 ± 46.30	32.1 ± 40.54	28.8 ± 42.19	20.8 ± 11.51

ABBREVIATIONS: n.d. = Not Detected.

NB. One subject in Pindolol Group had levels of 100, 210, 180, 186 and 24 at each stage respectively and was found to be overcompliant using pill-counts.

The mean value of compliance in this group of patients assessed by pill count, (91% at 26 weeks) is higher than levels previously reported. (130-132) The reasons for this high level may be explained by the circumstances in which these studies were performed. Throughout the investigation, the patients attended a separate clinic, with no limitation on time available for consultation. At the appropriate stages of investigation a thorough explanation of the disease process and individual tests was given. In addition the patient was seen by the same physician at each visit, thus allowing a close physician-patient relationship to be formed. As the patients were also participating in a research study, it is probable that they were a highly motivated group - in comparison to their counterparts attending a busy Cardiac Clinic.

Factors shown to be consistently influential in improved compliance are patient-practitioner interaction and patient satisfaction with the clinic visit and the practitioner. (140,141) Examination by a regular physician was shown by Alpert (140), to result in better compliance. Impersonality and brevity of the encounter have been shown to negatively affect patient compliance. (142) Compliant behaviour can also be obtained by improving the patient's perception of his illness and the benefits of therapy. (143) Providing the patient with a written explanation of his illness and prescription, as in this study, has been found to improve compliance. (144)

Thus, these investigations were conducted in an environment which encourages satisfactory compliance with drug therapy. The plasma beta blocker levels show satisfactory mean levels, although there were large inter-individual variations. This is a well recognised phenomenon during treatment with beta blockers and does not necessarily indicate a similar variation in pharmacological effect. (145,146) Such estimations only serve to support the clinical impression, patient response and pill count which suggest adequate compliance.

2.3. ADVERSE EFFECTS.

Adverse effects of beta blockers may include detrimental effects on left ventricular function, respiratory function and the plasma lipoprotein profile. These influences are described in detail later in this thesis. The purpose of this sub-section is to document adverse effects which were described by patients taking pindolol or propranolol during the investigations.

Several factors influence accurate detection and categorisation of adverse effects. Depending on the definition of a particular adverse effect the frequency may vary between series of patients. The method of detection can also lead to discrepancies in reported frequency.

The use of a physician completed questionairre may reflect more serious adverse effects while patient completed questionairres may lead to reporting of trivial as well as serious episodes. Using the latter it is possible that suggestion of an adverse effect will precipitate its occurance in some individuals. Another method of assessing adverse effects is to record spontaneously reported complaints from the patient and include direct questioning by the physician as to the presence of any unwanted symptoms or effect which the patient believes to be attributed to the drug. According to Rawlin's et al (147), adverse effects of beta blockers can be classified as follows:

Predictable

B_1 adverse effects : Hypotension, Bradycardia, Cardiac Failure } Exaggerations of the normally expected response.

B_2 adverse effects : Bronchospasm.
Vasoconstriction.
Metabolic function upset.
eg. carbohydrate homeostasis.

Unpredictable (Short-term)

Fatigue, sexual dysfunction, gastrointestinal symptoms.

During the course of the investigations contained in this thesis, patients were encouraged to volunteer any adverse effects at each assessment visit (2,6,12,26 and 52 weeks after commencing therapy) and were directly questioned regarding the presence of any "side effects", without specific adverse effects being mentioned.

Results.

Sixteen patients taking propranolol and 17 taking pindolol reported at least one adverse effect during one year's follow up. The frequency of these adverse effects is shown in Table 2.3 and the frequency in the first three

months and in the last 9 months shown in Figure 2.1. The most commonly occurring complaint was of fatigue which occurred in 43% of those on propranolol and 32% of those on pindolol. This complaint seemed to decrease after the first three months of treatment as did limb or muscle pain which occurred in 32% of those on pindolol, but in only 10% taking propranolol in the first three months of treatment, but was not reported by any patient thereafter. Complaints of cold extremeties were four times commoner in those taking propranolol and did not diminish in frequency with duration of treatment.

Central nervous system side effects were more common in those taking pindolol, four subjects (21%) describing vivid dreams or nightmares and two subjects describing hallucinations. One of these subjects described seeing a large block of ice at the foot of his bed on several occasions, associated with a feeling of cold. Another believed he was seeing small animals moving around his house. Three subjects complained of increasing anxiety and irritability, one undergoing what his family described as a "personality change", becoming very short tempered, intolerant and aggressive. In addition three subjects on pindolol complained of insomnia.

Comment.

Most subjects in each group complained of at least one adverse effect, but no patient felt his symptoms severe enough to warrant discontinuation of medication. Because

TABLE 2.3 FREQUENCY OF ADVERSE EFFECTS DURING ONE YEARS TREATMENT WITH PINDOLOL AND PROPRANOLOL. PERCENTAGES IN BRACKETS.

	TREATMENT GROUP	
Side Effect	Pindolol (n=19)	Propranolol (n=21)
Oedema	1 (5)	1 (5)
Anxiety/Irritability	3 (16)	1 (5)
Blurred Vision	1 (5)	1 (5)
Cold Periphery	1 (5)	4 (19)
Dyspnoea	1 (5)	1 (5)
Fatigue/Lethargy	6 (32)	9 (43)
Frequency/Nocturia	1 (5)	1 (5)
Gastrointestinal	5 (26)	5 (24)
Headaches	- (-)	2 (10)
Insomnia	3 (16)	- (-)
Lighthheadedness/Dizziness	1 (5)	2 (10)
Limb/Muscle Pain	6 (32)	2 (10)
Paraesthesiae	1 (5)	2 (10)
Pruritus	- (-)	1 (5)
Rhinorrhoea	- (-)	3 (14)
Vivid Dreams/Hallucinations	4 (21)	- (-)
Weight Gain	2 (11)	- (-)

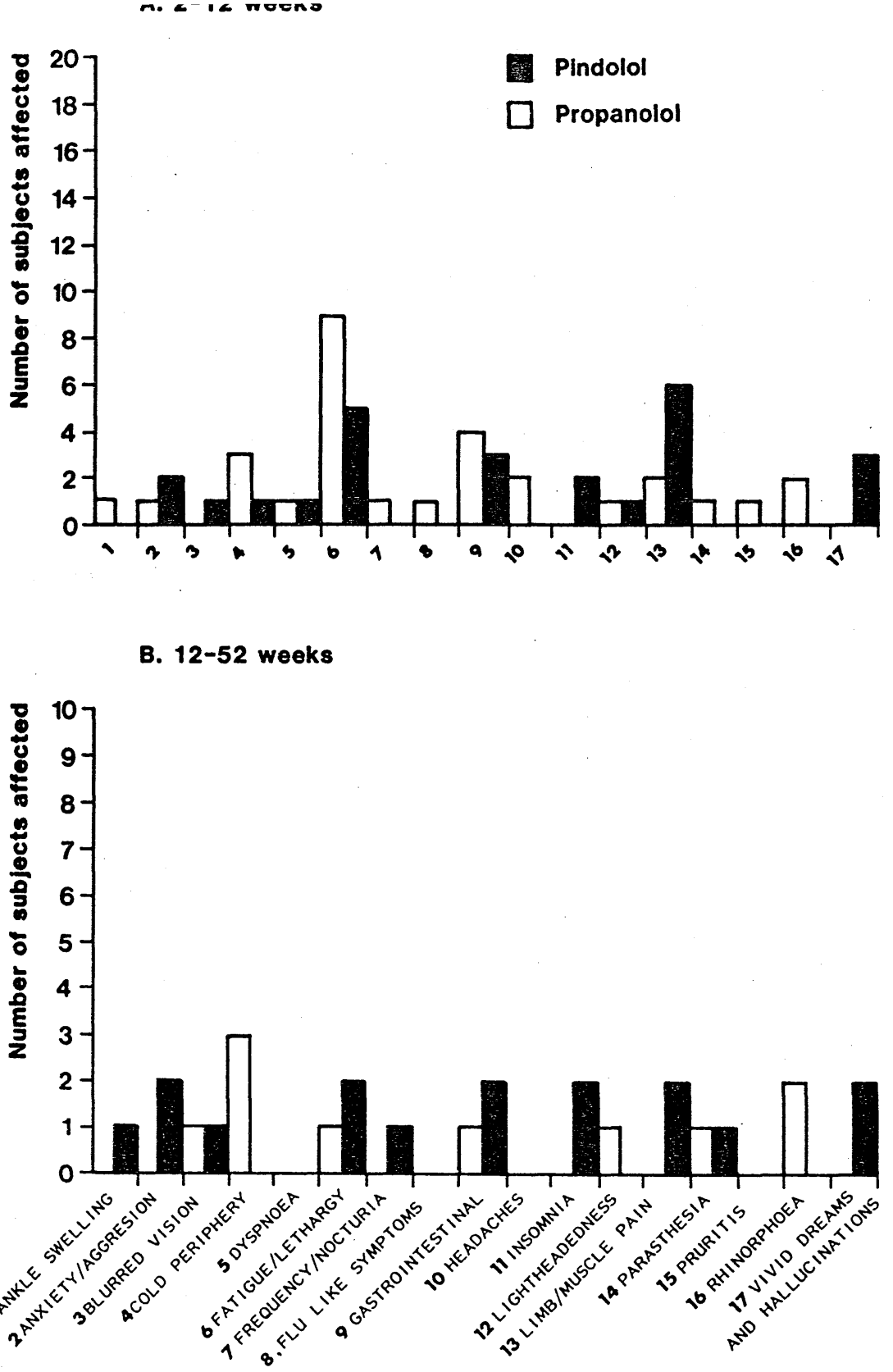


FIGURE 2.2

Frequency of adverse effects during treatment with propranolol and pindolol. A. during the first three months of therapy and B. during the last 9 months of therapy.

of the small numbers, firm conclusions cannot be drawn from this evaluation regarding the difference between propranolol and pindolol in terms of adverse effects. However, some striking features are evident from the data. Bizarre dreams, visual hallucinations, nervousness and insomnia were more common with pindolol, and this has been the experience of others (148), although propranolol is also known to cause these complaints. (149) White (150) reported a case similar to those outlined above concerning a patient who developed visual hallucinations lasting 15-20 minutes after only two days therapy with propranolol. Gershon (151) suggested that the psychosis may be caused by the blockade of post-synaptic beta adrenergic receptors, with inhibition of noradrenaline release from nerve endings or antagonism of serotonin in the CNS also playing a role. It is not clear why pindolol should be associated with a higher frequency of CNS adverse effects, although it is known to have the highest CSF/plasma concentration ratio of the beta blockers studied by Patel and Turner (152) suggesting that greater concentrations may be present within the brain.

The higher frequency of complaints of cold extremeties in those taking propranolol may be related to blockade of peripheral B_2 receptors, allowing predominant alpha stimulation and thus resulting in vaso-constriction. The role of alpha mediated vasoconstriction in the face of a falling cardiac output is uncertain.

Complaints of cold extremeties, with or without Raynaud's phenomenon is a well recognised side effect of several beta blockers (108,153); but is also common among patients taking other anti-hypertensives, and also before treatment is commenced. (154) In a study of 758 hypertensives Feleke et al (154), found that 44% complained of cold extremeties and of this number 40% were taking beta blockers and 18% diuretics. No significant difference was found in the prevalence of symptoms among patients taking propranolol, pindolol or cardio-selective beta blockers. Some workers have measured limb blood flow in response to beta blockers. Ohlsson and Lindell (155) found that in 9 patients already on beta blockers, changed to pindolol, limb blood flow increased and Vandenburg (156) found that although both oxprenolol (weak ISA) and propranolol reduced forearm blood flow, this was significantly greater after a single oral dose of propranolol. It is presumed that ISA protects against unopposed alpha adrenergic vasoconstriction by maintaining vasodilatation by providing some stimulation of the peripheral B_2 vasodilator receptors.

It is noteworthy that no subject complained of sexual dysfunction during the study as this has been found to be a relatively common complaint of beta blockade. (157) This may be explained by the natural reluctance and embarrassment in divulging such information to the investigator. The most frequent adverse effect of both drugs was fatigue or lassitude. This was reported as early as 1965 following single oral and intravenous doses of

propranolol. (158) Stone (159), claims that 30% of patients on beta blockers complain of leg weakenss and inability to move faster on hills or stairs. The reason for this fatigue is not clear and may in part be related to a placebo effect.

One uncommon adverse effect reported in those taking propranolol in this study is rhinorrhoea. This has previously been reported in two subjects taking propranolol and may be an effect more common with propranolol than other beta blockers. (160)

Conclusions.

In summary there is no standard method of collecting and reporting side effects. The methods used in this study found fatigue/lassitude to be the commonest complaint in both groups with patients taking pindolol experiencing more central nervous system adverse effects and fewer complaints of cold extremeties. No adverse effect was thought serious enough by either the patient nor the author to warrant discontinuation of the drug.

SECTION 3

THE EFFECT OF CHRONIC BETA BLOCKADE ON LEFT VENTRICULAR FUNCTION: POSSIBLE INFLUENCE OF I.S.A. IN CHRONIC STABLE ANGINA PECTORIS.

This study was carried out in collaboration with Mr. M. Cooke, Principal Physicist, Department of Clinical Physics, West Graham Street, Glasgow.

3.1. INTRODUCTION.

From the results of short-term, intravenous experiments, it is known that pure beta blockers are prone to reduce cardiac output to a greater extent than those with ISA. Svendson (46) found that a reduction in cardiac output experienced with propranolol and atenolol was reduced by administering practolol (weak ISA) and more so by pindolol (potent ISA). Taylor et al (51) confirmed that beta blockers with ISA produced less depression of left ventricular function than other beta blockers when given intravenously to subjects with ischaemic heart disease. These studies compliment several earlier investigations observing a consistent negative inotropic effect of pure beta blockers given intravenously. (161-163) Conversely there is evidence that beta blockers with ISA given acutely may attenuate this effect and preserve myocardial function, while affecting adequate beta blockade. (46) In terms of oral administration, the effect of propranolol on left ventricular performance is less consistent. One study found that propranolol reduced the echocardiography derived ejection fraction and posterior wall motion while others have failed to observe significant changes. (164-166)

The results of acute intervention studies may not reflect the effects of long-term oral treatment on left ventricular performance. In this respect several authors have reported the effects of continued oral treatment. Tarazi and Dustan (167) showed that during chronic adminis-

tration with propranolol, heart rate and cardiac output remained depressed. Guazzi et al (168), however, have reported an increase in cardiac output in some hypertensive patients being treated with propranolol for months or years. Man in't Veld et al (48,49) investigated the effects of chronic oral therapy with pindolol in patients severely disabled by orthostatic hypotension and confirmed that heart rate, stroke volume, cardiac output and mean arterial pressure were increased by pindolol suggesting a potential benefit of beta blockers possessing ISA. However, extrapolation to the patient with angina pectoris may not be appropriate. Of the chronic studies, Frishman et al (58), examined the effect of pindolol and propranolol on echocardiographic left ventricular performance and found an increased left ventricular ejection fraction (EF) after pindolol and reduced EF after propranolol compared to control values. However, part of the reason for this finding may relate to the high oral dosage of pindolol used which may not have resulted in an equipotent beta blocking effect when compared to the propranolol dose used. In a recent controlled cross-over study between oral propranolol and pindolol in equipotent doses over 4-6 weeks Manyari et al (60) failed to find any significant change in EF with both drugs in 23 patients with chronic effort angina pectoris who had normal or near normal left ventricular function before treatment.

The cummulative effect of oral propranolol or pindolol in the long-term on left ventricular function has not been reported, despite the use of these drugs in

patients with ischaemic heat disease, hypertension and cardiomyopathy for extended periods.

The purpose of this investigation was to establish the effect of pure beta blockade on left ventricular performance at intervals over the course of one year and to compare this wih a beta blocker possessing ISA. In addition, the study protocol allowed for the determination of the effect of long-term therapy with beta blockers on the haemodynamic responses to cold stimulation and isometric exercise, and the possible effect of ISA.

Previous studies of this sort have used thermodilution (46), dye dilution (56), echocardiographic measurements (58), measurements of systolic time intervals (57), and recently measurement of left ventricular performance by radionuclide ventriculography (RNV). (60)

The latter method was chosen for the purposes of this thesis and this section relates to the findings of the experiments using RNV.

Following it's description by Zaret et al (169) in 1970, RNV has become accepted as an accurate and reproducible measure of left ventricular performance. It provides a safe, non-invasive, repeatable method for determining indices of myocardial performance. There is now indisputable evidence that this technique provides an estimate of left ventricular EF which correlates very well with that derived by contrast cineangiography (170-173) (r = 0.76-

0.94). In addition it provides a means of measuring ventricular performance during exercise and other interventions.

Serial measurements of left ventricular function by calculation of the EF and other indices provides an objective means of assessing the effect of drugs on myocardial performance. Gated RNV is a scintiphotographic technique that records the distribution of a blood pool tracer in the heart throughout the cardiac cycle. The images recorded are used to calculate left ventricular EF and other indices of left ventricular performance. As it is noninvasive and presents a negligible radiation risk to the patient, it is particularly suitable for repeated investigation. The usefulness of the technique has in the past been limited by reproducibility of left ventricular EF measurements. (174) However, a high degree of automation is now available when analysing the images, thus circumventing the problems previously encountered and improving reproducibility. This aspect is explored in detail in Section 4. It is important to study the effects of beta blocker therapy on left ventricular function, not only at rest, but during daily environmental stress of which cold and isometric exercise are two, both recognised to precipitate angina in certain individuals. The choice of these interventions is discussed in greater detail in the following section of this thesis. Briefly, the cold pressor test has been shown to induce changes in the haemodynamic profile including an acute increase in blood pressure, probably secondary to a neurogenic increase in

peripheral vascular resistance (175), and an increase in heart rate. (176,177) These effects increase myocardial oxygen demand and can induce changes in left ventricular performance. As this intervention is easy to apply without the risk of motion artefact induced by dynamic exercise, it was chosen at the commencement of this investigation. It is stressed, that although this technique may have limitations as an aid in the detection of CAD, it was not used for this purpose in this study. SIHG testing was applied for similar reasons. It is a safe and simple test which yields predictable elevations of heart rate and blood pressure (178), but does not induce the degree of ischaemic stress manifested by angina or ST changes comparible to bicycle ergometry. (179) This intervention may unmask latent abnormal ventricular performance in patients with CAD, and the effect of beta blockade on this change with exercise may be of importance.

3.2. PATIENTS AND METHODS

Patient Group.

Patients were selected as described previously (p 70). Forty male subjects seen consecutively at a Cardiology Clinic, with ischaemic heart disease manifesting as chronic stable angina (New York Heart Association class II or III), were recruited to the study if they were untreated or inadequately controlled on previous therapy. The subjects had a mean age of 53.4 years (SD $\pm$ 7.9) and a range of 38-68 years. No patient was admitted to the study if there was any evidence of, or previous history of diabetes mellitus, renal failure, chronic obstructive airways disease or asthma, valvular or congenital heart disease, unstable angina, clinical or x-ray evidence of cardiac failure or cardiac conduction abnormalities. All subjects were in sinus rhythm and none had suffered a myocardial infarction in the previous year. Apart from glyceryl trinitrate and the trial medication, no other drug therapy was permitted durng the course of the study. Informed written consent was obtained from all patients and the study protocol was approved by the local Ethics Committee. Their physical characteristics are summarised in Table 3.1.

Study Protocol.

A treadmill exercise test using a modified Bruce Protocol (125) was first performed. Horizontal or downsloping ST segment depression of at least 1 mm.,

TABLE 3.1 PRETREATMENT CHARACTERISTICS OF PATIENTS RECRUITED (n = 40), RECORDED AT THE FIRST HOSI VISIT. BODY MASS INDEX (QUETELET INDEX) IS EXPRESSED AS WEIGHT IN Kg/HEIGHT^2 IN CMS x 10 VALUES ARE EXPRESSED AS MEANS ± STANDARD DEVIATION, OR AS A PERCENTAGE.

	Patients Receiving Pindolol (n = 19)	Patients Receiving Propranolol (u = 21)	P Value
Age (years)	54.1 ± 9.75	52.8 ± 5.95	NS
Quetelet Index ($Kg/cm^2 x 10^3$)	2.45 ± 0.30	2.49 ± 0.29	NS
Height (m)	1.75 ± 0.07	1.74 ± 0.06	NS
Weight (Kg)	75.2 ± 9.96	75.1 ± 10.42	NS
Heart Rate (bpm)	68 ± 8.6	71 ± 10.3	NS
Systolic BP (mmHg)	128 ± 17.7	134 ± 28.8	NS
Diastolic BP (mmHg)	73 ± 13.9	79 ± 15.0	NS
Current Smokers (> 10/day)	37%	38%	-
Ex-Smokers	42%	24%	-
Previous MI.	32%	29%	-

0.08 secs. in duration after the J point for at least three consecutive cardiac cycles, in a lead with a normal resting recording occurring in conjunction with exercise induced chest pain, supported a diagnosis of CAD.

If patients were taking medication this was gradually tailed off over two weeks and after a further two weeks, patients were randomly allocated to treatment with either pindolol 2.5 mg. t.i.d. or propranolol 40 mg. t.i.d. for two weeks, increasing thereafter to 5 mg. t.i.d. and 80 mg. t.i.d. respectively at which they were maintained for the duration of the study, (p. 71). These doses (16:1 ratio) have previously been shown to exert a similar beta blocking effect (180) and are the dosage regimens most often used in clinical practice.

Left ventricular performance was assessed before the commencement of beta blockade and then at intervals of 2,6,12,26 and 52 weeks afterwards.

Assessment of Left Ventricular Performance.

Left ventricular performance was assessed using RNV. This is carried out by using a scintilation camera with a collimated detector to record the distribution of a radioactive tracer within the heart. The aquisition of data is synchronized to the R wave of the ECG using a gating device, and stored for analysis in a computer interfaced to the gamma camera. Figures 3.1 and 3.2 outline the basic principles behind this technique.

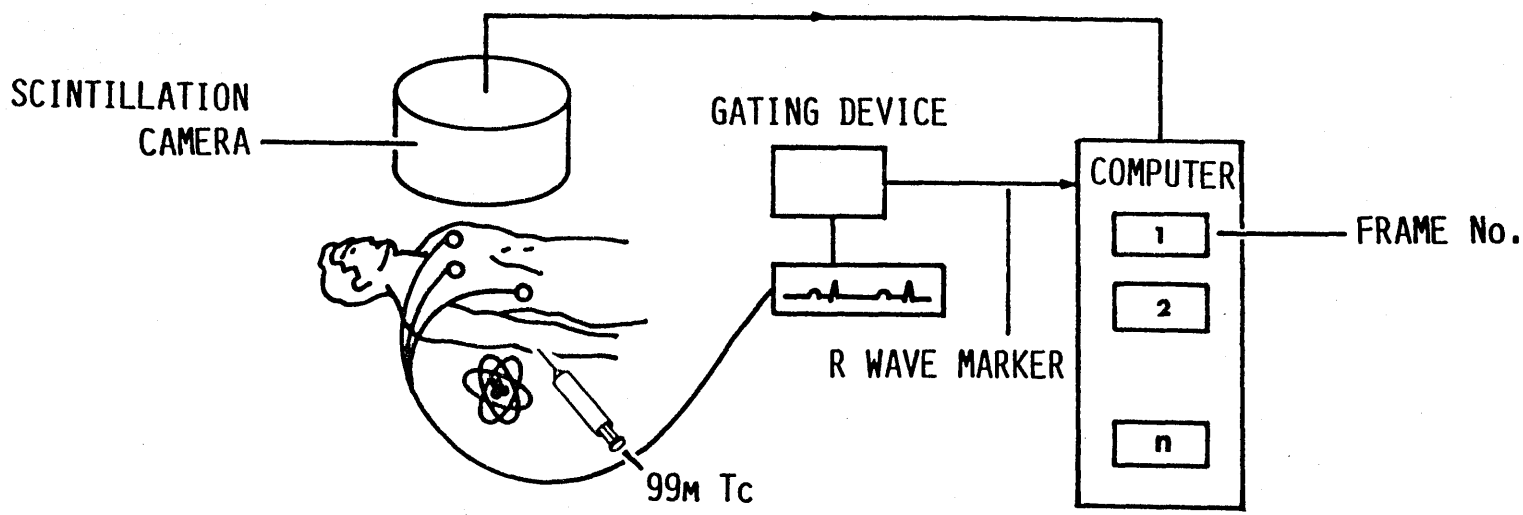


FIGURE 3.1

Material and equipment for multiple gated equilibrium blood pool scintigraphy. Twenty minutes following an intravenous injection of stannous pyrophosphate; 740 M Bq (20 mCi) of 99 m Tc is injected intravenously. After allowing five minutes for red blood cell labelling and equilibration of the radio-isotope in the blood pool, imaging is commenced. Counts are acquired by the camera head and stored by a computer. The collection of images is synchronised to the ECG. (See Figure 3.2).

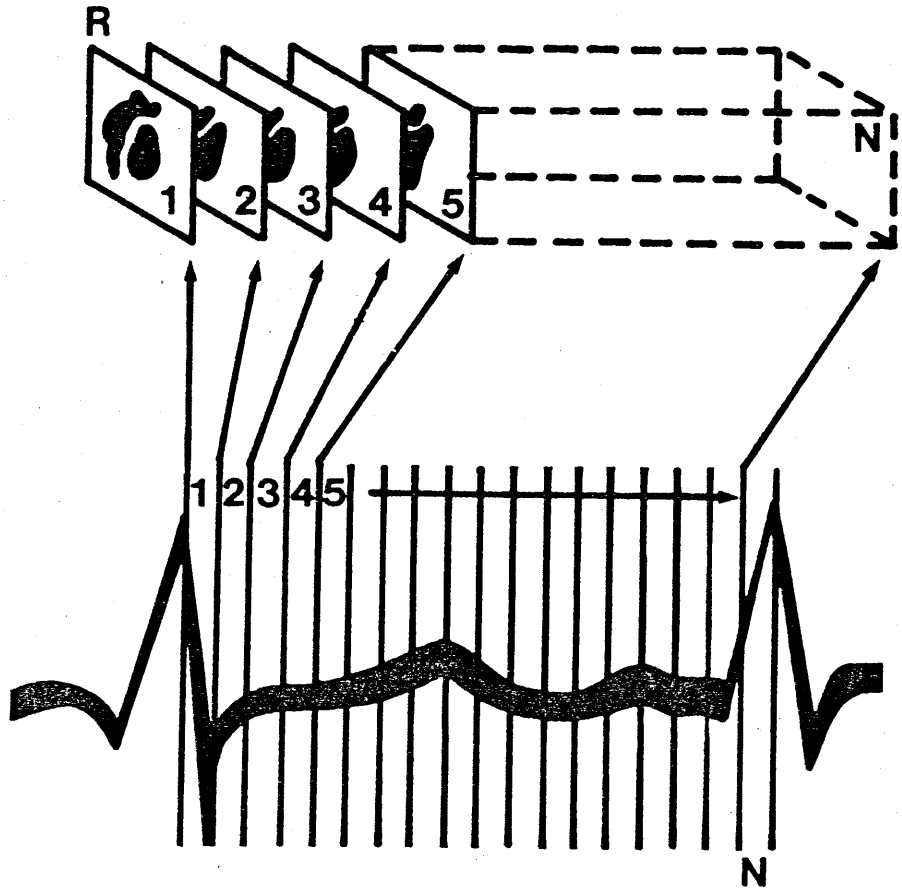


FIGURE 3.2

The method by which the computer generates multiple gated images. The cardiac cycle is divided into a preselected number of frames of equal duration (n = 16 in this study). Scintigraphic data from successive beats are placed into separate parts of the computer memory, depending on the temporal relation of the scintigraphic data to the R wave marker (R). For each frame (1....N), scintigraphic data from successive beats are accumulated.

Twenty to 30 minutes following an intravenous injection of 15 mg. stannous pyrophosphoate into a right antecubital vein, an intravenous injection of 740 MBq (20 mCi) 99m Tc was administered, thus effecting in vivo labelling of the red blood cells as described by Pavel et al (181) and Stokely et al. (182) This method has been found to result in a mean red blood cell labelling of > 95% during the first hour after injection of the radio-isotope and has been found to produce cardiac images of high quality which are not substantially different to those obtained with in vitro red cell labelling. (183) This method of labelling was chosen because of it's ease of application.

Radionuclide ventriculography was performed within 120-180 minutes after the last dose of beta blocker and at the same time of day (1400-1600 hours). Imaging was performed in the left anterior oblique projection which best separated right and left ventricles (usually 35-45°) and with a 10° caudel tilt. The same angle was used at each study interval. A Technicare Sigma 410 large field camera (year of manufacture: 1978) was used with a general, all purpose, low energy (140 KeV) parallel hole collimator. This system was calibrated daily, before each set of investigations, using a 99m Tc flood field, and uniformity correction performed by microprocessor based camera electronics. An ECG signal from the patient obtained on an Elcomatic EM810 monitor was used to trigger the computer to record images synchronised with the R wave.

An ADAC (CGR) 7310 computer with a 40 M Byte Winchester disc and a double 1 M Byte floppy disc drive was used to store images in histogram mode in 16 sequential frames in a 64 x 64 data matrix with the zoom set at x 3. Data collection was halted automatically after 6 minutes for resting studies and 5 minutes for stress studies. The aquisition protocol accepted all cardiac cycles within $\pm$ 20% of the central frequency, thus excluding ectopic beats. During resting studies a fixed framing rate was set by the computer at the start. The computer then calculated an average beat to beat interval and set the centre frequency for the study. During stress studies a variable framing rate option was used to track increasing heart rate. This operates in a similar fashion to the fixed rate but a beat outside the "window" causes the computer to set itself on a new centre frequency and so increasing heart rate does not halt imaging. Before analysis of the data computer electronics "normalises" the heart rate, and thus the LV volume curve is independent of heart rate.

The composite 16 frame dynamic study was then stored on disc for later analysis at the end of the study.

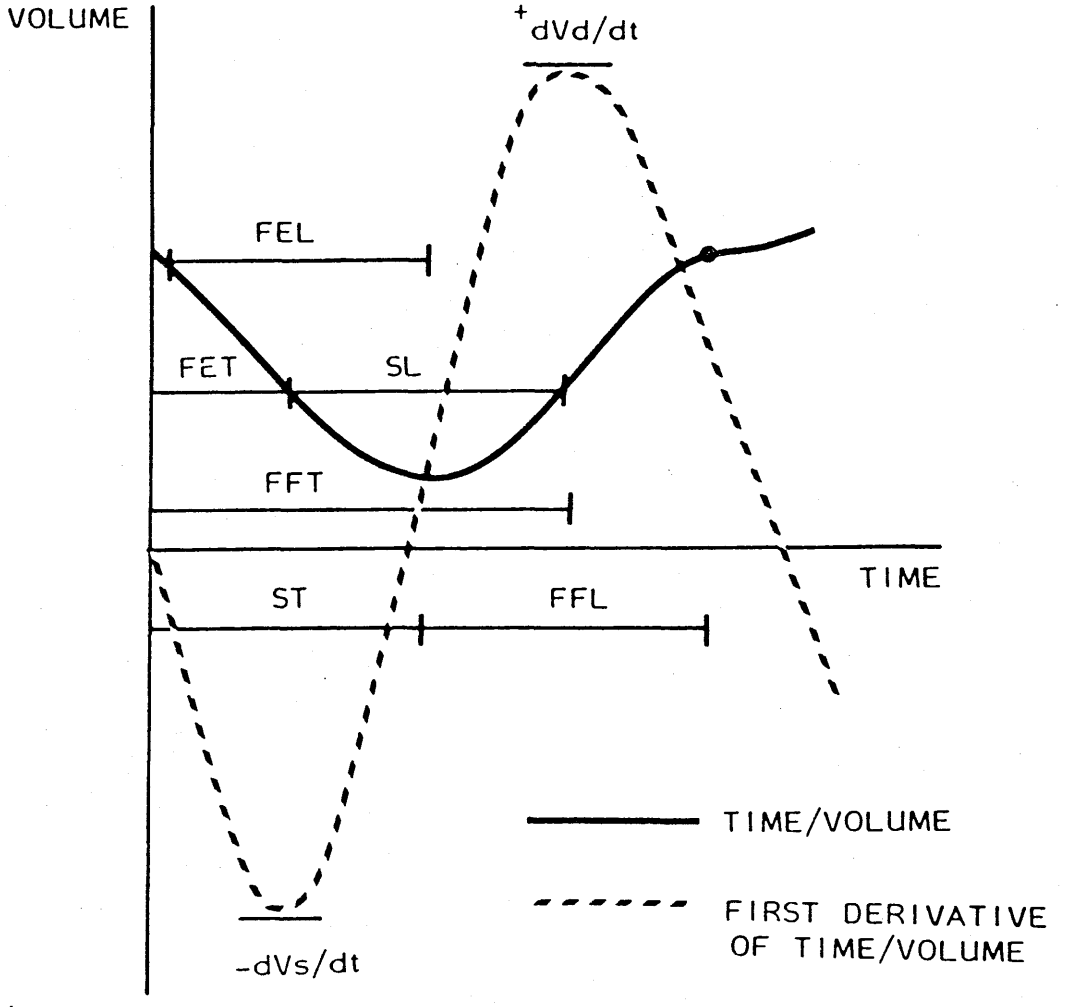
Studies were performed after 5-10 minutes supine rest and during sustained isometric handgrip (SIHG) and a cold pressor test (CPT). SIHG was performed by asking the patient to squeeze the bulb of a hand dynamometer (Martin Vigorimeter) to the maximum extent, 30% of this load was maintained for 5 minutes, during which time heart rate and blood pressure were recorded every minute in the left arm using a Hitachi HME-20

pulse and blood pressure monitor. The performance of this monitor has been evaluated for the purpose of this thesis (184) and is described in detail in the following section. During SIHG care was taken not to allow the patient to perform a Valsalva manouvre. After SIHG when pulse and blood pressure had fallen to basal values (usually 10 minutes) imaging was repeated during cold pressor stimulation. The cold pressor tests were applied by immersing the right hand in a mixture of crushed ice and water to the level of the styloid process for 5 minutes. Throughout the test mixing of ice and water was maintained to ensure an adequate cold stimulus. Blood pressure and heart rate were recorded as previously described. In both stresses, imaging was commenced 30 seconds after the start of the stress test.

Image analysis was performed using the Stanford Automatic LV Analysis program, which constructs an activity time curve from which indices of left ventricular performance can be calculated (Figure 3.3.). The method is described in detail in the literature, (185,186) but briefly, the edge detection algorithm is based on a one-dimensional LaPalcian filter applied to the end-diastolic image vertically, horizontally, and along both diagonals. A search is made for the first edge which completely encloses the left ventricle, and the left ventricle is located by calculation of the x-y co-ordinates of the centre of gravity of an amplitude image constructed by the system.

FIGURE 3.3.

Left ventricular activity time curve and first derivative with report parameters.



Abbreviations:

FET: Fast ejection time. The point on the curve when maximal ventricular emptying occurs in relation to the total curve (%).
-dVs/dt: Maximum rate of negative change of ventricular volume with time (ie. ventricular emptying).
FEL: The duration of fast ventricular ejection in terms of percentage of the total curve.
ST: Total duration of systole as a percentage of total curve.
SL: Percentage of curve occupied by interval between peak systolic and diastolic volume change.
FFT: Fast filling time - point on the curve at which fastest filling of the ventricle occurs after closure of the aortic valve. (% of total curve)
+dVd/dt: Maximum rate of positive change of ventricular volume with time. (ie. ventricular filling).
FFL: Fast filling length - duration of period of fast ventricular filling after closure of the aortic valve (% of total curve).

The program transforms the data to frequency domain, and retains the zero, first, second, and third harmonics, as well as the diastolic image. The program locates the left ventricle on the left part of the stroke volume image, and identifies the edges of the ventricle on the diastolic image. A left ventricular area of interest (AOI) is created and subsequently used for interpolative background subtraction. The AOI is also used to create a 100-point volume curve using the frequency components. From this curve the system calculates ejection fraction, including dv/dt, (maximum rate of filling or emptying). The times when maximum filling and emptying occur and the length of filling and emptying. All of these latter parameters are expressed in terms of percentage of the total curve. Although EF, dVs/dt and dVd/dt are of recognised value and are frequently used, the other parameters are of some value when demonstrating a change in both systolic and diastolic function. Unfortunately at present, there is little uniformity between centres in their choice of report parameters, EF excepted.

Global ejection fraction is calculated from the following equation:

$$EF(\%) = \frac{\text{End diastolic counts - end systolic counts}}{\text{End Diastolic Counts}} \times \frac{100}{1}$$

Statistical Analysis.

Each parameter of haemodynamic response was analysed

by two-way analysis of variance to compare the mean response at the six stages. If a significant difference was indicated by the F Value obtained, post-hoc comparisons of weeks 2,6,12,26 and 52 with basal values were performed using a Student's paired t-test and a Wilcoxon signed rank test for paired observations or a Student's unpaired t-test and a Mann-Whitney test for unpaired observations. In all cases, the most conservative estimate of significance is reported. Heart rate and blood pressure changes were compared using Student's paired t-test and the Wilcoxon signed rank test. Unless otherwise stated, results are expressed as mean $\pm$ SD.

3.3. RESULTS

Of the forty patients recruited, one subject failed to complete the study, defaulting from further follow-up at the 12 week stage. Two other subjects (one from the propranolol group and one from the pindolol group) were excluded from analysis as their radionuclide ventriculograms were unsatisfactory. Of the remaining 37 subjects, randomisation of treatment resulted in an even distribution of patients to propranolol (n = 19) or pindolol (n = 18).

Angina Pectoris.

All but one subject (propranolol) had a subjective improvement of at least one division on the New York Heart Association classification, such that all patients were NYHA class I or II while taking the peak beta blocking dose. The remaining subject continued to suffer 3-4 daily episodes of short-lived angina on effort, and ultimately underwent coronary artery bypass graft after completion of the study. The mean frequency of anginal attacks per week fell from 5 ± 5.3 to 1 ± 2.4 at one year for those taking pindolol and 7 ± 6.0 to 3 ± 6.5 at one year in those taking propranolol (Table 3.2). There was no significant difference between the two drugs in terms of their ability to suppress angina pectoris.

TABLE 3.2 FREQUENCY OF ANGINA PECTORIS THROUGHOUT THE STUDY (Episodes/Week).

Week No.	BASAL	2	6	12	26	52
Pindolol Group (n=18)	5.3 ± 5.3	2.9 ± 5.1	1.6 ± 3.1	1.1 ± 2.1	2.0 ± 4.0	1.3 ± 2.4
Propranolol Group (n=20)	6.7 ± 6.0	2.2 ± 6.2	2.6 ± 6.7	1.8 ± 3.7	2.4 ± 6.5	2.9 ± 6.5

Results are expressed as Mean ± S.D.

Heart Rate and Blood Pressure.

Resting heart rate was significantly reduced by propranolol after six weeks treatment, when compared to basal values ($p < 0.01$), falling from a mean of 70 ± 10.4 bpm before treatment to 59 ± 7.7 bpm at 52 weeks (Table 3.3). Likewise, both systolic ($p < 0.01$) and diastolic ($p < 0.05$) blood pressure fell significantly (Table 3.3). There was no significant change in resting heart rate at any time during treatment with pindolol (Table 3.4), although systolic and diastolic blood pressure fell throughout the study, this only reached significance at six weeks ($p < 0.05$).

Radionuclide Ventriculography.

Cold Pressor and Sustained Isometric handgrip Tests.

In general, both these interventions were well tolerated, although several patients complained of hand pain during the CPT. Seven patients experienced difficulty or complications with the tests. One patient (propranolol) experienced a prolonged episode of angina pectoris immediately after cold pressor testing at the 52 week stage. This was accompanied by 2-3 mm. ST segment depression and hypotension. He was admitted to the Coronary Care Unit for observation and made an uneventful recovery with no ECG or enzyme evidence of a myocardial infarction. The CPT was presummed to have precipitated a severe episode of angina, possibly by

TABLE 3.3 MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO SUSTAINED ISOMETRIC HANDGRIP AT INTERVALS THROUGHOUT 1 YEARS TREATMENT WITH PROPRANOLOL.

Week of Treatment		TIME FROM START OF ISOMETRIC HANDGRIP TEST (minutes)					
		BASAL	1	2	3	4	5
0	H.R.	70 ± 10.4	77 ± 11.4	81 ± 10.9	83 ± 12.1	86 ± 16.0	88 ± 17.1
	S.B.P.	134 ± 28.0	155 ± 32.4	165 ± 31.4	173 ± 29.3	169 ± 25.9	184 ± 30.7
	D.B.P.	79 ± 14.7	93 ± 18.1	96 ± 17.9	97 ± 17.6	103 ± 12.1	98 ± 17.9
2	H.R.	74 ± 21.9	67 ± 6.3	61 ± 7.8	64 ± 6.5	68 ± 8.3	68 ± 8.6
	S.B.P.	112 ± 13.0	143 ± 15.2	148 ± 22.2	147 ± 23.4	164 ± 32	167 ± 20.7
	D.B.P.	72 ± 9.0	88 ± 8.4	90 ± 12.0	94 ± 12.7	98 ± 15.9	100 ± 15.6
6	H.R.	58 ± 6.7	63 ± 7.2	66 ± 7.6	66 ± 8.5	66 ± 9.2	67 ± 8.6
	S.B.P.	115 ± 17.3	131 ± 23.3	144 ± 28.3	147 ± 27.3	159 ± 30.8	161 ± 33.7
	D.B.P.	69 ± 13.3	81 ± 12.6	85 ± 14.8	88 ± 13.7	89 ± 14.5	92 ± 12.3
12	H.R.	57 ± 6.7	61 ± 9.3	63 ± 9.4	63 ± 10.6	64 ± 10.3	66 ± 9.5
	S.B.P.	114 ± 15.8	131 ± 21.7	139 ± 21.0	145 ± 22.8	156 ± 23.1	160 ± 27.0
	D.B.P.	70 ± 9.6	79 ± 10.6	81 ± 11.4	86 ± 13.7	86 ± 12.6	90 ± 14.1
26	H.R.	57 ± 6.7	59 ± 7.0	61 ± 6.7	61 ± 7.0	62 ± 6.6	67 ± 9.1
	S.B.P.	116 ± 18.9	127 ± 20.7	137 ± 22.4	149 ± 25.7	152 ± 27.9	152 ± 20.3
	D.B.P	64 ± 12.8	73 ± 13.6	79 ± 15.7	82 ± 18.2	85 ± 19.7	82 ± 18.3
52	H.R.	59 ± 7.7	64 ± 10.8	63 ± 9.4	63 ± 10.9	68 12.6	71 ± 12.3
	S.B.P.	118 ± 26.4	132 ± 28.0	138 ± 29.1	152 ± 30.0	159 24.3	166 ± 25.1
	D.B.P.	67 ± 11.4	75 ± 14.6	80 ± 14.1	85 ± 15.4	89 17.2	98 ± 12.6

ABBREVIATIONS: H.R. = Heart Rate - expressed as b.p.m.
S.B.P. = Systolic Blood Pressure (mmHg).
D.B.P. = Diastolic Blood Pressure (mmHg).

Results expressed as mean ± S.D.

TABLE 3.4 MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO SUSTAINED ISOMETRIC HANDGRIP AT INTERVALS THROUGHOUT 1 YEARS TREATMENT WITH PINDOLOL.

Week of Treatment		TIME FROM START OF ISOMETRIC HANDGRIP TEST (minutes)					
		BASAL	1	2	3	4	5
0	H.R.	67 ± 8.6	77 ± 11.6	79 ± 11.9	83 ± 13.1	84 ± 13.4	84 ± 13.2
	S.B.P.	128 ± 17.7	151 ± 25.1	158 ± 27.3	166 ± 28.3	171 ± 29.6	175 ± 28.4
	D.B.P.	73 ± 13.9	84 ± 15.2	86 ± 18.2	92 ± 19.2	93 ± 18.9	98 ± 11.9
2	H.R.	66 ± 7.6	74 ± 11.3	78 ± 12.2	78 ± 13.9	79 ± 15.1	76 ± 11.6
	S.B.P.	117 ± 8.8	139 ± 15.2	157 ± 28.3	166 ± 32.2	173 ± 27.1	165 ± 19.1
	D.B.P.	67 ± 10.8	86 ± 13.3	99 ± 15.0	93 ± 22.9	96 ± 14.2	93 ± 11.7
6	H.R.	70 ± 7.7	72 ± 8.5	73 ± 9.6	75 ± 11.8	75 ± 10.0	74 ± 9.3
	S.B.P.	115 ± 11.33	130 ± 15.6	139 ± 18.4	148 ± 18.4	154 ± 21.0	156 ± 17.2
	D.B.P.	66 ± 11.7	77 ± 13.1	83 ± 13.6	84 ± 16.2	89 ± 17.0	88 ± 16.9
12	H.R.	66 ± 7.1	73 ± 8.4	74 ± 7.4	75 ± 8.6	76 ± 9.1	77 ± 9.4
	S.B.P.	119 ± 16.4	136 ± 15.2	143 ± 17.0	154 ± 20.0	163 ± 24.7	163 ± 20.3
	D.B.P.	68 ± 9.9	80 ± 9.4	85 ± 13.4	89 ± 15.6	94 ± 7.4	94 ± 17.2
26	H.R.	66 ± 5.6	72 ± 6.8	72 ± 6.7	73 ± 7.8	74 ± 8.9	75 ± 8.5
	S.B.P.	121 ± 20.0	130 ± 17.1	140 ± 18.5	150 ± 19.1	162 ± 25.0	162 ± 24.1
	D.B.P.	65 ± 14.0	72 ± 17.3	77 ± 18.1	82 ± 21.1	81 ± 19.2	87 ± 18.9
52	H.R.	66 ± 5.7	72 ± 7.3	74 ± 8.6	74 ± 8.7	76 ± 8.9	77 ± 9.9
	S.B.P.	121 ± 14.3	132 ± 15.7	140 ± 18.5	150 ± 21.3	157 ± 21.2	164 ± 19.9
	D.B.P.	66 ± 14.9	74 ± 17.7	77 ± 18.9	83 ± 21.4	88 ± 23.7	90 ± 23.9

ABBREVIATIONS: As for Table 3.3.

inducing coronary vaso-constriction. Another patient experienced mild angina pectoris between three and five minutes of the SIHG test before treatment and during the CPT after two weeks treatment. Both of these episodes were accompanied by a 1-2 mm. ST segment depression, but were promptly relieved by sublingual glyceryl trinitrate after completion of the test. A further episode of angina at 12 weeks, after SIHG was not accompanied by any ST segment changes.

Three patients experienced severe hand pain during the CPT. One patient who suffered from rheumatoid arthritis experienced prolonged pain in the hand used for cold pressor testing up to two days later. He was therefore excused further investigation using this intervention.

Only one subject found difficulty sustaining 30% of maximum voluntary handgrip for five minutes. This subject developed an increased frequency of ventricular ectopic beats (VEBs) (1:6) during the test. Another subject developed a similar frequency of VEBs during SIHG, but did not find any difficulty maintaining his grip.

Haemodynamic Responses.

Prior to treatment both SIHG and CPT caused highly significant increases in heart rate and blood pressure in both groups (Figures 3.4-3.7). Sustained

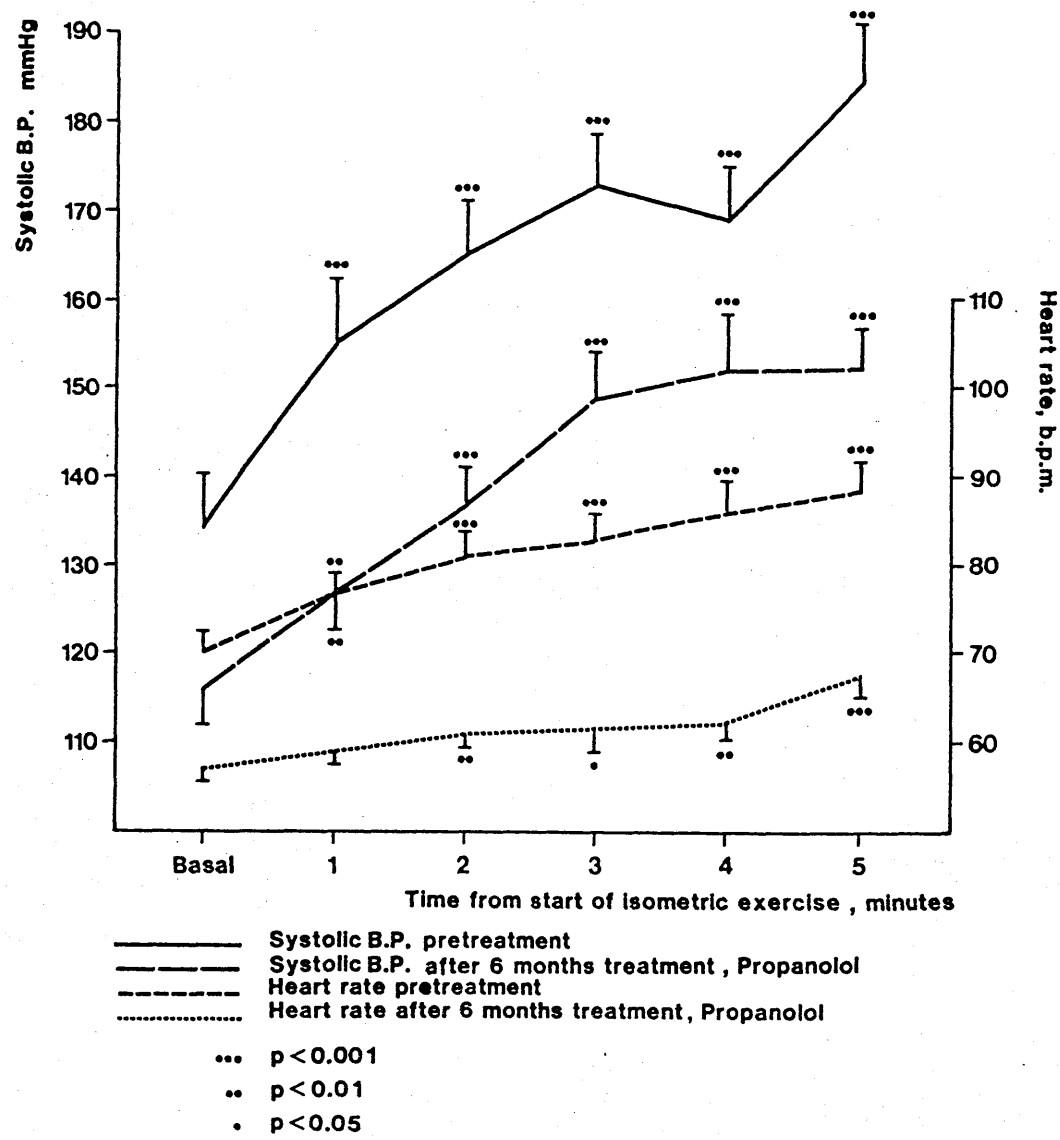


FIGURE 3.4

Comparative responses of mean heart rate and systolic blood pressure, before and after six months treatment with propranolol to isometric handgrip test. Results are expressed as mean ± SE.

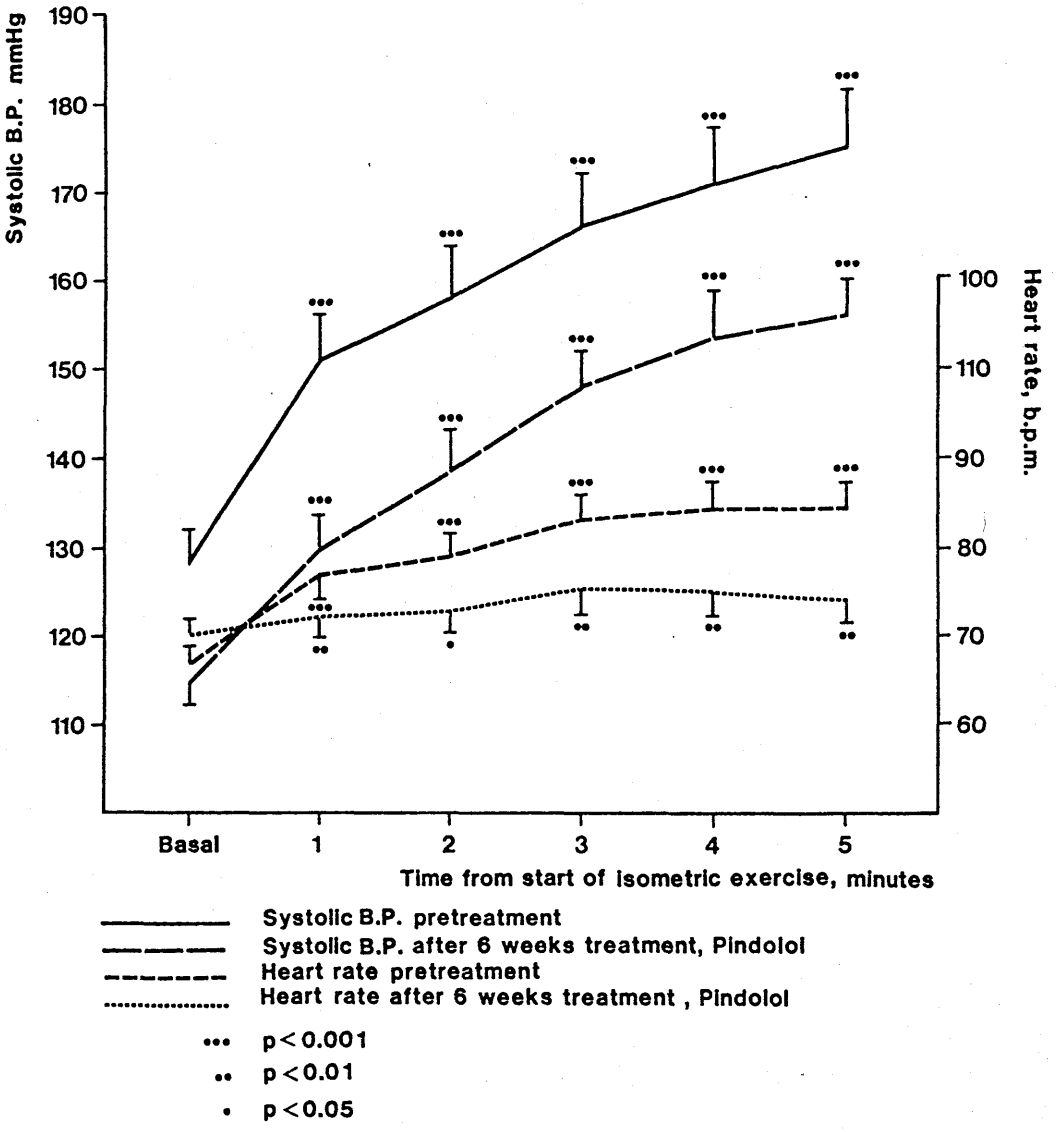


FIGURE 3.5

Comparative responses of mean heart rate and systolic blood pressure, before and after six weeks treatment with pindolol to isometric handgrip test. Results are expressed as mean ± SE.

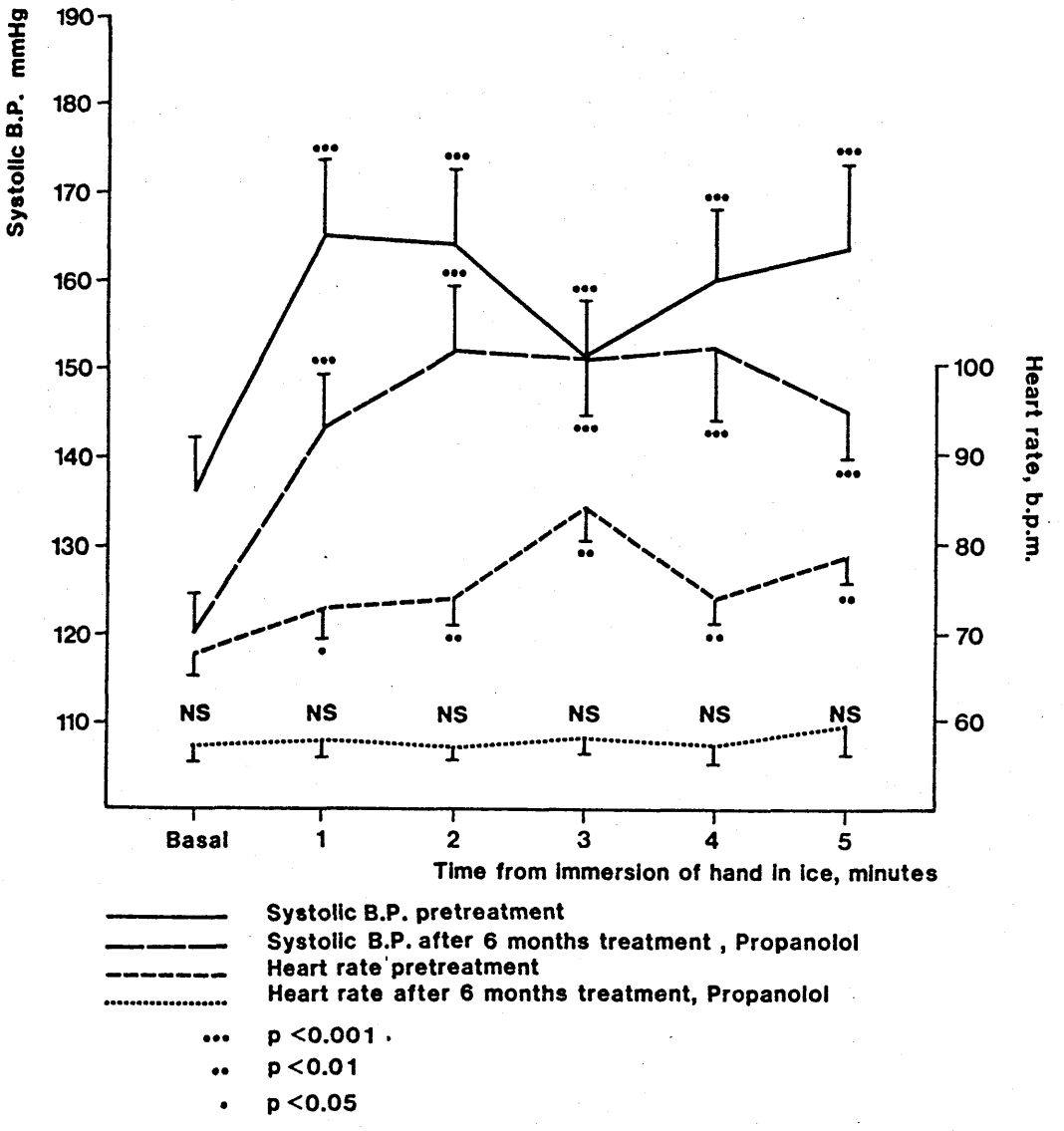


FIGURE 3.6

Comparative responses of mean heart rate and systolic blood pressure, before and after six months treatment with propranolol to cold pressor testing. Results are expressed as mean ± SE.

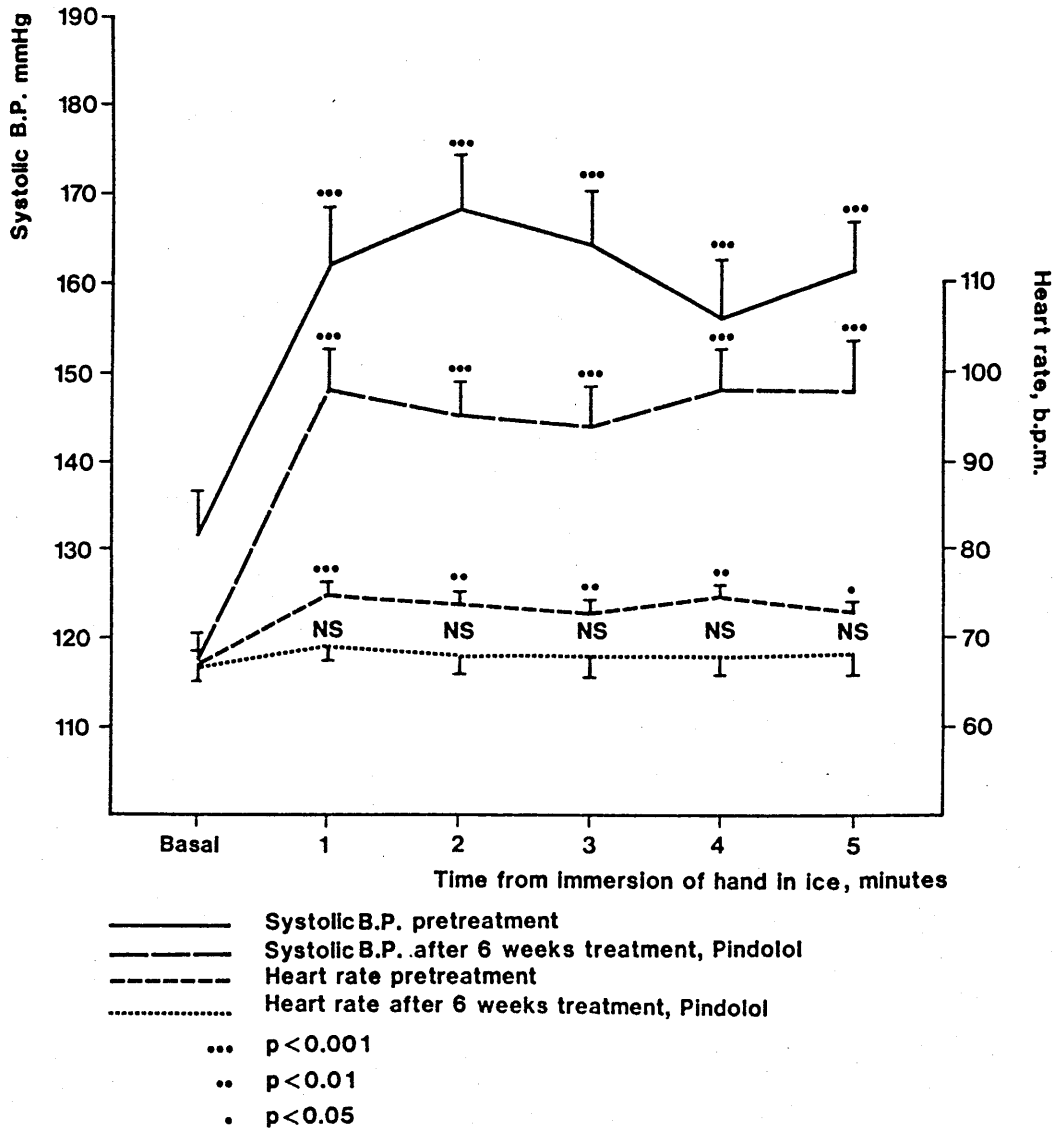


FIGURE 3.7

Comparative responses of mean heart rate and systolic blood pressure before, and after six weeks treatment with pindolol to cold pressor testing. Results are expressed as mean ± SE.

isometric handgrip caused a sequential rise in systolic blood pressure and heart rate in both groups (Figures 3.4 and 3.5) while the CPT resulted in a more variable, but significant, increase in these indices with some decay noted in the increments of heart rate and systolic blood pressure between 3 and 5 minutes (Figures 3.6 and 3.7). The mean response to each of these interventions at each study interval is shown in Table 3.3 (SIHG responses during treatment with propranolol), Table 3.4 (SIHG responses during treatment with pindolol), Table 3.5 (CPT responses during treatment with propranolol), and Table 3.6 (CPT responses during treatment with pindolol).

Both drugs attenuated the rise in heart rate and systolic blood pressure, the maximal attenuation of response occurred after 26 weeks treatment with propranolol for both CPT and SIHG, but after six weeks treatment with pindolol. Systolic blood pressure and heart rate rises were attenuated to a similar extent with both drugs (Figures 3.4 - 3.7).

Left Ventricular Function.

There was no significant difference between the pre-treatment resting indices of left ventricular function in the two groups (Table 3.7). Resting EF was 49 ± 10.7% in those assigned to propranolol and 52 ± 16.3% in those to pindolol (p = NS). During SIHG, this fell significantly by a mean of 4 ± 4.2% in those in the

TABLE 3.5 MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO COLD PRESSOR TEST AT INTERVALS THROUGHOUT 1 YEARS TREATMENT WITH PROPRANOLOL

Week of Treatment		TIME FROM IMMERSION OF HAND IN ICE (minutes)					
		BASAL	1	2	3	4	5
0	H.R.	68 ± 10.7	73 ± 13.7	74 ± 12.9	84 ± 15.5	74 ± 11.2	76 ± 12.0
	S.B.P.	136 ± 28.1	165 ± 39.8	164 ± 37.2	151 ± 29.0	160 ± 36.8	163 ± 41.5
	D.B.P.	78 ± 11.8	96 ± 17.5	92 ± 14.4	89 ± 11.4	95 ± 14.2	92 ± 10.7
2	H.R.	55 ± 6.1	59 ± 6.2	59 ± 6.0	60 ± 7.5	59 ± 6.7	59 ± 10.1
	S.B.P.	123 ± 20.4	159 ± 39.1	140 ± 21.7	154 ± 32.7	154 ± 40.3	160 ± 37.5
	D.B.P.	73 ± 8.2	93 ± 13.3	92 ± 13.7	94 ± 17.3	93 ± 15.8	93 ± 14.0
6	H.R.	56 ± 5.6	59 ± 8.2	61 ± 9.5	64 ± 8.4	62 ± 9.3	61 ± 9.3
	S.B.P.	117 ± 19.3	149 ± 34.3	153 ± 36.0	143 ± 26.2	152 ± 35.2	150 ± 33.8
	D.B.P.	71 ± 10.7	89 ± 16.3	87 ± 13.5	85 ± 12.3	87 ± 15.8	85 ± 13.6
12	H.R.	56 ± 8.0	58 ± 8.6	58 ± 9.4	59 ± 9.0	58 ± 8.6	58 ± 7.9
	S.B.P.	118 ± 13.1	151 ± 23.6	150 ± 19.8	151 ± 22.7	148 ± 22.6	151 ± 22.8
	D.B.P.	73 ± 8.1	87 ± 10.6	88 ± 11.9	87 ± 7.0	84 ± 10.6	84 ± 9.0
26	H.R.	57 ± 7.2	58 ± 6.3	57 ± 6.2	58 ± 7.0	57 ± 7.1	59 ± 13.0
	S.B.P.	120 ± 20.1	143 ± 29.7	152 ± 31.9	151 ± 30.0	152 ± 33.9	145 ± 22.6
	D.B.P.	70 ± 12.7	85 ± 16.0	84 ± 13.5	83 ± 14.0	82 ± 14.9	80 ± 13.7
52	H.R.	58 ± 9.4	66 ± 17.4	64 ± 14.3	61 ± 9.6	62 ± 15.2	60 ± 13.5
	S.B.P.	119 ± 22.0	150 ± 30.1	161 ± 31.7	159 ± 30.2	154 ± 32.6	152 ± 17.3
	D.B.P.	67 ± 13.0	84 ± 18.9	83 ± 18.4	84 ± 22.6	86 ± 22.5	88 ± 16.3

ABBREVIATIONS: As for Table 3.3.

TABLE 3.6 MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO COLD PRESSOR TEST AT INTERVALS THROUGHOUT 1 YEARS TREATMENT WITH PINDOLOL.

Week of Treatment		TIME FROM IMMERSION OF HANDS IN ICE (minutes)					
		BASAL	1	2	3	4	5
0	H.R.	67 ± 6.8	75 ± 9.7	74 ± 10.1	73 ± 9.1	75 ± 8.6	73 ± 8.7
	S.B.P.	132 ± 18.6	162 ± 26.5	168 ± 29.3	164 ± 25.4	156 ± 26.4	161 ± 23.7
	D.B.P	76 ± 12.6	93 ± 16.4	91 ± 16.5	91 ± 17.8	88 ± 14.4	89 ± 14.5
2	H.R.	64 ± 9.2	68 ± 12.4	69 ± 9.9	70 ± 14.2	69 ± 10.7	71 ± 13.0
	S.B.P.	118 ± 9.2	153 ± 12.3	156 ± 19.0	154 ± 19.1	152 ± 10.6	154 ± 18.2
	D.B.P.	71 ± 7.2	91 ± 13.5	95 ± 15.9	90 ± 15.2	91 ± 14.1	89 ± 14.3
6	H.R.	67 ± 7.6	69 ± 7.0	68 ± 7.6	68 ± 7.7	68 ± 8.7	68 ± 8.5
	S.B.P.	118 ± 11.6	148 ± 17.5	145 ± 15.1	144 ± 17.1	148 ± 18.7	148 ± 20.1
	D.B.P.	68 ± 10.5	84 ± 17.2	81 ± 16.2	82 ± 15.4	80 ± 16.2	82 ± 14.9
12	H.R.	65 ± 6.3	70 ± 9.9	67 ± 8.7	67 ± 8.7	66 ± 8.6	69 ± 10.9
	S.B.P.	125 ± 13.4	155 ± 22.2	159 ± 21.6	154 ± 22.6	157 ± 17.8	153 ± 15.5
	D.B.P.	72 ± 6.8	91 ± 14.5	87 ± 15.1	85 ± 13.4	84 ± 15.2	90 ± 19.7
26	H.R.	65 ± 7.8	68 ± 8.3	69 ± 9.6	66 ± 6.6	67 ± 7.3	67 ± 6.4
	S.B.P.	121 ± 17.9	147 ± 18.0	157 ± 23.2	154 ± 21.3	154 ± 20.9	149 ± 20.1
	D.B.P.	64 ± 14.4	80 ± 19.2	79 ± 18.5	75 ± 17.8	75 ± 17.3	76 ± 12.6
52	H.R.	66 ± 6.3	70 ± 5.9	72 ± 11.2	70 ± 6.8	70 ± 8.4	68 ± 8.8
	S.B.P.	125 ± 16.5	147 ± 20.7	154 ± 22.3	155 ± 26.5	159 ± 26.9	154 ± 21.6
	D.B.P.	65 ± 10.5	83 ± 15.7	81 ± 18.2	80 ± 21.9	79 ± 16.5	77 ± 17.9

ABBREVIATIONS: As for Table 3.3.

TABLE 3.7 COMPARISON OF RESTING PRE-TREATMENT RADIONUCLIDE VENTRICULOGRAPHY BETWEEN THOSE ASSIGNED TO PROPRANOLOL (n = 19) AND PINDOLOL (n = 18).

	PROPRANOLOL GROUP	PINDOLOL GROUP	p VALUE
FET	17.8 ± 2.22	16.9 ± 1.55	NS
dVs/dt	-4.4 ± 0.54	-4.6 ± 0.52	NS
FEL	34.7 ± 4.81	33.1 ± 4.66	NS
ST	40.2 ± 5.32	38.2 ± 3.94	NS
SL	44.2 ± 6.14	44.1 ± 8.86	NS
FFT	62.0 ± 6.96	61.0 ± 8.25	NS
dVd/dt	3.6 ± 0.39	3.6 ± 0.59	NS
FFL	33.7 ± 6.74	32.6 ± 7.22	NS
EF	49.3 ± 10.70	51.7 ± 16.26	NS

ABBREVIATIONS: As for Figure 3.3.

propranolol group (Figure 3.8) and by 5 ± 8.8% in the pindolol group (Figure 3.9) (p = NS between the two groups). During CPT, there was a highly significant fall in EF in both groups, but the difference between the groups was not statistically significant,, falling by 5 ± 5.3% in the propranolol group (Figure 3.10) and 8 ± 8.5% in the pindolol group (Figure 3.11).

There was no significant change in the resting EF in those taking pindolol throughout the study. However, the resting EF in those taking propranolol was significantly higher six weeks ($p < 0.02$) and six months ($p < 0.01$) following commencement of the beta blocker. Individual resting EF changes during treatment with propranolol and pindolol are shown in Figures 3.12 and 3.13 respectively.

Neither beta blocker significantly altered the response to SIHG or CPT at any stage of therapy (Table 3.8 and Figures 3.8-3.11).

In the group taking propranolol, the maximum rate of ventricular emptying in systole (dVs/dt) increased both at rest and during SIHG and CPT in a sequential manner throughout treatment (Tables 3.9-3.10). Fast ejection length, (FEL), systolic time (ST), systolic length (SL), fast filling time (FFT) and fast filling length (FFL) all fell during treatment at each stage of therapy, at rest and during SIHG and CPT. Although there was no significant change in the maximal rate of ventricular

TABLE 3.8 MEAN EJECTION FRACTION RESPONSE TO CHRONIC BETA BLOCKADE WITH PROPRANOLOL AND PINDOLOL

	PROPRANOLOL GROUP			PINDOLOL GROUP		
Week No.	R	SIHG	CPT	R	SIHG	CPT
Basal	49 ± 10.7	49 ± 9.2	44 ± 9.1	52 ± 16.3	47 ± 18.1	43 ± 16.2
2	51 ± 10.0	44 ± 7.4 (n = 11)	44 ± 7.0	60 ± 16.8	50 ± 17.1 (n = 10)	46 ± 16.6
6	53 ± 12.2*	47 ± 11.2	45 ± 9.13	52 ± 16.6	47 ± 18.4	45 ± 17.9
12	53 ± 12.0	47 ± 10.2	45 ± 8.5	53 ± 17.9	44 ± 18.1	45 ± 17.2
26	55 ± 9.3**	49 ± 11.2*	46 ± 7.7	52 ± 18.2	45 ± 17.5	46 ± 17.7
52	53 ± 10.0	46 ± 11.6	46 ± 10.2	53 ± 19.1	47 ± 19.4	47 ± 19.4

ABBREVIATIONS: R = Rest; SIHG = Sustained Isometric Handgrip; CPT = Cold Pressor Test.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 3.9 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PROPRANOLOL GROUP: REST.

	BASAL	2 (n = 11)	6	12	26	52 weeks
FET	17.8 ± 2.22	18.5 ± 2.07	18.0 ± 2.08	17.7 ± 2.19	17.2 ± 2.61	17.0 ± 2.08
dVs/dt	-4.4 ± 0.54	-4.7 ± 0.48	-4.6 ± 0.48	-4.8 ± 0.45**	-4.8 ± 0.48***	-4.8 ± 0.47**
FEL	34.7 ± 4.81	29.4 ± 4.20	31.1 ± 3.19**	29.5 ± 3.17	30.1 ± 3.46**	30.6 ± 3.04**
ST	40.2 ± 5.32	35.7 ± 3.61	36.6 ± 3.42*	35.1 ± 3.62***	34.9 ± 3.38***	34.8 ± 3.15***
SL	44.2 ± 6.14	35.6 ± 5.87**	37.8 ± 4.66***	36.7 ± 4.41***	39.7 ± 10.40	40.6 ± 10.38
FFT	62 ± 6.96	52.2 ± 7.57*	55.8 ± 4.22***	54.4 ± 4.62***	56.9 ± 9.48	57.6 ± 9.82
dVd/dt	3.6 ± 0.39	4.0 ± 0.56	3.7 ± 0.36	3.6 ± 0.59	3.7 ± 0.47	3.7 ± 0.50
FFL	33.7 ± 6.74	30.4 ± 3.42	30.3 ± 3.02	31.6 ± 3.56	31.1 ± 3.94	31.1 ± 3.76
EF	49.3 ± 10.70	51.2 ± 9.97	53.2 ± 12.16*	53.4 ± 12.03	55.5 ± 9.30**	53.2 ± 9.97

ABBREVIATIONS: As for Figure 3.3.

TABLE 3.10 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PROPRANOLOL GROUP: SIHG.

	BASAL	2 (n = 11)	6	12	26	52 weeks
FET	21.1 ± 7.03	18.9 ± 4.73	19.2 ± 5.39	17.8 ± 2.15	16.6 ± 1.54	17.1 ± 2.47
dVs/dt	-3.7 ± 0.76	-4.1 ± 0.34**	-4.1 ± 0.64**	-4.2 ± 0.57**	-4.4 ± 0.52***	-4.4 ± 0.52***
FEL	43.4 ± 7.54	36.4 ± 4.97**	38.0 ± 8.11**	35.6 ± 4.00***	35.5 ± 4.91***	36.3 ± 5.15***
ST	47.0 ± 5.96	42.0 ± 4.49**	42.8 ± 7.43*	40.4 ± 4.17***	40.2 ± 4.78***	41.0 ± 4.27***
SL	51.8 ± 8.53	41.7 ± 5.44*	43.2 ± 5.23***	41.8 ± 3.76***	42.8 ± 3.85***	44.3 ± 4.27**
FFT	72.9 ± 10.35	59.9 ± 3.91***	62.4 ± 7.36***	59.6 ± 3.52***	59.4 ± 3.48***	61.4 ± 5.93***
dVd/dt	3.4 ± 0.69	3.9 ± 0.37	3.7 ± 0.49	3.6 ± 0.55	3.6 ± 0.51	3.6 ± 0.58
FFL	40.6 ± 7.78	28.1 ± 2.84**	29.5 ± 4.95***	30.0 ± 6.20***	29.2 ± 3.41***	31.7 ± 8.31**
EF	45.6 ± 9.25	43.7 ± 7.43	47.2 ± 11.23	47.2 ± 10.18	49.2 ± 11.17*	46.3 ± 11.57

ABBREVIATIONS: As for Figure 3.3.

TABLE 3.11 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PROPRANOLOL GROUP: COLD PRESSOR TEST.

	BASAL	2 (n = 11)	6	12	26	52 weeks
FET	19.9 ± 6.16	20.9 ± 7.15	19.6 ± 6.28	17.7 ± 2.38	19.0 ± 6.99	16.4 ± 2.24
dVs/dt	-4.0 ± 0.61	-4.1 ± 0.48	-4.3 ± 0.48*	-4.3 ± 0.60*	-4.4 ± 0.62*	-4.4 ± 0.72*
FEL	39.3 ± 7.64	35.0 ± 3.41	33.9 ± 4.68*	33.7 ± 3.93**	36.2 ± 8.52	35.9 ± 6.24
ST	45.5 ± 6.79	42.5 ± 8.73	40.1 ± 5.04**	38.8 ± 4.45***	40.6 ± 7.67*	40.4 ± 5.34**
SL	51.5 ± 11.38	39.6 ± 4.30**	41.2 ± 9.09***	40.8 ± 3.53***	41.3 ± 4.70***	44.2 ± 7.76*
FFT	71.4 ± 11.42	60.5 ± 8.45	60.8 ± 8.84***	58.5 ± 4.43***	60.1 ± 6.62**	60.4 ± 7.00**
dVd/dt	3.5 ± 0.56	4.1 ± 0.48*	3.7 ± 0.45	3.7 ± 0.58	3.8 ± 0.52	3.8 ± 0.62
FFL	36.7 ± 9.76	28.6 ± 2.58	31.0 ± 7.73**	30.2 ± 2.72*	29.7 ± 4.01**	29.8 ± 4.86**
EF	43.8 ± 9.10	43.6 ± 7.00	45.3 ± 9.13	45.1 ± 8.50	46.1 ± 7.66	45.6 ± 10.23

ABBREVIATIONS: As for Figure 3.3.

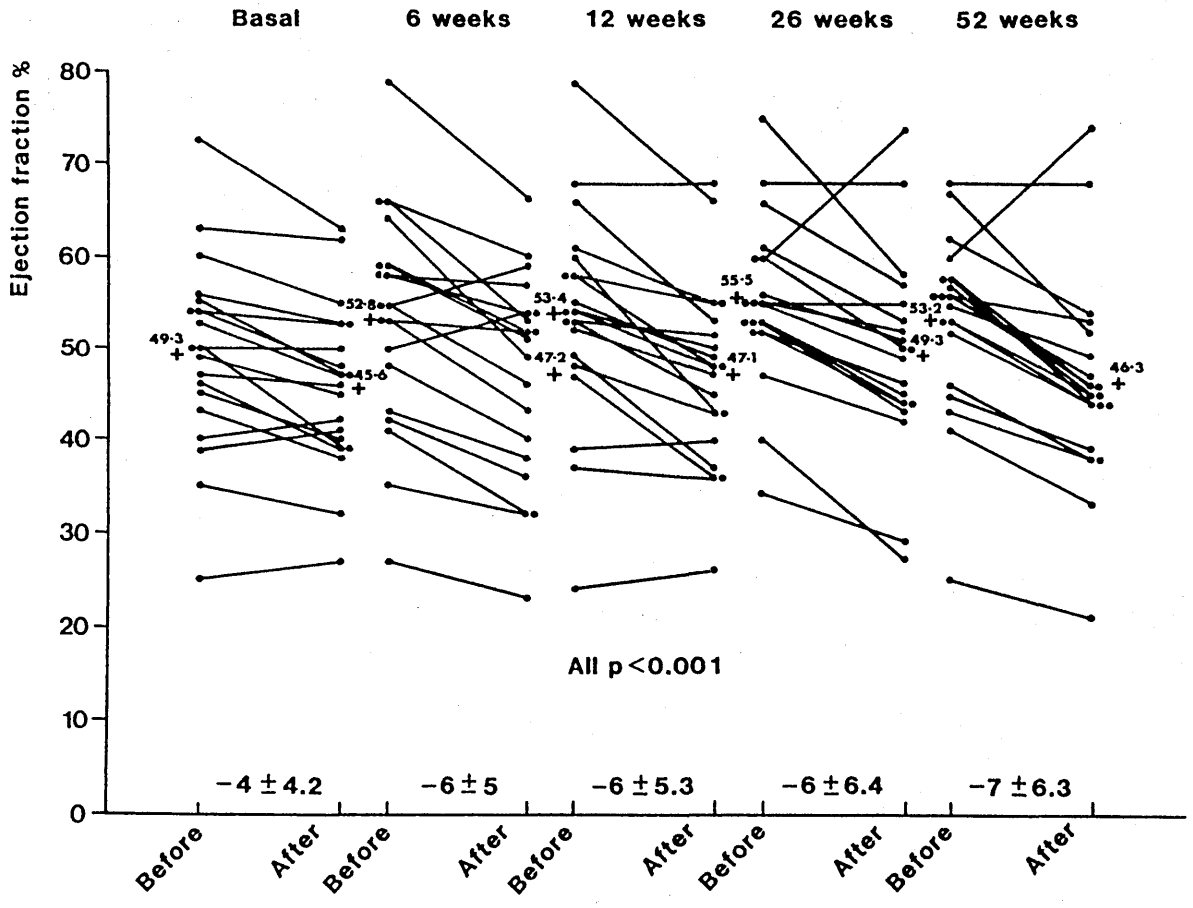


FIGURE 3.8

Group and individual ejection fraction responses to isometric handgrip at intervals during treatment with propranolol. Mean individual reduction indicated at the foot of each scatter plot.

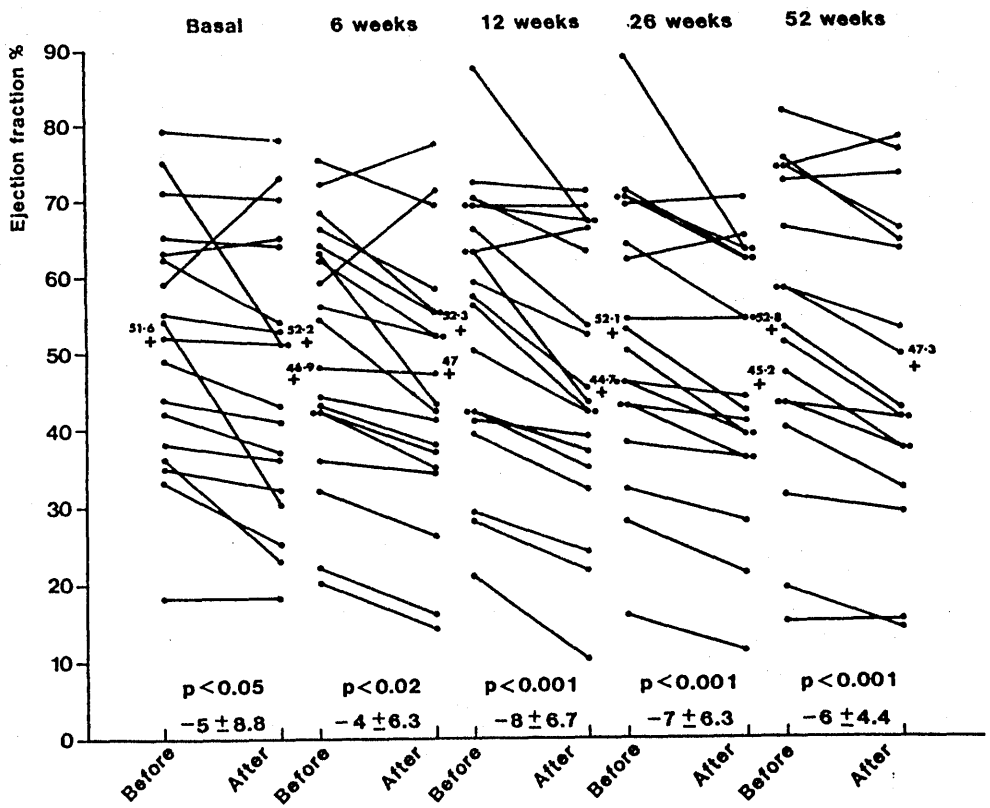


FIGURE 3.9

Group and individual ejection fraction responses to isometric handgrip at intervals during treatment with pindolol. Mean individual reduction indicated at the foot of each scatter plot.

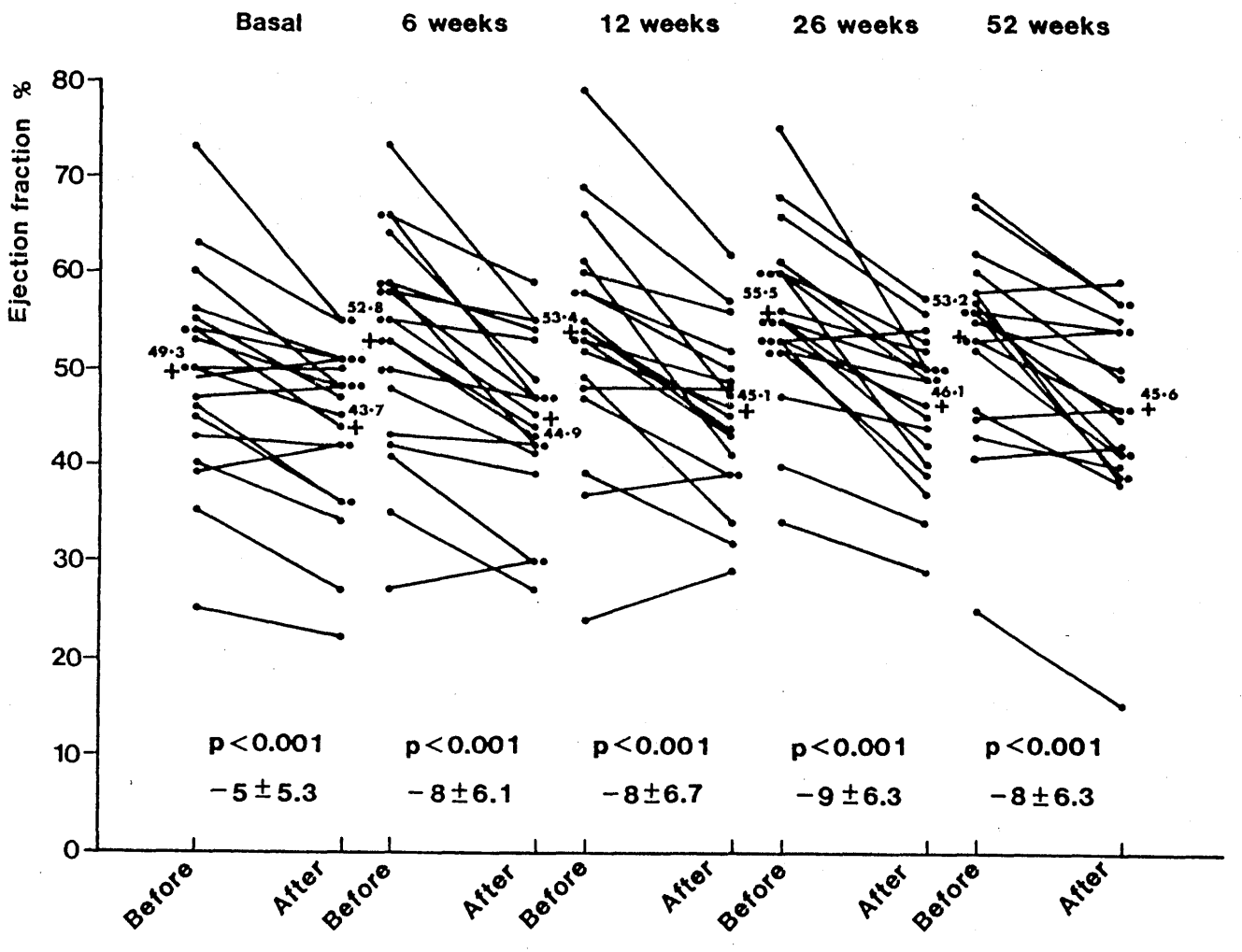


FIGURE 3.10

Group and individual ejection fraction responses to cold pressor testing at intervals during treatment with propranolol. Mean individual reduction indicated at the foot of each scatter plot.

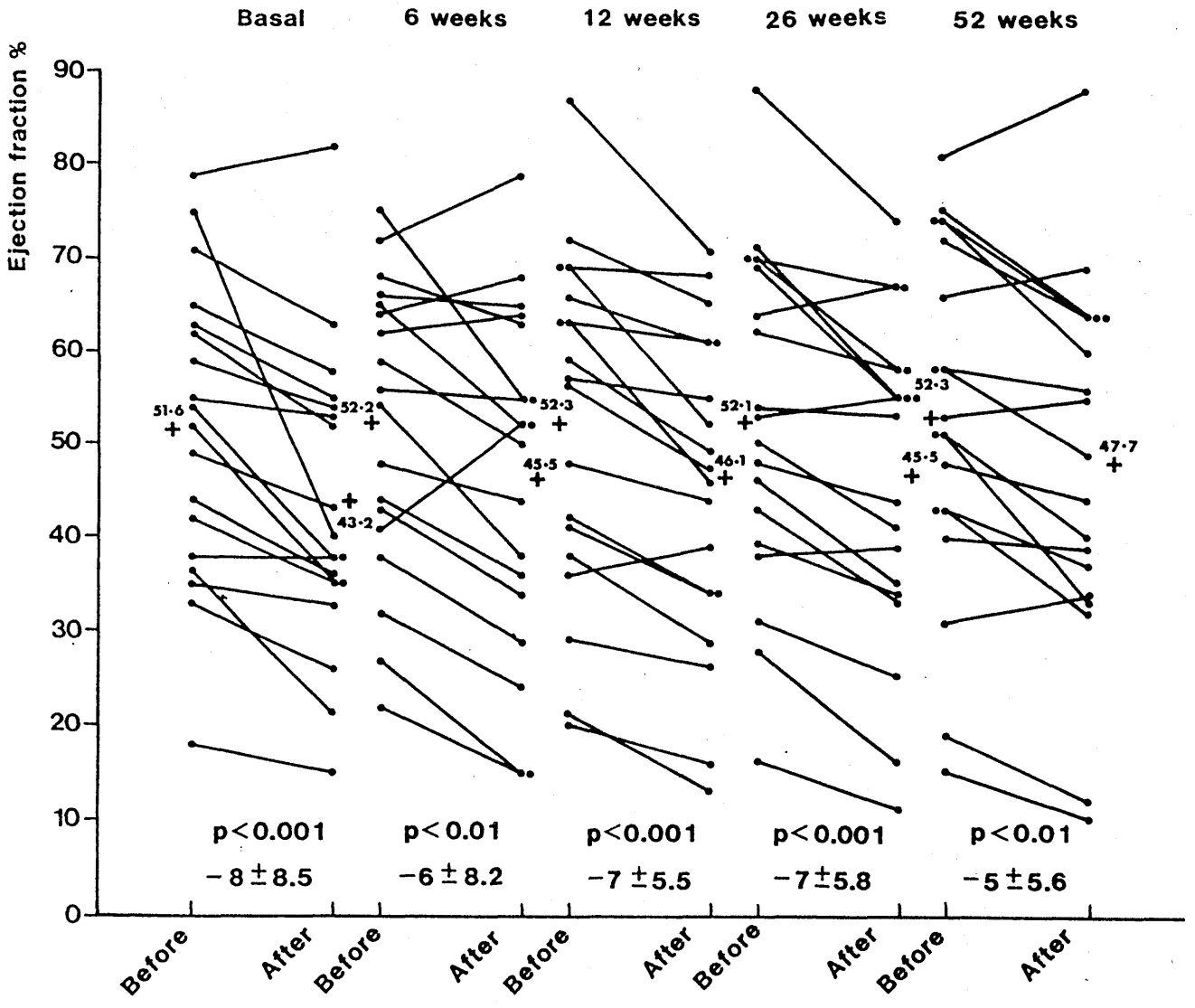


FIGURE 3.11

Group and individual ejection fraction responses to cold pressor testing at intervals during treatment with pindolol. Mean individual reduction indicated at foot of each scatter plot.

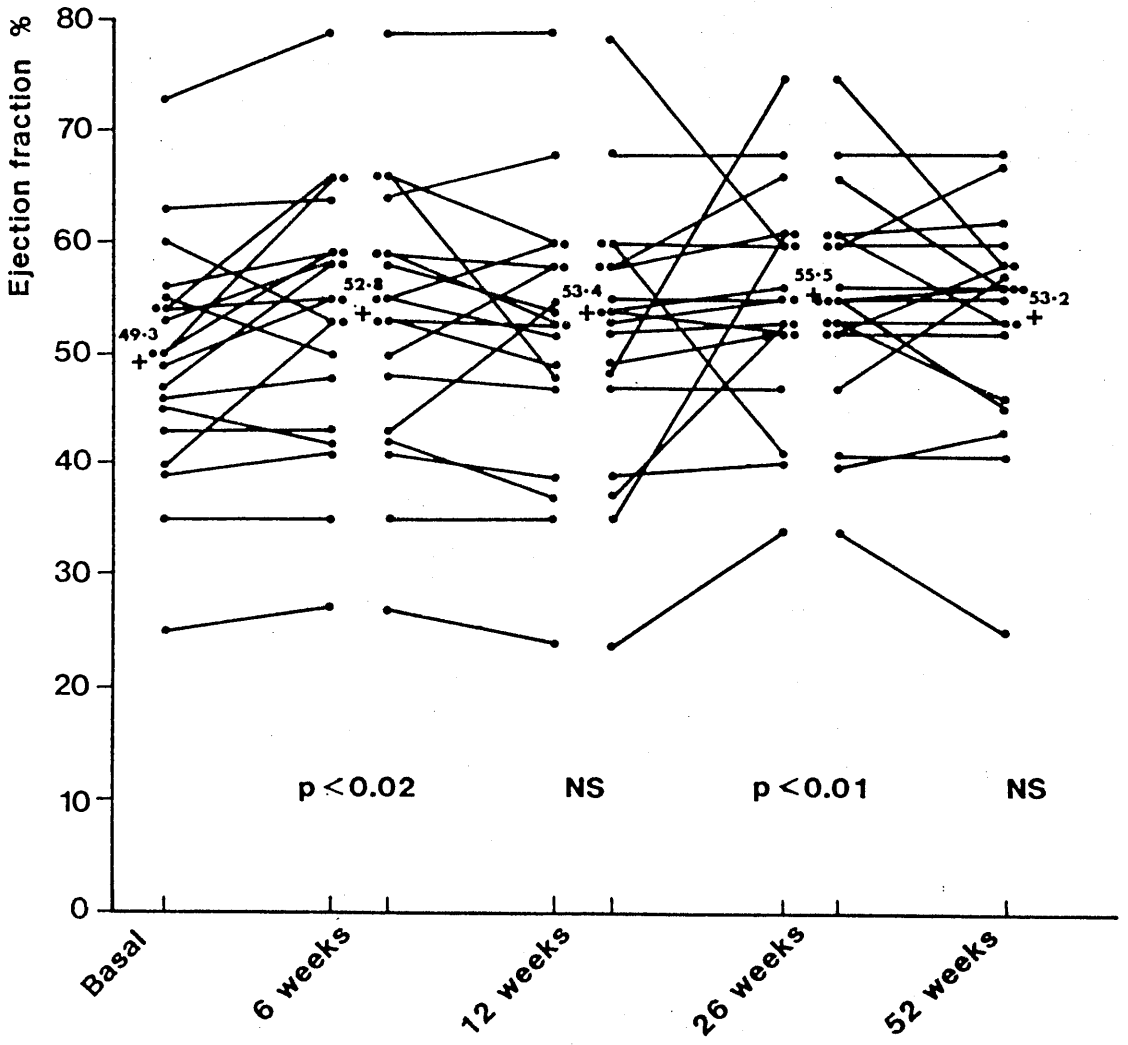


FIGURE 3.12

Group and individual resting ejection fraction responses to one years treatment with propranolol. Statistical comparisons made with basal values.

NS = Not significant.

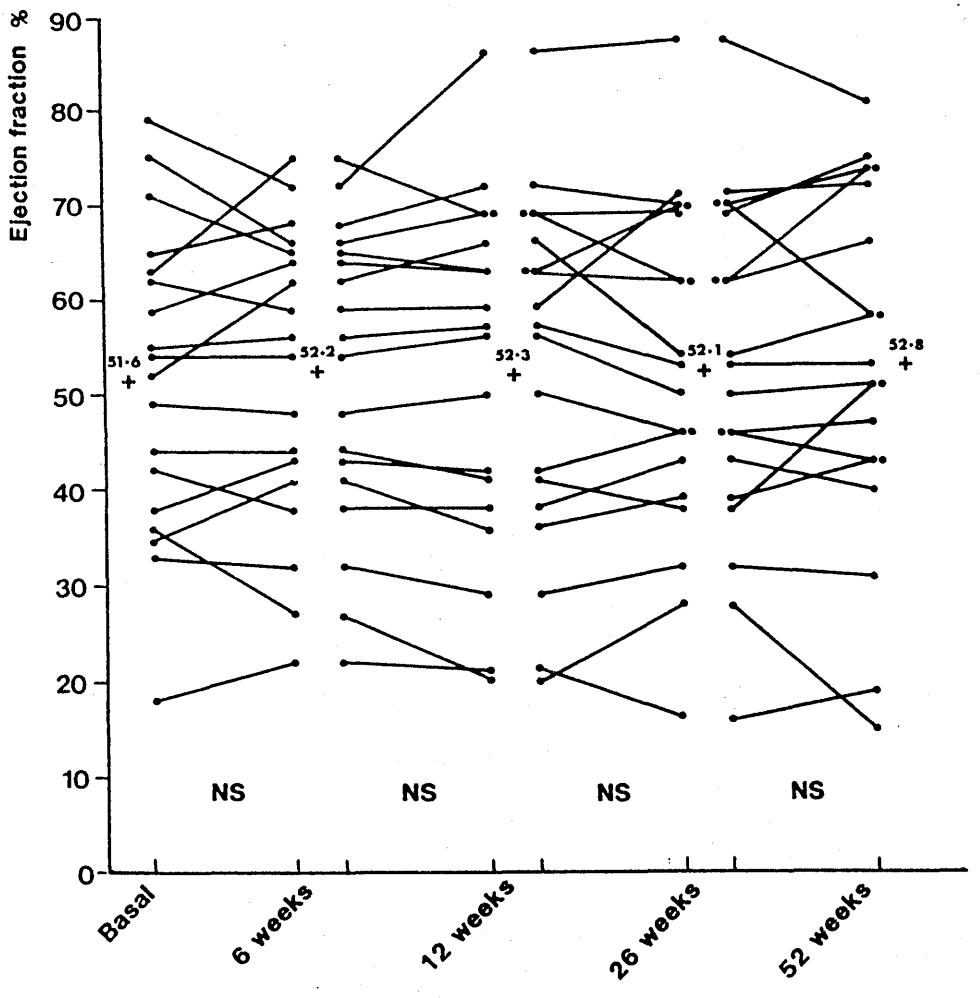


FIGURE 3.13

Group and individual resting ejection fraction responses to one years treatment with pindolol.

NS = No significant difference from basal value.

filling in diastole (dVd/dt) at rest. this increased significantly during SIHG and CPT. These results are shown in Tables 3.8-311.

In those taking pindolol there was no significant change in dVs/dt at rest or during CPT although this increased during SIHG at each stage of investigation. The maximal rate of diastolic filling (dVd/dt) fell at rest throughout the study, but did not change significantly during SIHG or CPT. (Refer to Tables 3.12-3.14 for details). At rest (Table 3.12), there were small reductions in FEL, ST, SL, and FFT up until 26 weeks after the start of therapy, but small rises occurred in SL and FFT at 52 weeks, in contrast to the sustained fall in these indices experienced during treatment with propranolol. Fast filling length (FFL) increased at all staged throughout treatment. During SIHG all of these parameters fell (Table 3.13) although this was not as marked as occurred during treatment with propranolol (Table 3.10). During CPT, however, small increases were observed in FEL, ST, SL, FFT and FFL (Table 3.14), which is in contrast to the findings during CPT in the propranolol group (Table 3.11).

In order to demonstrate any differential effect of these beta blockers on those with normal or near normal left ventricular EF or those with moderately subnormal EF, patients were subdivided into groups according to a basal resting EF of above or below 50%. This resulted in 10 patients with an ejection fraction below 50% in the propranolol

TABLE 3.12 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PINDOLOL GROUP: REST.

	BASAL	2 (n = 10)	6	12	26	52 weeks
FET	16.9 ± 1.55	17.2 ± 0.79	17.1 ± 1.23	17.3 ± 1.60	17.1 ± 1.16	17.4 ± 2.06
dVs/dt	-4.6 ± 0.52	-4.6 ± 0.23	-4.78 ± 0.27	-4.6 ± 0.37	-4.7 ± 0.33	-4.6 ± 0.45
FEL	33.1 ± 4.66	32.9 ± 3.07	30.6 ± 2.23*	33.8 ± 3.07	32.3 ± 4.50	32.0 ± 3.65
ST	38.2 ± 3.94	38.1 ± 2.77	36.1 ± 2.13*	38.7 ± 2.89	37.6 ± 3.97	37.2 ± 3.34
SL	44.1 ± 8.86	42.0 ± 4.42	41.9 ± 3.89	42.3 ± 4.19	43.0 ± 4.97	44.9 ± 9.17
FFT	61.0 ± 8.25	59.2 ± 3.94	59.0 ± 3.68	59.6 ± 3.84	60.1 ± 4.29	61.9 ± 8.54
dVd/dt	3.6 ± 0.59	3.8 ± 0.63	3.2 ± 0.60*	3.5 ± 0.49	3.3 ± 0.53**	3.2 ± 0.49*
FFL	32.6 ± 7.22	33.2 ± 7.02	36.2 ± 8.55	32.9 ± 7.80	35 ± 8.73	33.8 ± 9.12
EF	51.7 ± 16.26	59.9 ± 16.83	51.6 ± 16.56	52.6 ± 17.93	52.2 ± 18.21	52.8 ± 19.13

ABBREVIATIONS: As for Figure 3.3.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 3.13 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PINDOLOL GROUP: SIHG.

	BASAL	2 (n = 10)	6	12	26	52 weeks
FET	19.0 ± 4.27	18.6 ± 3.76	18.6 ± 3.50	19.2 ± 3.35	18.5 ± 3.43	19.6 ± 7.29
dVs/dt	-3.8 ± 0.54	-3.9 ± 0.55	-4.2 ± 0.58	-4.06 ± 0.40	-4.2 ± 0.56**	-4.3 ± 0.60*
FEL	40.6 ± 5.42	39.1 ± 6.95	35.8 ± 5.73*	38.3 ± 4.45	37.5 ± 5.51*	37.9 ± 7.70
ST	44.9 ± 4.21	44.2 ± 4.85	41.9 ± 5.66*	44.8 ± 4.94	42.8 ± 5.87	43.1 ± 5.71
SL	51.3 ± 9.72	50.5 ± 11.15	49.6 ± 8.56	48.3 ± 7.00	49.2 ± 9.84	48.8 ± 10.90
FFT	71.4 ± 10.95	68.3 ± 10.49	68.3 ± 9.87	67.5 ± 8.15	67.7 ± 10.01	68.4 ± 12.45
dVd/dt	3.4 ± 0.63	3.4 ± 0.46	3.4 ± 0.55	3.3 ± 0.58	3.3 ± 0.71	3.4 ± 0.78
FFL	39.3 ± 11.48	37 ± 8.74	39.2 ± 10.54	35.5 ± 10.35	37.7 ± 9.89	35.6 ± 9.11
EF	46.9 ± 18.12	50.5 ± 17.10	47.3 ± 18.43	44.4 ± 18.11	45.2 ± 17.54	47.3 ± 19.40

ABBREVIATIONS: As for Figure 3.3.

TABLE 3.14 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN PINDOLOL GROUP: COLD PRESSOR TEST

	BASAL	2 (n = 10)	6	12	26	52 weeks
FET	18.2 ± 2.55	18.7 ± 5.31	18.6 ± 4.06	17.6 ± 2.01	17.7 ± 2.80	21 ± 11.71
dVs/dt	-4.2 ± 0.39	-4.1 ± 0.71	-4.4 ± 0.42	-4.1 ± 0.46	-4.2 ± 0.47	-4.2 ± 0.81
FEL	37.2 ± 3.98	39.7 ± 10.25	35.1 ± 5.95	38.1 ± 5.96	38.2 ± 6.47	39.1 ± 10.21
ST	42.6 ± 3.60	45.6 ± 7.71	41.2 ± 4.89	42.9 ± 4.86	42.3 ± 5.26	43.1 ± 8.92
SL	47.1 ± 6.07	48.5 ± 11.62	48.2 ± 9.74	50.2 ± 11.85	47.5 ± 9.66	46.1 ± 11.71
FFT	65.2 ± 7.02	67.2 ± 11.61	66.8 ± 10.50	67.7 ± 11.33	65.2 ± 9.65	67.1 ± 10.79
dVd/dt	3.4 ± 0.55	3.8 ± 0.64	3.3 ± 0.56	3.4 ± 0.63	3.3 ± 0.73	3.4 ± 0.88
FFL	34.1 ± 9.36	33.0 ± 7.94	38.6 ± 11.23*	36.0 ± 9.20	38.4 ± 12.57	36.6 ± 12.44
EF	43.2 ± 16.2	46.2 ± 16.60	44.7 ± 17.88	45 ± 17.23	45.6 ± 17.69	47.4 ± 19.38

ABBREVIATIONS: As for Figure 3.3.

group and 8 in the pindolol group and 9 with an EF ⩾ 50% in those taking propranolol and 10 in those taking pindolol (Table 3.15).

In those with subnormal EFs, the resting EF improved significantly throughout treatment with propranolol rising from a basal value of 39 ± 10.5 to 51 ± 8.5 at 26 weeks (Table 3.15). No significant change was noted during treatment with pindolol. In these groups, small increases in EF during SIHG and CPT were observed in the propranolol group, but small falls occurred in the pindolol group.

In those with a basal resting EF ⩾ 50%, small increases in resting EF occurred at rest in both the propranolol and pindolol groups. During SIHG, no significant changes occurred in EF or between the different treatment groups. During CPT, no change in response occurred in those taking propranolol, but there was an increase in EF in those taking pindolol, although there was no significant change in the fall in EF from rest to CPT between the groups taking propranolol and pindolol. These results are summarised in Table 3.15.

TABLE 3.15 EJECTION FRACTION RESPONSE TO PINDOLOL AND PROPRANOLOL BASED ON INITIAL RESTING EF OF GREATER THAN OR LESS THAN 50%.

	Propranolol Group			Pindolol Group		
	< 50% (n=10)			< 50% (n=8)		
	R	SIHG	CPT	R	SIHG	CPT
BASAL	39.3 ± 10.51	38.8 ± 6.04	38.3 ± 9.13	36.8 ± 9.26	31.9 ± 9.01	30.9 ± 9.40
6	46.8 ±* 11.56	39.7 ± 9.69	40.4 ± 8.11	36.0 ± 10.40	31.2 ± 11.83	31.2 ± 12.97
12	49.6 ±* 12.91	42.3 ± 8.06	41 ± 7.57	35.6 ± 9.24	28.6 ± 11.61	29.4 ± 10.74
26	51.3 ±** 8.51	43.3 ± 10.98	43.5 ± 8.64	36.0 ± 10.29	30.0 ± 11.79	29.6 ± 11.39
52	49.9 ±* 11.61	42.2 ± 7.37	42.1 ± 11.55	36.1 ± 13.17	30.9 ± 10.97	31.4 ± 13.22
	⩾ 50% (n=9)			⩾ 50% (n=10)		
	R	SIHG	CPT	R	SIHG	CPT
BASAL	57.6 ± 6.94	53.1 ± 6.03	49.9 ± 3.62	63.5 ± 9.12	60.8 ± 12.37	53 ± 13.70
6	60.3 ± 8.60	56.3 ± 5.34	50.7 ± 7.16	64.1 ± 6.66	60.1 ± 11.04	57 ± 11.98
12	57.7 ± 9.99	51.7 ± 10.14	49.1 ± 7.93	66.1 ± 9.08	57.5 ± 11.66	57.5 ± 8.97
26	60.2 ± 8.12	55.4 ± 10.42	49.0 ± 5.48	64.4 ± 11.08	57.4 ± 10.11	58.3 ± 9.18
52	56.9 ± 6.55	52.4 ± 11.29	49.4 ± 7.30	66.2 ± 10.50	60.4 ± 13.66	60.9 ±* 12.77

ABBREVIATIONS: < = Less than.

⩾ = Greater than or equal to.

R = Rest.

SIHG = Sustained Isometric Handgrip.

CPT = Cold Pressor Test.

Results are expressed as mean ± S.D.

* $p < 0.05$; ** $p < 0.001$.

Discussion.

In keeping with other studies, the present study demonstrated that both propranolol and pindolol have similar antianginal efficacy. (9,60,66) Few studies have assessed the influence of ISA on left ventricular function, in patients with ischaemic heart disease. (50,60,187) Frishman et al (58) using M-mode echocardiography found that pindolol increased the EF, but propranolol caused a decrease. That study can be faulted on the grounds of the technique used for assessing LV performance which has accepted limitations (188,189), and also because the doses of propranolol (up to 40 mg. q.i.d.) and pindolol (up to 10 mg. q.i.d.) may not have exerted equivalent beta blocking activity. Two studies have assessed the influence of ISA on LV function using RNV. (60,187) Using equipotent doses of propranolol and pindolol Manyari et al (60) in a short-term study failed to find any difference between the drugs in 23 patients with CAD and normal or near normal resting EF. Kaul et al (187) using acebutalol and propranolol also over a short period of treatment (5 days) found that both drugs improved exercise EF, but exerted approximately similar effects.

In the present study, pindolol was used as the prototype of a beta blocker with ISA, as it is recognised as having the most potent ISA of commercially available beta blockers. The doses of propranolol and pindolol were at levels that previously have been accepted to produce effective and equipotent beta blockade and are the

most commonly used in clinical practice. The patients allocated to each treatment group were similar in terms of severity of angina pectoris, age, resting heart rate, blood pressure and left ventricular EF. All the radionuclide studies were analysed blindly using a semiautomatic analysis protocol at the end of the study, thus removing any observer error or bias from the results. In addition all patients recruited to the study were either previously untreated or had their medication, (always a nitrate or beta-blocker), gradually withdrawn over a two week period, a further two week period off all medication except sublingual glyceryl trinitrate before baseline evaluation. Thus, rebound phenomenon were unlikely to have occurred.

Multiple gated equilibrium nuclear angiography, used in this study, is a non-invasive technique which has been shown to reliably assess left ventricular function (190,191), and provides a useful method for evaluating the effect of pharmacological interventions. (60-62)

Heart Rate and Blood Pressure.

Resting heart rate was significantly reduced, throughout the study by propranolol, but not by pindolol, as one may expect. Both drugs, however, lowered systolic and diastolic blood presure, but this was less marked in the pindolol group. During cold pressor stimulation and SIHG, both groups showed highly significant increases in heart rate and blood pressue. This effect was inhibited

by both beta blockers, with propranolol causing a significantly greater attenuation of heart rate during both interventions.

Cold Pressor Test and Sustained Isometric Handgrip.

Both these interventions were well tolerated. Cold pressor stimulation precipitated angina pectoris in only two subjects, in one case this was severe enough to warrant admission to the Coronary Care Unit. This undesired effect may be due to the induction of coronary vasoconstriction mediated by alpha adrenergic receptors. (192,193) One case of transient complete coronary occlusion has been reported with this technique in a male with variant angina (194), and in one case acute myocardial infarction occurred (195), indicating that individuals with CAD and a tendency to vasoconstriction may be at increased risk when exposed to cold.

Both beta blockers attenuated the rise in blood pressure experienced with CPT to a similar extent. Houben et al in a short-term study using normal volunteers (196), found that propranolol and metoprolol did not inhibit the rise in blood pressure with CPT. It is possible that established beta blockade is necessary for such attenuation to occur. It might be expected that a pure beta blocker will cause an augmentation of the CPT induced increase in blood pressure, as a result of unopposed alpha agonistic activity causing vasoconstriction. However, other mechanisms must be operative

to result in the attenuation observed in this study.

Sustained isometric handgrip was found to be well tolerated and easy to perform and maintain. Only two patients developed an increased frequency of VEBs. Like CPT an attenuation of HR and BP response occurred following both beta blockers, but this was most marked with propranolol.

For the purposes of this thesis, both interventions have been assessed with regard to heart rate, blood pressure and EF responses in normals and subjects with CAD. Their usefulness for detection of CAD and their reproducibility have also been evaluated, and the findings are discussed in the following section.

Radionuclide Ventriculography.

In our laboratory the spontaneous variability of EF measurements is 5.0%, which is comparable to other centres (171,197), and the use of an automatic analysis protocol minimises observer error. Pindolol had no effect on resting EF or that recorded during SIHG, although there were small increases in response to CPT at each study interval. Propranolol, on the other hand, caused significant increases in resting EF at 6 and 26 weeks, and a small increase in EF during SIHG, but no significant change during CPT, perhaps due to the increased LV afterload secondary to unopposed alpha adrenergic vasoconstriction.

Global EF is the most useful single parameter of ventricular function. But, it depends on variables other than intrinsic myocardial contractility and may be influenced by changes in HR, preload or afterload. Thus, if propranolol decreases HR and BP, the negative effects on LV performance may be masked. Other indices of LV performance such as the maximum rate of LV emptying (dVs/dt) and filling (dVd/dt) have been proposed as a sensitive index to pharmacological changes in inotropic state. (198,199)

Propranolol increased dVs/dt both at rest and during CPT and SIHG throughout the study while pindolol only increased dVs/dt during SIHG. Diastolic function, expressed in terms of dVd/dt did not change at rest in those taking propranolol, but improved during both CPT and SIHG, whereas in those taking pindolol, there was a fall in dVd/dt at rest throughout the study, and no change during CPT or SIHG. Other indices of systolic function (FEL, SL) and diastolic function (FFT, FFL) all improved throughout the study in those taking propranolol. The effect on these variables in those taking pindolol was less consistent with small rises in SL and FFT observed after 52 weeks and FFL increasing at all stages throughout therapy. The response during SIHG was more favourable, but not as marked as those noted during propranolol and the changes noted during CPT were also less favourable. Thus, both global EF responses and other indices of LV systolic and diastolic performance appear to be enhanced

during treatment with propranolol, but either unchanged or worsened during treatment with pindolol. By subdividing the patients into those with normal or near normal EFs and those with subnormal EFs, it was possible to assess any benefit of ISA in those with subnormal LV performance in whom any beneficial effect would be more important. (58,200) Propranolol was shown to increase resting EF by a highly significant margin at rest, while no benefit was shown with pindolol and small increases in EF occurred during SIHG and CPT in the propranolol group, but small reductions occurred with pindolol. Thus, even in those with subnormal LV function, propranolol had significant and consistent advantages at rest, and during CPT and SIHG, over pindolol. However, these results do not disprove the potential value of ISA in patients with severely compromised LV function as this group of patients was not studied.

The changes in ejection fraction found with both drugs (with the exception of those on propranolol at 26 weeks), were within the spontaneous variability of EF found in our department. However, the author feels that this may be partially offset by the fact that this was a controlled study, two-way analysis of variance was used to establish significance and the variability of the technique was calculated using the results from normal volunteers who are known to have greater variability of LV performance.

In those with subnormal basal EF (<50%), however, the rise in EF observed in the propranolol group at rest

was well in excess of that which could be explained by spontaneous variability.

Previous Studies.

Previous studies reporting the effects of intravenous and oral beta blockers on LV function have not shown uniform results. The effect of long-term oral beta blockade, or the influence of ISA has not been reported.

Intravenous Administration.

Svendson et al (46), examined the acute effects of equipotent doses of propranolol, atenolol, practolol and pindolol on cardiac output, heart rate and blood pressure at rest only. Propranolol reduced cardiac output by 26-28% and heart rate 15-17%. Practolol (weak ISA) caused cardiac output to fall by 12-17% and heart rate by 7-10%, but with pindolol (potent ISA) no change occurred in cardiac output or heart rate. Taylor et al (201) investigated the acute haemodynamic effects of propranolol in twelve patients with CAD, and found depressed LV function. Similarly from the same centre Silke et al (202,203) investigated the haemo-dynamid effects of propranolol and pindolol in a randomised study of patients with CAD at rest and during exercise and found that propranolol caused a reduction in cardiac output and reduction in heart rate while

pindolol did not affect these parameters at rest. During exercise the fall in cardiac output observed in the propranolol group was attenuated by pindolol. In addition to cardiac output, studies of the effect of intravenous propranolol on the maximum rate of change in ventricular systolic pressure (dP/dt) have shown significant reductions. (204,205)

Thus, acute, intravenous studies consistently demonstrate an impairment of LV performance after the administration of pure beta blockers with some protection against this being proferred by those with ISA. The effects of oral administration may differ, however.

Oral Administration.

Frishman et al (58), using M-mode echocardiography found that resting EF was increased after administration of pindolol, but fell with propranolol. This study had several shortcomings already discussed (page 123). Tarazi and Dustan (167) showed that chronic oral administration of propranolol resulted in depressed HR and cardiac output. However, Guazzi et al (168) reported an improved cardiac output in some patients who had been treated with propranolol for months or years.

Of particular relevance to the present study are a number of investigations which have reported this effect of beta blockers on RNV derived LV function.

The first of these was carried out by Marshall et al. (61) This was performed in 22 subjects with CAD who were given a mean of 165 $\pm$ 13 mg. propranolol per day. First pass RNV was used to determine resting EF and LV ejection rate. No exercise evaluations were performed. Although the group were described as having chronic stable angina pectoris, two patients had angina at rest (NYHA Class IV), four subjects had a history of congestive cardiac failure and were taking digoxin or diuretics and an additional seven were receiving anti-arrhythmic drugs. No change in EF or ejection rate was found, but these results must be interpreted with caution as this was an uncontrolled study, the dosage of beta blocker was not standardised and several participants were taking concomitant medication. In addition it is not clear how long after base line evaluation, the second RNV evaluation was performed.

Another study assessing the effect of propranolol on LV function (62), using multiple gated radionuclide angiography in 10 subjects with CAD taking 120-400 mg. of propranolol per day, this time assessed the effect of long-term treatment on rest and exercise LV function.

They found that propranolol caused a significant fall in EF at rest, but EF improved in every patient by a mean of 22% during exercise ($p < 0.001$). However, this study was also uncontrolled, utilised a wide range of dosage regimens and was complicated by the fact that five participants were also taking long-acting nitrates. Again, using first pass RNV, Port et al (206) examined the effect of two days treatment with propranolol in 12 normal young men, finding EF and cardiac output reduced at rest and during exercise after propranolol. Using long-term treatment Manyari et al (60) in a controlled cross-over study involving equipotent standard doses of propranolol and pindolol, failed to demonstrate any benefit of ISA on LV function. This study involved 23 patients with an age range similar to that in the present study, with normal or near normal pretreatment LV function. Although resting EF was unchanged by both drugs 4-6 weeks after treatment, there were small improvements during exercise, but no difference between the drugs could be discerned. More recently, Kaul et al (187), assessed the difference between five days administration of acebutalol (moderate ISA) and propranolol on LV function using gated radionuclide ventriculography. Acebutalol caused an exercise induced increase in EF, whereas this was not marked with propranolol. However, they do conclude that propranolol and acebutolol are equivalent in influence on LV function. Another recent study, (207) examined the effects of two weeks treatment with timolol and propranolol on first pass RNV. The results with both drugs were combined and showed that the EF was unchanged at rest, but increased significantly

during exercise.

Thus, the findings of intravenous and oral studies differ considerably with the exception of Manyari et al (60), who assessed LV function 4-6 weeks after commencement of beta blockade, no study has adequatly evaluated the chronic effects of beta blockade on LV performance. Until the present study, the cummulative effect of chronic administration of propranolol was not known and the influence of ISA was in doubt. I have demonstrated an advantage of propranolol over pindolol on LV performance in patients with chronic stable angina. It is doubtful whether ISA has any beneficial effect, on LV function, even with pre-treatment impairment, over pure beta blockade in chronic administration although acute studies suggest a possible benefit. The results of the present study do not disprove the potential value of ISA in those with severe LV dysfunction, as this group was not a subject of this investigation.

Beta Blockade and LV function: Possible Mechanisms.

In acute studies it has been postulated that beta blockers with ISA will result in less depression of heart rate and left ventricular contractility compared with a pure beta blocker, by a number of mechanisms:

1. Direct stimulation of B_1 receptors.

2. By stimulation of pre-synaptic B_2 receptors by which the further release of noradrenaline from the terminal sympathetic neurone is enhanced.

3. By stimulation of non-inervated B_2 adrenoceptors in peripheral arteriolar resistance vessels, thereby countering the full blockade of these receptors and indirectly opposing reflex $alpha_1$ adrenoceptor vasoconstriction as a consequence of diminished LV pumping function.

4. By enhancing renin released and subsequent activation of angiotensin which directly augments the sympathetic outflow from the vasomotor centre of the central nervous system.

These mechanisms may be the major reasons for the apparent benefits of ISA observed in acute, intravenous administration of pindolol, but do not explain the lack

of influence found by Manyari (60), or the advantage of a pure beta blocker in this study.

All beta blockers reduce myocardial oxygen demand by reducing HR and BP at rest and during exercise. Thereby, the blood flow to ischaemic areas is increased as the fall in heart rate, causes an increase in diastolic filling time and improved perfusion of the coronary vasculature. This latter factor may be responsible for the benefits for pure beta blockade found in this study. Heart rate, both at rest and during CPT and SIHG was reduced to a greater extent with propranolol while changes in systolic BP were similar. This implies a reduction in the double product, which is an accepted determinant of myocardial oxygen consumption. (208,209) However, pure beta blockers may also be expected to cause peripheral vasoconstriction by blockade of vasodilator B_2 receptors in the peripheral circulation, thereby increasing systemic vascular resistance which may further impair the ischaemic left ventricle. In addition, propranolol has been reported to induce an increase in coronary artery tone. (210-212) These latter effects may cause impairment on LV performance.

It is likely that the resultant effect of a beta blocker, whether with or without ISA, on LV performance will be a balance between the above effects. In the patients involved in this study it is probable that the reduction in double product and hence myocardial oxygen

consumption was the dominant influence, making the effect of ISA less disernible.

3.5. CONCLUSIONS.

Previous studies of pure beta blockade on left ventricular performance have not shown uniform results. Many, report intravenous administration and have usually found a negative inotropic effect in terms of cardiac output, stroke volume, dP/dt and ejection rate. Some studies failed to find any impairment in LV performance Of the studies examining the effect of oral administration, most have been acute and have usually found no change in parameters of LV function. The significance of ISA in this respect has until now been in some doubt, with several acute intravenous studies involving pindolol suggesting a benefit over pure beta blockers, but longer studies involving oral administration finding no difference between pure beta blockers and those with ISA. This study examined the long-term effect of propranolol and pindolol in patients with chronic angina pectoris and failed to demonstrate any advantage of ISA in LV function - showing instead an improvement in LV function indices during treatment with propranolol, both at rest and during SIHG and CPT.

The differences between this study and others may relate to the different dosage regimes and pretreatment characteristics. In the present study the groups were evenly matched in terms of age, resting heart rate, BP, EF and severity of angina pectoris. The dosage regimes of pindolol and propranolol were those most commonly used in clinical practise and are accepted to result in equivalent

beta blocking effect. In addition, the patients were treated exclusively with a beta blocker and sublingual trinitrate, no other medication being allowed.

It is concluded that ISA is an unhelpful property in terms of LV function during chronic therapy for stable angina pectoris.

SECTION 4.

VALIDATION OF METHODOLOGY

4.1. Repeatability of Radionuclide ventriculography and the effect of Cold Pressor Stress and Sustained Isometric Handgrip Exercise on heart rate, blood pressure and left ventricular function in patients with coronary artery disease and a control group.

4.2. Assessment of Hitachi HME-20 Pulse and Blood Pressure Monitor.

4.1. INTRODUCTION

During assessment of myocardial peformance using various techniques it has become apparent that stressing the heart may uncover latent abnormalities. This is especially true in patients with chronic stable angina who may have normal ventricular function at rest, but when stressed, may develop abnormalities, as the myocardial oxygen supply - demand equilibrium has been upset. Several interventions have been contrived to stress the heart during radionuclide ventriculography (RNV). These have included the administration of drugs such as angiotensin (213,214) and phenylephrine (215), to increase left ventricular afterload, and the provocation of myocardial ischaemia by atrial pacing. (216,217) Both the cold pressor test (CPT) (176,218) and sustained isometric handgrip exercise (SIHG) (219,220) have become popular as safe, simple interventions of particular use during RNV. These methods have been employed in preferance to dynamic exercise because movement artefact is reduced, and because both tests can be applied to virtually every patient, unlike dynamic exercise which demands a high degree of patient co-operation and may be more likely to precipitate symptoms in patients with ischaemic heart disease, when compared to CPT and SIHG, and may result in cancellation of the study. Even when the patient is immobilised in a large polystyrene bead bag with subsequent vacuum pumping, there has been a reported loss of approximately 15% of studies. (221) The performance of serial imaging at each stage of exercise is time consuming and the equipment used

can be cumbersome. Often gamma camera systems are housed in small spaces which are unable to accommodate additional equipment for dynamic exercise and great demands are placed on camera time. It is for these reasons that both CPT and SIHG are used in our department. Both of these tests are relatively fast and easy to perform with the minimum of additional equipment. In our experience very few studies have to be abandoned because of the onset of symptoms in patients with CAD or intolerance to the test. In the studies contained in this thesis RNV was used serially to examine left ventricular performance in subjects with CAD and it was therefore important to use interventions which were unlikely to precipitate symptoms and unnecessarily prolong aquisition time. Although it is appreciated that dynamic exercise is a more physiological intervention, these other factors prompted the use of CPT and SIHG. Since I was not concerned with the detection of CAD in these patients and since they were effectively acting as their own controls the choice of intervention did not seem inappropriate.

There follows a description of the effects of both CPT and SIHG when used with RNV and their usefulness in the detection of CAD in our department.

Cold Pressor Test.

Exposure to cold precipitates angina in those with CAD in both the natural and laboratory environment. (175, 222,223) Because of this, the cardiovascular responses to

cold stimuli have been of interest. The CPT was originally described by Hines and Brown in 1932 (224) and the haemodynamic responses described by Green in 1965. (175) The CPT is now used in conjunction with RNV and has been shown to induce left ventricular dysfunction in a proportion of patients with CAD. (176,225) The CPT is an accessible, less cumbersome and time consuming procedure than dynamic exercise and the haemodynamic changes elicited are usually brief, (175,226,227) while those with exercise may last 30 minutes. (228)

Several reports have challenged the usefulness of CPT in the detection of CAD, in comparison to the sensitivity and specificity of dynamic exercise (176,229), but no study has yet examined the reproducibility of the test in the context of comparative left ventricular function studies to determine relative change over a period of time. As imaging and processing protocols vary considerably between centres, and as the performance of the CPT may also differ, I undertook these studies to determine the effects of the CPT in patients with CAD and a normal control group in our laboratory on heart rate, blood pressure and left ventricular performance. An assessment was also made of its reproducibility.

Isometric Handgrip Test.

Isometric exercise is defined as a form of exercise where the contracting muscles develop force without shortening. Sustained isometric handgrip stress

has previously been used as an alternative to dynamic exercise in several studies. (219,230-232) It too is an easily applied intervention which has been shown to induce predictable increases in heart rate and blood pressure which return to basal levels within seconds of release (127,233) and to induce left ventricular dysfunction in diseased states. (234) The test has pronounced chronotropic, inotropic and pressor effects, which do not produce the degree of ischaemic stress manifested by angina pectoris or ST segment depression experienced with dynamic exercise. (179)

Several investigators have found a modest increase in heart rate and blood pressure during isometric handgrip when compared to dynamic exercise, with a 15-40% increase in systemic blood pressure, heart rate and cardiac output being reported. (235,236) Such changes increase myocardial oxygen demand, and if this supply is compromised by coronary atherosclerosis, then abnormalities of left ventricular function may occur.

The test itself, requires patient co-operation and motivation, but blood pressure recording and radionuclide imaging can be performed easily without risk of distorted results.

Although the test is a potentially useful intervention for the non-invasive detection of CAD (230,231,237) there are conflicting reports on the sensitivity of the test in this respect. (178,230) In a similar way to the

CPT, SIHG testing has predominantly been evaluated with respect to the detection of CAD. I am not aware of any report which has assessed reproducibility of the technique and it's potential for serial evaluation of left ventricular function during exercise.

Patients and Methods.

Four groups of patients were investigated.

1. Sixteen asymptomatic male volunteers were recruited from hospital staff and associates. All were in sinus rhythm and were normotensive and life-long non-smokers. Each subject had a normal rest and maximal graded exercise electrocardiogram using a modified Bruce protocol as previously described. (125) Chest x-ray was normal including the cardiothoracic ratio, and no subject was taking any medication at the time of the study. No subject had evidence of valvular or congenital heart disease, respiratory disease or peripheral vascular disease and they were presumed to have normal hearts. Their physical characteristics are shown in Table 4.1.

2. Twenty male patients with a diagnosis of CAD and stable angina pectoris (New York Heart Asssociation Grade II or III), confirmed by a positive exercise electrocardiogram as previously described (page 70) and either confirmatory evidence of CAD at coronary arteriography (n = 8) or a documented history of myocardial infarction (n = 12). Evidence of significant CAD at coronary arteriography was taken as at least one stenosis of a major coronary artery of $\geqslant$ 70% of the luminal diameter and a myocardial infarction was diagnosed on the basis of a

prolonged episode of central chest pain, with characteristic ECG and cardiac enzyme changes, occurring at least one year prior to the study. These subjects had a mean age of 53 ± 6.7 years and had a wide range of resting ejection fractions. (range of 18-63). Their other physical characteristics are shown in Table 4.1. None had a history or evidence of respiratory disease, valvular or congenital heart disease, unstable angina, cardiac arrhythmias or conduction abnormality or of cardiac failure. Apart from glyceryl trinitrate no other medication had been taken in the two weeks prior to the study.

3. Twenty male subjects with chronic stable angina as defined above and confirmed by an exercise electrocardiogram who had no previous history of myocardial infarction and had a normal or near normal resting EF (range of 50-79%). These subjects had a mean age of 54 ± 8.1 years (mean ± SD), and had received no medication apart from oral Glyceryl Trinitrate in the two weeks prior to the study. Exclusion criteria were as described above in Group 2. Six patients in this group were common to Group 2.

4. To assess variability of resting ejection fraction and its response to CPT and SIHG, a group of 20 subjects were drawn from groups 1 and 2 above, with chronic stable angina. These subjects underwent

TABLE 4.1 PHYSICAL CHARACTERISTICS OF CONTROLS AND SUBJECTS WITH CAD.

	Group 1. Controls.	Group 2. CAD Subjects (Range of Resting EF's: 18-63%)	Group 3. CAD Subjects (Normal or near normal resting EF: 50-79%)
Age.	46 ± 7.0 (36-60)	53 ± 6.7 (39-62)	54 ± 8.1 (38-67)
Resting HR.	63 ± 8.8	67 ± 8.7	67 ± 9.7
Resting SBP.	119 ± 13.9	131 ± 21.7	135 ± 25.7
Resting DBP.	69 ± 9.5	75 ± 12.2	80 ± 12.3
Resting EF.	60.2 ± 11.4	43.8 ± 10.8	60.7 ± 8.3

Results are expressed as mean ± Standard Deviation

RNV with CPT and SIHG on three occasions 3 and 6 months apart. All these subjects were taking Propranolol 80 mg. t.i.d. and GTN for chest pain and this treatment was unchanged for the duration of the study.

Study Protocol.

Radionuclide ventriculography was performed at the same time of day in each subject as previously described in Section 3.

The normal control group underwent imaging at rest on two separate occasions to assess the reproducibility of the technique. In all subjects, resting aquisition time was 5 minutes. Thereafter both an isometric handgrip test followed by a CPT were performed on the right hand. The time between these studies was at least 10 minutes, blood pressure and heart rate having returned to basal levels before the CPT was commenced. After the basal study at rest, SIHG was performed using a hand dynamometer (Martin Vigorimeter). Initially, the patients maximum voluntary contraction was determined and he was asked to maintain 30% of this value for a period of 5 mins 30 secs., allowing a lag period of 30 seconds before imaging commenced. Imaging was performed for 5 minutes in each case. In previous studies, the duration of the CPT and time of commencement of imaging varied - some starting 15-30 seconds after immersion of the hand in iced water with a 2-3 minute aquisition time (218,225,229), while Wainwright

et al delayed the start of imaging for 1 minute and acquired for 5 minutes. (176) In our hands, haemodynamic changes are evident 15-30 seconds after immersion of the hand in ice, with maximal changes occurring between 1 and 3 minutes and being maintained for 5 minutes. (unpublished observations) Because of these observations and as we were using a general purpose collimeter we felt it appropriate to commence imaging after 30 seconds and to acquire for 5 minutes. In addition, as this protocol was almost identical to that of Wainwright et al (176), this permitted comparison with that study. The CPT was administered by immersing the right hand in a mixture of crushed ice and water to the level of the styloid process. Throughout the test, mixing of water and ice round the hand was performed to ensure maintenance of the cold stimulus. Heart rate and blood pressure were monitored every minute before, during and after both interventions by a Hitachi HME-20 pulse and blood pressure monitor.

Statistical Analysis.

Discrete variables were analysed using Student's paired t test and a Wilcoxon signed rank test for paired observations. Unpaired observations were analysed using a Student's unpaired t test and a Mann Whitney test. (The most conservative estimates of significance are reported).

The variability of sequential EF measurements and the reproducibility of interventions, was estimated by

calculating the coefficient of variance. Values of <10% were accepted to indicate low variance and satisfactory reproducibility. Values of 10-20% indicated moderate reproducibility and values >20%, unacceptable reproducibility. The 95% confidence interval about a resting EF; used to define a subsequent significant change during CPT or SIHG in the individual subject was determined by calculation of the pooled variance as described by Caldwell et al. (238) Sensitivity and specificity were calculated as previously described (239), and expressed in percent units.

Results.

Both the CPT and SIHG were tolerated well by all subjects. In each case the tests were completed without the development of chest pain or ECG evidence of ischaemia. Several individuals complained of pain in the immersed hand during the CPT which was most marked in the first 1-2 minutes after immersion and in the first few minutes after withdrawal. Groups 1, 2 and 3 were similar in terms of age and resting heart rate, although both resting systolic and diastolic blood pressure was higher in those with CAD. Their physical characteristics are summarised in Table 4.1.

Heart Rate and Blood Pressure.

Both heart rate and systolic blood pressure rose in response to SIHG (Table 4.2) and CPT (Table 4.3) at each minute during these interventions. There was a mean increase of 27% in group 2's heart rate in response to SIHG at the 5 minute stage, but only a 15% increase in group 1's response (normals). Similarly a mean increase of 39% in systolic blood pressure occurred in group 2, but only a 27% increase occurred in group 1, although diastolic blood pressure increased in each group to a comparable degree.

During the CPT those with CAD (Group 2) increased heart rate by 13% and systolic blood pressure by 24% and in the controls (Group 1) these parameters increased by

TABLE 4.2 COMPARATIVE MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO SUSTAINED ISOMETRIC HANDGRIP STRESS IN SUBJECTS WITH CAD (GROUP 2 : n = 20) AND A NORMAL CONTROL GROUP (GROUP 1 : n = 16).

		TIME FROM START OF ISOMETRIC HANDGRIP TEST (MINUTES)					
		BASAL	1	2	3	4	5
CAD Group	Heart Rate	67 ± 9.6	75 ± 12.3	79 ± 12.0	81 ± 12.6	83 ± 14.6	85 ± 15.6
	SBP	127 ± 21.8	151 ± 28.3	160 ± 27.7	169 ± 25.6	165 ± 16.2	176 ± 26.1
	DBP	74 ± 16.3	86 ± 20.8	91 ± 21.4	93 ± 22.8	98 ± 20.9	99 ± 16.1
Normal Control Group	Heart Rate	65 ± 8.1	68 ± 6.9	71 ± 9.9	72 ± 9.3	72 ± 8.3	75 ± 11.8
	SBP	117 ± 16.5	128 ± 15.3	136 ± 17.5	142 ± 22.8	153 ± 29.9	149 ± 22.8
	DBP	67 ± 15.4	76 ± 15.1	78 ± 15.0	80 ± 14.9	89 ± 15.7	85 ± 20.4

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

Results are expressed as mean ± Standard Deviation.

TABLE 4.3 COMPARATIVE MEAN HEART RATE AND BLOOD PRESSURE RESPONSES TO COLD PRESSOR TEST IN SUBJECTS WITH CAD (Group 2 : n = 20) AND A NORMAL CONTROL GROUP (Group 1 : n = 16).

		TIME FROM IMMERSION OF HAND IN ICE (MINUTES)					
		BASAL	1	2	3	4	5
CAD Group	Heart Rate	67 ± 8.7	74 ± 12.3	74 ± 13.5	74 ± 11.4	75 ± 11.1	76 ± 11.9
	SBP	131 ± 21.7	160 ± 29.4	162 ± 28.6	153 ± 23.0	160 ± 29.3	161 ± 36.1
	DBP	75 ± 12.2	94 ± 21.0	91 ± 17.7	89 ± 17.7	94 ± 17.7	91 ± 15.7
Normal Control Group	Heart Rate	63 ± 7.8	66 ± 9.6	69 ± 10.5	69 ± 10.0	65 ± 10.2	65 ± 8.2
	SBP	119 ± 13.9	148 ± 26.2	156 ± 25.3	156 ± 27.1	153 ± 26.1	154 ± 21.6
	DBP	69 ± 9.5	89 ± 20.2	88 ± 15.9	84 ± 17.1	87 ± 11.7	79 ± 17.6

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

Results are expressed as mean ± Standard Deviation.

10 and 31% respectively with similar changes occurring in diastolic blood pressure in both groups. (Table 4.3)

In both tests the haemodynamic response was evident during the first minute and was maintained for the 5 minute period of imaging. Maximum group and individual responses of heart rate to SIHG are shown in Figure 4.1. Heart rate increased by a mean of 21 ± 14.2 bpm. ($p < 0.001$) in the CAD group (Group 2), and by 14 ± 13.4 bpm ($p < 0.01$) in the normal subjects (Group 1) - but the difference between groups was not statistically significant. Systolic blood pressure increased by a mean 51 ± 18.1 mmHg. in CAD subjects ($p < 0.001$) and 38 ± 21.7 mmHg. in controls ($p < 0.01$), but this difference in response was not statistically significant. (Figure 4.2)

During the CPT, maximal heart rate increased by 14 ± 11.8 bpm in CAD subjects (group 2), but by only 8 ± 6.7 in controls (group 1), this difference not reaching statistical significance. (Figure 4.3)

Systolic blood pressure increased by a mean of 39 ± 18.6 mmHg. ($p < 0.001$) in CAD subjects and by 44 ± 23.0 ($p < 0.001$) in controls, the difference in response not being significant. (Figure 4.4)

During SIHG heart rate increased in all subjects with CAD, but fell in one normal subject while systolic blood pressure rose in all subjects. During CPT heart rate fell in only one subject with CAD, but fell in two

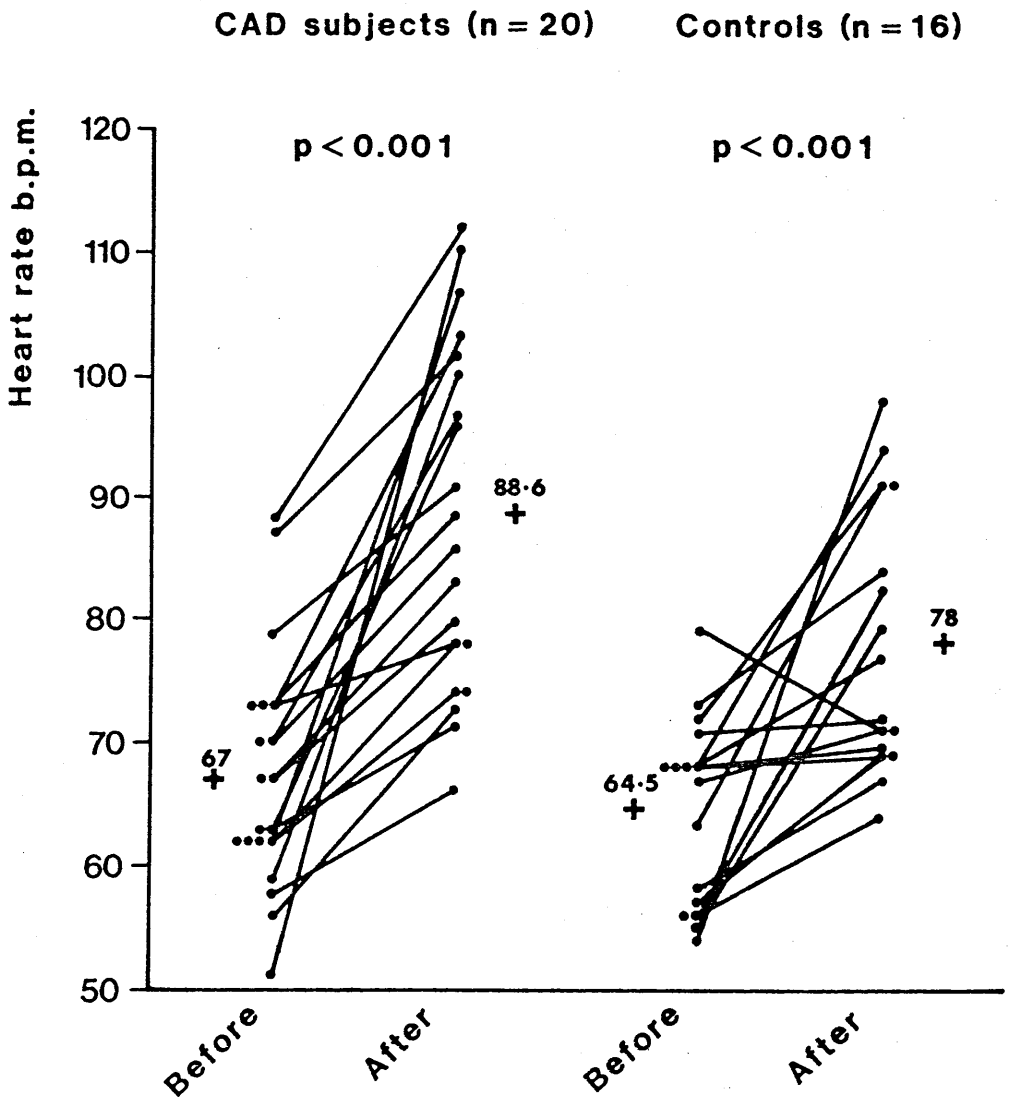


FIGURE 4.1

Scatter plot of maximal heart rate response to sustained isometric handgrip in subjects with CAD (Group 2) and a control group.

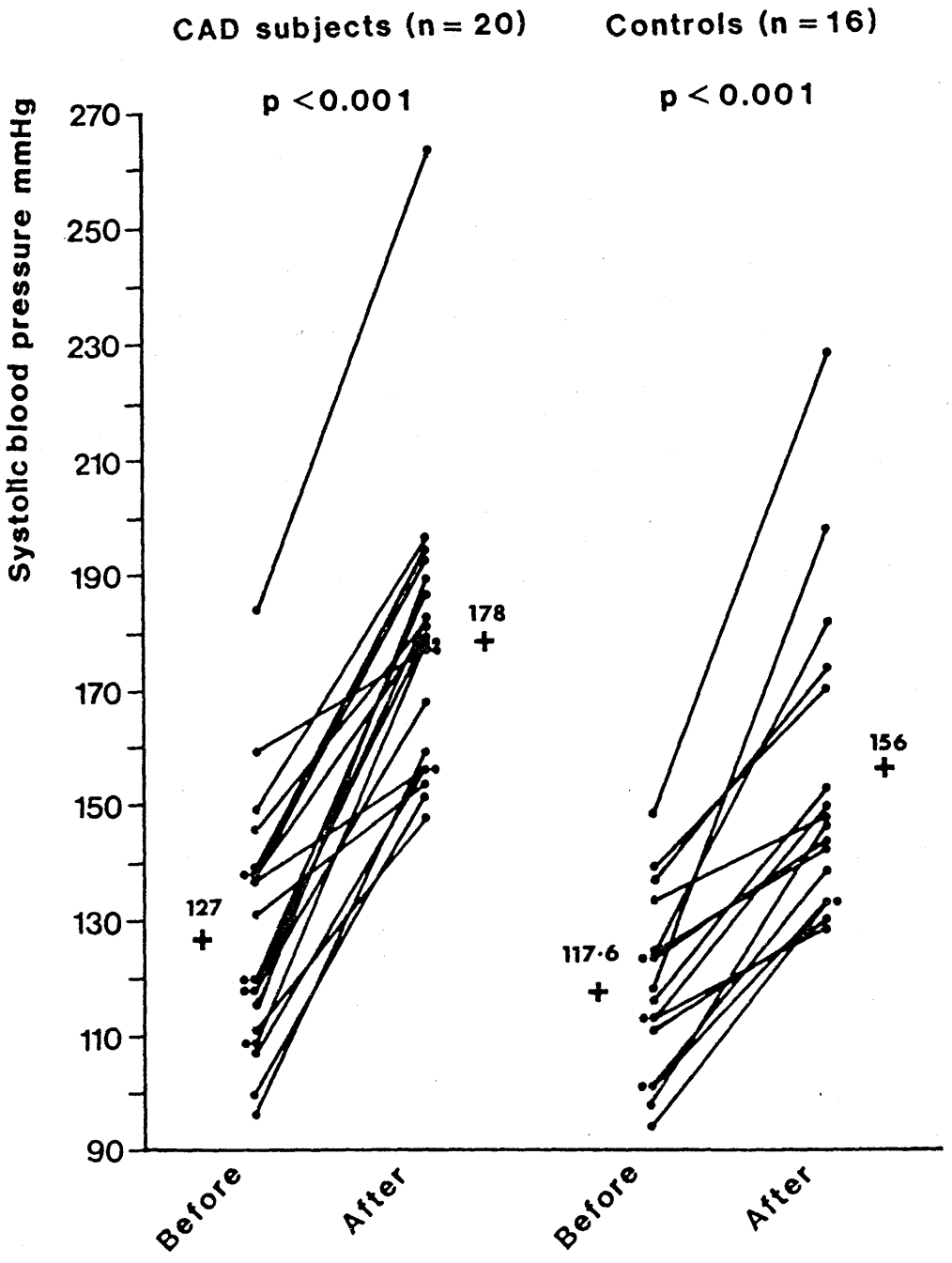


FIGURE 4.2

Scatter plot of maximal systolic blood pressure response to sustained isometric handgrip in subjects with CAD (Group 2) and a control group.

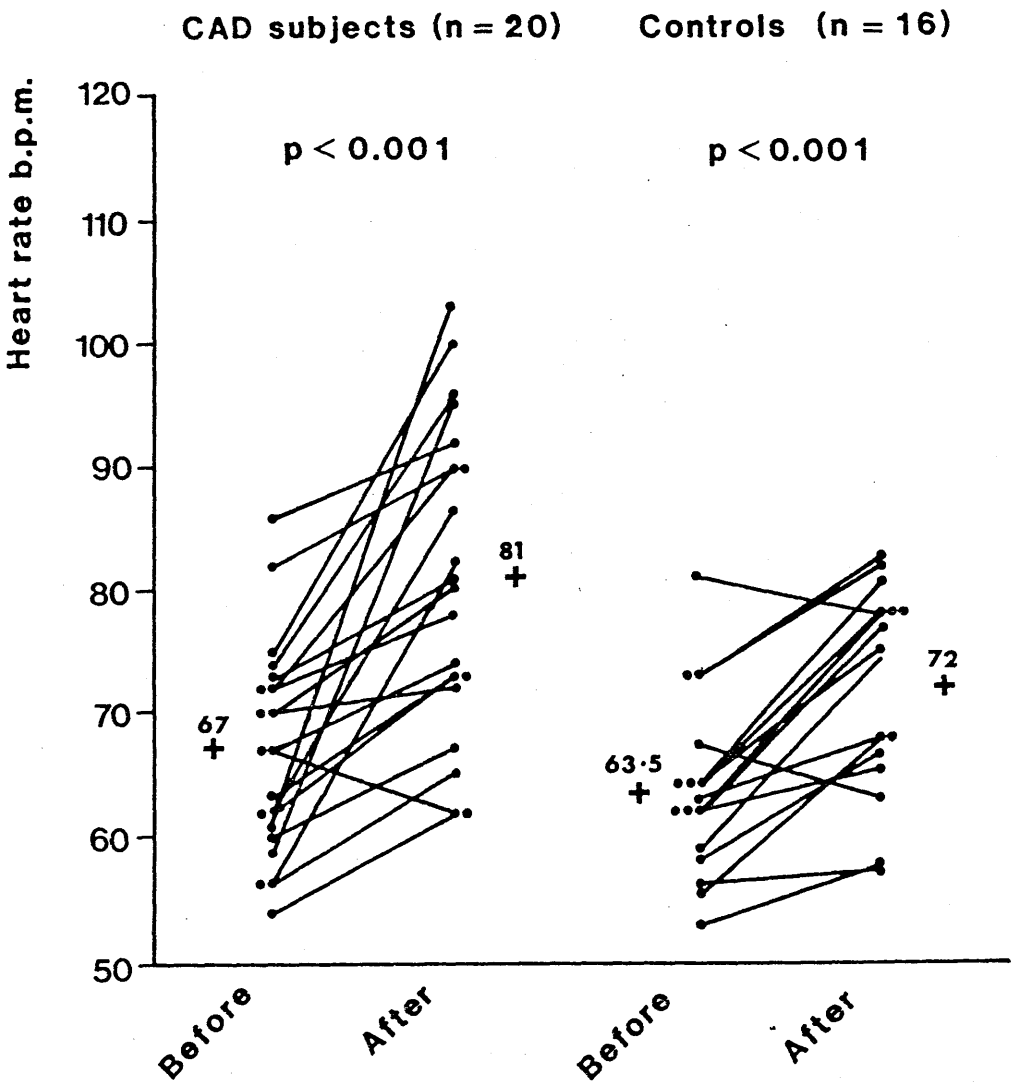


FIGURE 4.3

Scatter plot of maximal heart rate response to cold pressor test in subjects with CAD (group 2) and a control group.

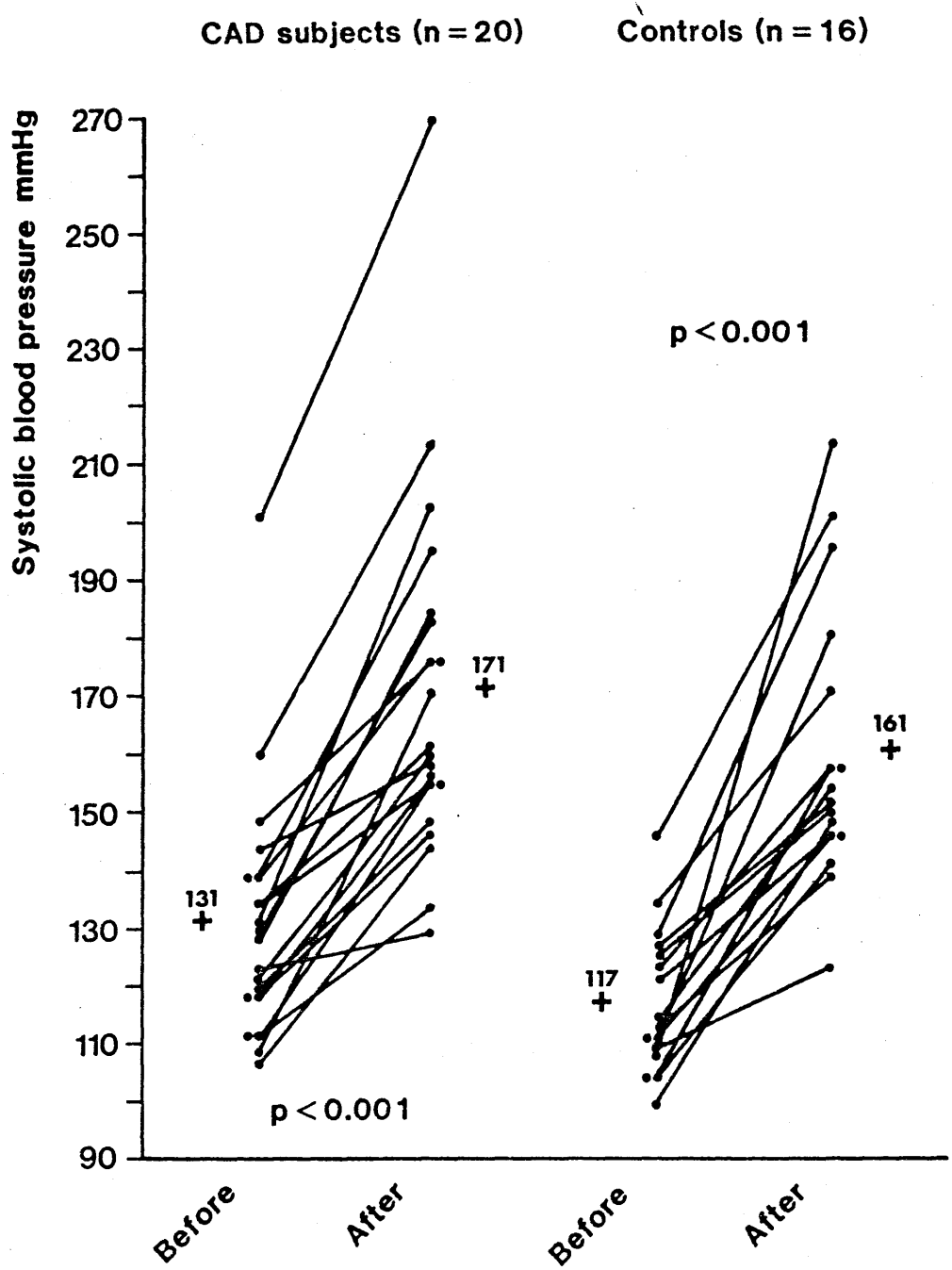


FIGURE 4.4

Scatter plot of maximal systolic blood pressure response to cold pressor test in subjects with CAD (group 2) and a control group.

controls (Figure 4.3). Systolic blood pressure rose in all subjects.

SIHG caused greater heart rate and blood pressure responses compared to cold pressor test, but these differences were not statistically significant. Maximal haemodynamic responses tended to occur from minutes 3-5 during SIHG and in minutes 1-3 during CPT. There was no difference in the timing of these maximal responses between CAD subjects and normals.

Variability of EF Determinations.

The variability of EF measurements was determined using the results of the 16 normal control subjects (Group 1), each of whom underwent two sequential resting studies. The difference of 1.25% between the means was not statistically significant (Table 4.4). From the individual mean of the two resting values and knowledge of the pooled variance, the 95% confidence limits for a significant change of a subsequent EF measurement is given by the equation:

$$\bar{x} \pm 2.12 \sqrt{S^2(1/n + 1}$$

- where $\bar{x}$ is the observed measurement, the value of 2.12 represents the t-value, taken from the distribution of t, where the number of observations is 16 at the 5% significance level; S^2 is the pooled variance, and n is the number of resting observations per patient. Thus, for

the 16 subjects, S^2 = 19.6 per cent units, n = 2 and the 95% confidence interval for a given patient may be estimated as $\bar{x} \pm 11.49$ EF percent units. This implies that the individual change of EF to any intervention must be 12% (absolute value) or more to be considered significant at the 5% level. Variations of less than 12% can be attributed to physiological and statistical fluctuations. At rest this would imply that a value would have to be 12% below the normal mean value to be regarded as an abnormal EF response.

The coefficient of variance between these two resting studies was 5.1% indicating satisfactory reproducibility. (Table 4.4) The results of sequential resting RNV studies in the normal subjects are summarised in Table 4.5. No statistically significant differences were observed for each parameter between the two resting studies. Linear regression analysis of EF response revealed a correlation coefficient of 0.85 between the two resting studies.

The patients recruited into group 4 underwent three separate studies 3 and 6 months apart. The responses to SIHG and CPT are shown in Tables 4.6 and 4.7 respectively. The coefficient of variance was 10% for SIHG indicating acceptable reproducibility, and that for the CPT was 9% indicating satisfactory reproducibility.

TABLE 4.4 COEFFICIENT OF VARIANCE FOR EJECTION FRACTION RESPONSE IN TWO SEPARATE STUDIES, IN NORMAL CONTROLS (GROUP 1).

PATIENT NO.	R_1	R_2	SD
1	73	72	0.707
2	67	77	4.110
3	57	58	0.707
4	57	55	1.414
5	58	59	0.707
6	47	43	2.828
7	60	47	9.190
8	81	82	0.707
9	65	61	2.828
10	57	56	0.707
11	58	69	7.778
12	55	53	1.41
13	62	58	2.828
14	71	74	2.121
15	58	52	4.24
16	58	48	7.07
Column Mean ± S.D.	61.5 ± 8.20	60.25 ± 11.42	3.0854 ± 2.739
Overall Mean	60.87 ± 9.807		

Coefficient of Variance $= \frac{\text{Mean SD}}{\text{Overall Mean}} \times \frac{100}{1} = 5.06\%$

ABBREVIATIONS: R_1 = First Resting Study.
R_2 = Second Resting Study.
SD = Standard Deviation.

TABLE 4.5 RESULTS OF SEQUENTIAL RESTING RADIONUCLIDE VENTRICULOGRAMS IN CONTROL SUBJECTS (n = 16).

	$Rest_1$	$Rest_2$	Difference
FET	18.3 ± 3.24	18.6 ± 2.87	NS
dVs/dt	-4.3 ± 0.46	-4.3 ± 0.42	NS
FEL	34.2 ± 4.46	33.4 ± 3.72	NS
ST	39.3 ± 3.41	39.1 ± 4.00	NS
SL	39.1 ± 4.52	39.9 ± 4.30	NS
FFT	57.4 ± 2.94	58.5 ± 4.27	NS
dVd/dt	4.0 ± 0.50	3.94 ± 0.37	NS
FFL	28.6 ± 3.10	30.1 ± 3.01	NS
EF	61.5 ± 8.21	60.2 ± 11.42	NS

Abbreviations: As for Figure 3.3.

TABLE 4.6 COEFFICIENT OF VARIANCE FOR EJECTION FRACTION RESPONSE TO ISOMETRIC HANDGRIP ON THREE SEPARATE OCCASIONS.

Patient No.	S_1	S_2	S_3	SD
1	37	46	44	4.72
2	48	53	54	3.21
3	43	58	46	7.93
4	48	44	44	2.3
5	55	57	53	2
6	36	42	45	4.58
7	45	55	46	5.5
8	26	29	21	4.04
9	40	27	38	7.0
10	50	51	47	2.08
11	43	50	52	4.73
12	51	52	39	7.23
13	52	62	73	10.5
14	71	62	78	8.02
15	69	70	64	3.21
16	66	65	63	1.53
17	67	54	66	4.85
18	53	54	49	2.65
19	43	63	52	10.02
20	34	32	41	4.73
Column Mean ± SD.	48.8 ± 12.22	51.3 ± 11.79	50.7 ± 13.14	5.04
Overall Mean ± SD	50.3			
$\frac{\text{Mean SD}}{\text{Overall Mean}} \times \frac{100}{1}$	Coefficient of Variance = 10.02%			

ABBREVIATIONS: S_{1-3} = Studies 1-3.
SD = Standard Deviation

TABLE 4.7 COEFFICIENT OF VARIANCE FOR EJECTION FRACTION RESPONSE TO COLD PRESSOR TEST ON THREE SEPARATE OCCASIONS.

Patient No.	S_1	S_2	S_3	SD
1	34	39	41	3.60
2	52	50	55	2.52
3	48	50	59	5.86
4	44	49	38	5.51
5	50	56	54	3.06
6	39	44	41	2.52
7	43	42	39	2.08
8	29	29	15	8.08
9	32	34	40	4.16
10	39	37	38	1.0
11	45	52	45	4.04
12	56	53	57	2.08
13	49	45	46	2.08
14	49	55	64	7.54
15	65	67	60	3.61
16	52	55	64	6.22
17	61	58	69	6.46
18	61	53	49	6.38
19	46	58	56	6.42
20	39	34	37	2.52
Column Mean ± SD.	46.6 ± 9.74	48.0 ± 9.77	48.3 ± 12.80	4.287
Overall Mean.	47.67			
$\frac{\text{Mean SD}}{\text{Overall Mean}} \times \frac{100}{1}$	Coefficient of Variance = 8.99			

ABBREVIATIONS: S_{1-3} = Studies 1-3.
SD = Standard Deviation.

Radionuclide Ventriculography.

The results of RNV in groups 1, 2 and 3 in response to SIHG and CPT are summarised in Tables 4.8, 4.9, and 4.10 respectively. In all three groups LVEF fell in response to SIHG and CPT. In normals this was only significant for CPT however. Both CPT and SIHG tended to reduce dVs/dt and increase FEL, ST, SL, FFT in all groups. FFL was not significantly changed in groups 1 and 3, but was increased significantly by SIHG in group 2.

The group and individual changes in LVEF in both groups 1 and 3 to both interventions are shown in figures 4.5 and 4.6. SIHG caused a mean reduction of 5 ± 8.3% in subjects with CAD and 4 ± 6.5% in controls. This difference was not statistically significant. The CPT caused a mean reduction of 10 ± 8% in subjects with CAD compared to 7 ± 5.6% in controls. This difference was not statistically significant. Two subjects in each group increased LVEF in response to SIHG; and one subject in each group increased LVEF during the CPT.

The resting LVEF in groups 1 and 3 were similar, although that in group 2 was significantly lower ($p < 0.01$). Two subjects in group 3 showed a significant fall in EF ($\geq$ 12%) in response to SIHG, compared to no normal subjects. In response to CPT, six subjects in group 3 showed a significant reduction in EF, while only two subjects in group 1 had falls of this magnitude. LVEF increased significantly (+14%) in only one subject who had CAD.

TABLE 4.8 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN CONTROL SUBJECTS. (Group 1: n = 16)

	Rest	Isometric Handgrip	Cold Pressor
FET	18.6 ± 2.87	18.8 ± 2.40	20.7 ± 6.09
dVs/dt	-4.3 ± 0.42	-3.9 ± 0.37**	-3.9 ± 0.51
FEL	33.4 ± 3.72	37.6 ± 3.12**	38.2 ± 6.57*
ST	39.1 ± 4.00	43.6 ± 3.20***	44.7 ± 5.10***
SL	39.9 ± 4.30	45.1 ± 5.77**	42.2 ± 7.43
FFT	58.5 ± 4.27	63.9 ± 6.77**	62.9 ± 5.46**
dVd/dt	3.94 ± 0.37	3.7 ± 0.35*	3.9 ± 0.53
FFL	30.1 ± 3.01	30.3 ± 5.39	28.8 ± 5.10
EF	60.2 ± 11.42	57.9 ± 10.18	54.4 ± 10.64***

Abbreviations: As For Figure 3.3.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results are expressed as mean ± Standard Deviation.

TABLE 4.9 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN SUBJECTS WITH CAD AND A RANGE OF RESTING EJECTION FRACTIONS: (Range 18-63%) (Group 2: n = 20).

	Rest	Isometric Handgrip	Cold Pressor
FET	17.2 ± 1.62	21.1 ± 6,70*	19.6 ± 5.96
dVs/dt	-4.5 ± 0.62	-3.8 ± 0.73***	-4.1 ± 0.59*
FEL	33.8 ± 5.41	41.9 ± 7.44***	37.2 ± 6.63*
ST	39.1 ± 5.59	45.7 ± 5.62***	46.6 ± 6.41***
SL	44.9 ± 8.68	49.9 ± 7.06**	50.4 ± 11.07**
FFT	66.2 ± 8.47	70.9 ± 9.96***	70.0 ± 11.13***
dVd/dt	3.4 ± 0.41	3.3 ± 0.54	3.4 ± 0.45
FFL	33.5 ± 7.34	39.9 ± 9.22**	37.1 ± 9.18
EF	43.8 ± 10.83	40.7 ± 10.59**	38.6 ± 11.87***

Abbreviations: As For Figure 3.3.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results are expressed as mean ± Standard Deviation.

TABLE 4.10 RESULTS OF RADIONUCLIDE VENTRICULOGRAPHY IN SUBJECTS WITH CAD AND NORMAL, OR NEAR NORMAL RESTING EJECTION FRACTIONS: (Range 50-79%) (Group 3: n = 20).

	Rest	Isometric Handgrip	Cold Pressor
FET	17.6 ± 1.87	18.9 ± 4.96	18.3 ± 3.18
dVs/dt	-4.6 ± 0.37	-3.8 ± 0.61***	-4.1 ± 0.48***
FEL	32.9 ± 3.32	40.8 ± 5.93***	32.9 ± 5.79***
ST	38.2 ± 3.07	44.8 ± 4.27***	43.9 ± 4.822***
SL	42.2 ± 5.56	50.3 ± 9.15***	48.9 ± 8.74**
FFT	59.8 ± 6.17	69.2 ± 10.55***	67.2 ± 9.90**
dVd/dt	3.6 ± 0.48	3.4 ± 0.74	3.4 ± 0.57
FFL	33.4 ± 6.24	38.7 ± 11.05	33.2 ± 8.39
EF	60.7 ± 8.28	55.7 ± 11.42*	51.1 ± 9.96***

Abbreviations: As For Figure 3.3.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results are expressed as mean ± Standard Deviation.

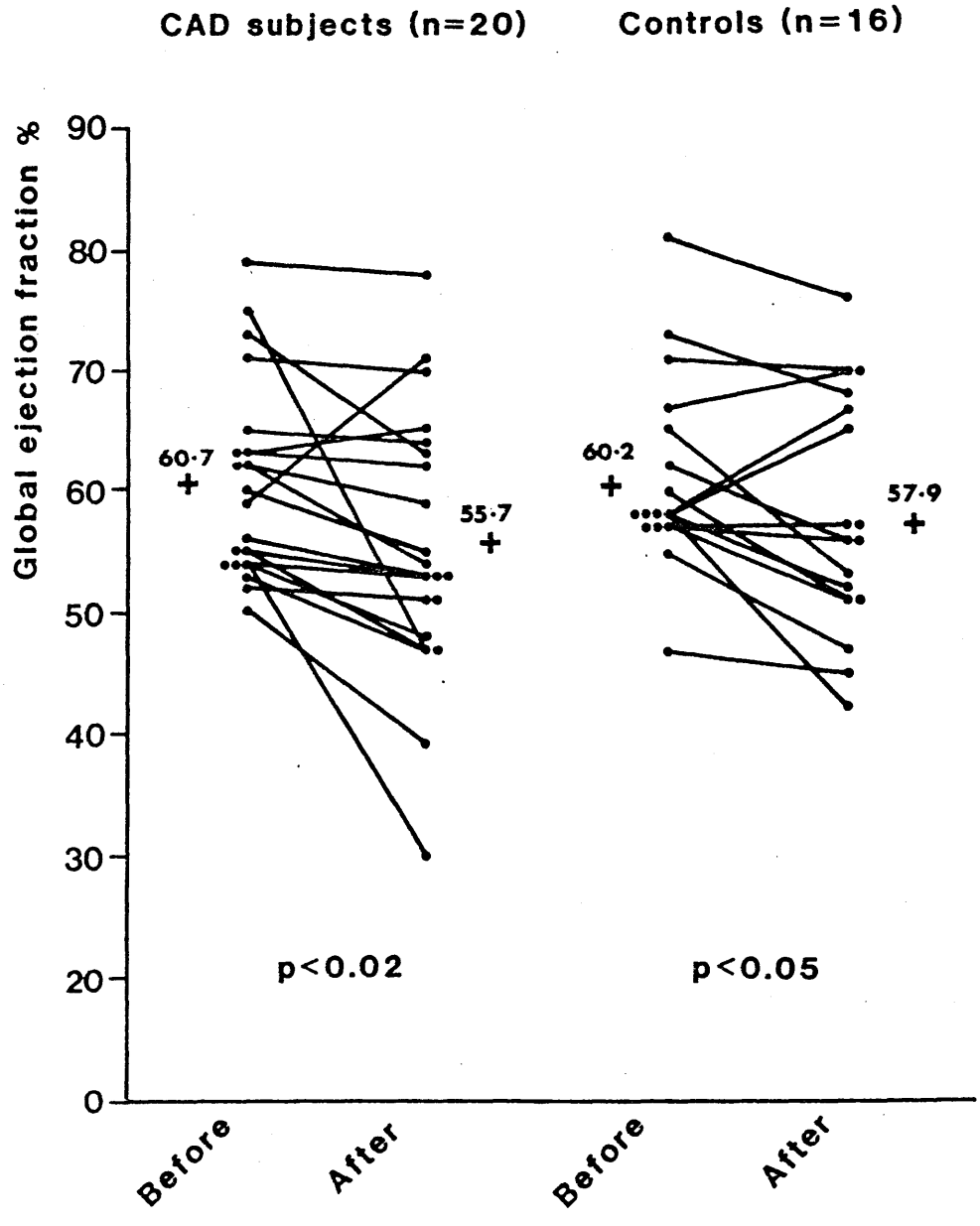


FIGURE 4.5

Individual and group ejection fraction response to sustained isometric handgrip in subjects with CAD and normal or near normal ejection fraction (Group 3) and controls (Group 1).

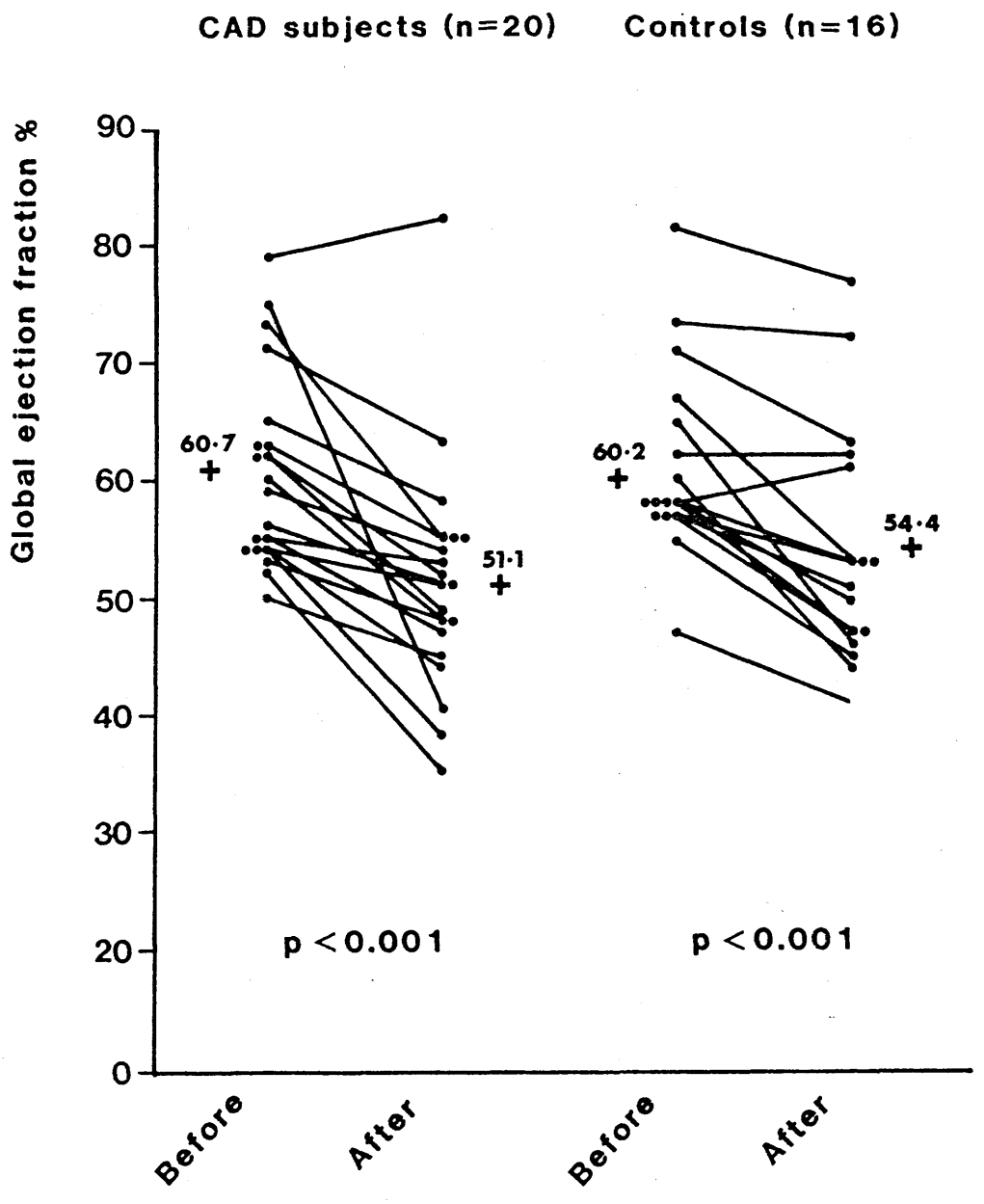


FIGURE 4.6

Individual and group ejection fraction responses to cold pressor test in subjects with CAD and normal or near normal ejection fractions (Group 3) and controls (Group 1).

Discussion.

The CPT and SIHG have been used in previous studies to unmask latent abnormalities of left ventricular function and aid in the diagnosis of CAD. (176,218,225,229,231,240-243) The reproducibility of the responses to these interventions has not been adequately assessed. It is possible that these interventions are useful for comparative studies because of their ease of application and ability to stress the myocardium without inducing angina pectoris or ST-segment changes indicative of ischaemia in comparison to dynamic exercises which causes these phenomenon in a high proportion of subjects undergoing RNV. (176) Thus, the variability of response between studies is of importance.

Cold Pressor Test.

Heart Rate and Blood Pressure.

The present study showed that in patients with CAD and normal controls, heart rate increased by a mean of 13% and 10% respectively and systolic pressure increased by 24 and 31% respectively, both being statistically significant. There was no significant difference between the two groups however. Previous studies (Table 4.11) have shown increases in heart rate ranging from +4 bpm (240) to +11 bpm (218,229) in normals and +1 (243) to +10 (229) in patients with CAD. Systolic blood pressure rises in this study were higher in both normal controls

TABLE 4.11 COMPARISON OF COLD PRESSOR STUDIES IN CONJUNCTION WITH RADIONUCLIDE VENTRICULOGRAPHY.

	Normal Group				CAD Group					
	n	HR (bpm)	SBP (mmHg)	EF(%)	n	HR (bpm)	SBP (mmHg)	EF(%)	Sensitivity	Specificity
Wainwright et al (176)	22	N	N	+2	24	N	N	-13	79%	100%
Manyari et al (225)	20	+8	+26	+3	20	+9	+30	-5	55%	95%
Wasserman et al (229)	12	+11	+27	-6	18	+10	+22	-5	N	N
Vojacek et al (243)	10	+5	+13	-3	12	+1	+29	-5	N	N
Verami et al (218)	18	+11	+28	0	34	N	N	-6	N	N
Dymond et al (177)	12	+12	+16	-5	12	+9	+29	-8	N	N
Rootwelt et al (240)	11	+4	N	+2	22	+6	N	-3	50	100
Present Study.	16	+8	+44	-7	20	+14	+39	-10	50	37.5

Abbreviations: HR = Heart Rate; SBP = Systolic Blood Pressure; EF = Ejection Fraction; N = Not Reported.
Results expressed are mean value for each parameter.

and subjects with CAD than previous studies. The explanation for this is not obvious. Only one of our subjects (aged 54 years, with CAD) was considered to have hypertension (resting blood pressure 184/103 mmHg.) Most studies have observed similar changes in blood pressure and heart rate between normal controls and patients with CAD (Table 4.11), but in this study no significant difference in response was found (Figures 4.1-4.4). Neither Rootwelt et al (240) or Raizner et al (244) observed significant heart rate response, in normals compared to other studies. (176,218,225,229,243) The variability of heart rate and systolic blood pressure response in these studies may be related to the application of the CPT. In the present study, the hand was immersed in iced water (0-2°c) up to the level of the styloid process and continuous mixing of the ice/water mixture was carried out to maintain a constant, adequate cold stimulus. In addition, a fresh ice/water mixture was prepared for each patient. If these latter manoevres are not carried out it is possible that an inadequate cold stimulus is applied, and this may explain the early decay in haemodynamic response experienced by Dymond et al (177), but not by others. (176,229) The maximal haemodynamic response to CPT has been found to occur at 60-90 seconds after initiation, and rapidly returns to basal values after withdrawal. (175,176,226,227) In this study the haemodynamic responses were evident throughout the 5 minutes of imaging although some decay was noted after three minutes.

The haemodynamic changes are mediated by a predominant alpha adrenergic stimulus (245), and increase in systemic and pulmonary vascular resistance. (175,246) These haemodynamic changes result in an increase in myocardial oxygen consumption. Such changes may be enough to precipitate ischaemia in those with pre-existing CAD. Other mechanisms may be active - and these will be discussed in the following paragraphs.

Radionuclide Ventriculography.

The CPT induced significant falls in LVEF in both normals and subjects with CAD, the difference between the two groups not being statistically significant. Two previous studies (229,243) have observed falls in the EF with CPT, while others have noted no change or a small increase. (176,218,225,240) In contrast, all studies are consistent in reporting falls in EF in patients with CAD ranging from a mean of -3 to -13% (Table 4.11). The other parameters derived from RNV with the exception of SL and FFL did not enhance the ability of CPT to distinguish patients with and without CAD. In normal controls (Group 1) SL increased, but this was not significant, although the increases occurring in Group 2 and 3 were significantly greater. FFL showed a mean reduction in normals; while it was prolonged by CPT in Group 2 (range of EF's), but not Group 3 (normal or near normal EF's). None of these changes reached statistical significance however.

Thus the response to CPT in normals is inconsistent. This may be explained by differences in study protocol, some studies imaging for two minutes (225) and others for five minutes (176), the latter study delaying imaging for one minute. Dymond et al (177) using sequential first-pass radionuclide ventriculography during CPT, found that EF fell significantly in both controls and subjects with CAD after one minute, but this fall was maintained at 2.5 and 4 minutes only in those with CAD. In both groups the maximum reduction in EF occurred after one minute, despite the maximum rise in BP being noted after 2.5 minutes. They postulate that changes in afterload induced by CPT are not the exclusive reason for changes in LV Function. They conclude that LV function changes rapidly during a period of cold stimulation and if the prime purpose is to detect CAD, then it would be prudent to delay onset of imaging for one minute as normal subjects will be less likely to show a fall in EF after this. In the present study which was completed before the publication of Dymond's Group (177), I commenced imaging after 30 seconds, as this had also been the practice of others who have assessed the CPT under similar circumstances. (218,225,229,243)

Mechanism of Cold Pressor Effects.

Cold pressor stimulation produces a modest rise in heart rate and marked rise in blood pressure, thus increasing the double product and hence myocardial oxygen consumption. This may compromise the supply in diseased coronary arteries leading to ischaemia and thereafter

a fall in EF. The increase in heart rate is partially caused by an increase in circulating plasma catecholamines. (247) The blood pressure elevation is independent of such adrenal activity, and it is likely that this is caused by activation of alpha adrenergic receptors (245), with an increase in systemic vascular resistance and LV after-load. However, as Dymond et al (177) pointed out, maximal increases in blood pressure do not coincide with the maximal temporal changes of LV function suggesting a further mechanism behind the fall in EF experienced in normals and subjects with CAD. Mudge et al (192), have studied coronary vascular resistance in response to CPT during cardiac catheterisation and found a 27% increase in patients with CAD after 50 seconds of CPT, but no changes in normals. This work has been confirmed by Feldman et al (248) who found decreases in coronary arterial diameter and increases in coronary resistance. Further evidence of coronary arterial spasm has been forthcoming from a study examining Thallium 201 myocardial perfusion imaging during CPT. Rodger et al (249), observed abnormalities of myocardial perfusion in both patients with CAD and normals. Goldhaber et al (250), have found that nifedipine prevents the fall in EF experienced in patients with CAD, thus further supporting the possibility that coronary spasm is involved in the changes in LV function.

As LV end diastolic pressure and thus LV preload and end diastolic volume, has been noted to increase by 60% in response to CPT (251), this will increase wall tension and may result in compression of intramural

coronary arteries and resistance to coronary flow which may further exacerbate the fall in coronary blood flow in addition to vasospasm. Thus, the mechanical burden of increased LV afterload and preload, increased coronary vascular resistance and double product compromise the LV. The resulting EF is probably a balance between these factors and the increased contractility mediated by the increase in endogenous circulating catecholamines which occurs with CPT.

Sustained Isometric Handgrip Exercise.

Heart Rate and Blood Pressure.

Heart rate and blood pressure rises were higher than during CPT, increasing by a mean of 21 bpm in patients with CAD and 14 bpm in normal controls. Blood pressure increased by 51 and 38 mmHg. respectively. These changes are consistent with previous reports of increases ranging from 15-40% in heart rate and blood pressure. (235,236) Bodenheimer (219), using a similar protocol to ourselves observed blood pressure increases of 32 mmHg. in normals and 33-44 mmHg. in patients with CAD. In the present study, the marked rise in heart rate and blood pressure was maintained for the five minute imaging period and tended to be a sequential rise with little decay in the response, unlike CPT. This was also the experience of Lind et al (252), who found increasing blood pressure as fatigue developed. The blood pressure elevation in normal hearts is due primarily to an increase in cardiac output.

(253) In LV impairment the blood pressure rise can be higher due to an increase in systemic vascular resistance mediated by alpha adrenergic receptors due to a fall in cardiac output. (253)

Radionuclide Ventriculography.

Although SIHG caused a fall in EF in normals, this did not reach statistical significance unlike the response to CPT. The falls in EF experienced in groups 2 and 3 were significant, however. Bodenheimer (231) found an increase in EF in normals by a mean of 3% and a reduction of 4% in subjects with CAD ($p < 0.005$), yielding 86% sensitivity and 87% specificity for the detection of CAD. The present study had a sensitivity of 80% and specificity of 84.2% in patients with a wide range of EF's (Group 2), but sensitivity fell to 25% if only subjects with normal or near normal resting EF were examined (Group 3). Other studies have observed that mean EF does not change in normal subjects (232), but individual normals may have falls of 5% or more. (232,254)

Mechanism of Haemodynamic effects of SIHG.

It is hypothesised that in normal hearts, heart rate and blood pressure rise, producing a rise in cardiac output in the presence of unchanging systemic vascular resistance. (178,252,255) This effectively increases afterload, but LV end diastolic and systolic volumes do not change and EF remains unaffected.(49,51) In the

failing or ischaemic left ventricle, the rise in heart rate and blood pressure occurs as in normals, but the increase in blood pressure is mainly due to an increase in systemic vascular resistence because of an unchanged or reduced cardiac output (178,230), and end systolic volume increases and ejection fraction falls.

However, handgrip induced vasoconstriction may also be important, as with CPT. (237,258) The afferent limb of this reflex appears to originate in skeletal muscle stretch receptors travelling centrally to the sympathetic vasomotor center. (259,261) The efferent limb travels in sympathetic nervous system fibres to impinge directly on the coronary arteries (262,263), and by increasing circulating catecholamines (254) which occurs during SIHG, leading to vasoconstriction.

Variability of EF Responses.

As a fully automatic method of analysing RNV's was used intra- and inter- observer variation was not relevant.

In order to demonstrate the reproducibility of the technique, two sequential resting studies were carried out in the normal controls. This yielded a coefficient of variance of 5%, and a correlation coefficient of 85%. No significant difference was observed in any parameter of LV function between studies. In addition the results were used to calculate the absolute change from normal that would be

regarded as significant. This spontaneous variability in EF of 12% or more to exclude nonrandom physiological change is more than that found in some laboratories (176, 232,240), but comparable to others. (171)

This variability is probably higher than a group with CAD would exhibit, as this has been shown to be greater in subjects with a normal EF. (171) In patients with normal LV performance, there is greater ventricular reserve and hence a greater probability of responding to a variety of stimuli with augmentation of cardiac pump function. In those with subnormal basal ventricular performance, the ventricle may already be working at close to maximal effort and will therefore have less tendency to manifest comparable spontaneous fluctuations in EF.

In the present study large individual interstudy differences, up to 13%, were noted although the mean difference was, -1.2 ± 6.16 between the first and second study. Largeindividual changes (up to 21%) with a mean change of +4.6 ± 4.70 has been observed by Wackers et al in a similar study population. (171)

The response to both CPT and SIHG was found to have acceptable reproducability, with a coefficient of variance of 9 and 10% respectively and no significant differences in the mean response on three separate occasions. This indicates that these interventions are suitable for studies involving temporal comparisons of LV performance in an individual in which myocardial stress

is thought desirable. In this respect both interventions are suitable alternatives to dynamic exercise.

Detection of Coronary Artery Disease.

Wainwright et al (176) claimed a sensitivity of 79% and specificity of 100% for CPT in detecting CAD. (Table 4.11) In that study a change of 8% in EF was regarded as abnormal, although there does not seem to be any clear reason for this limit from their data. All normal subjects increased EF in response to CPT by a mean of 2%. These results are surprising, as ventricular peformance, even in normals, is not enhanced when increasing LV afterload (215,264), by increasing systemic vascular resistance. According to Starling (265) the EF of the subsequent contraction falls, thereby increasing end diastolic volume. The increase in fibre length would then cause a more forceful contraction of the following beat - this continuing until a new equilibrium has been achieved, where stroke volume is maintained at the expense of increased end diastolic fibre length.

In the present study, only one normal subject increased EF during CPT with two subjects having significant ($\geq$ 12%) falls in EF. Although the mean EF fall was greater in patients with CAD (Figure 4.6). This yielded a sensitivity of 50% for patients with CAD and normal or near normal EF's ($\geq$ 50% : mean of 60%), but a specificity of only 37.5%, indicating that, in our laboratory using this protocol, CPT is an inadequate intervention for the detection of CAD. It is possible that the abnormal responses obtained in these normal controls may be due to subclinical cardiomyopathy, intervention

induced coronary artery spasm in the absence of symptoms or ECG changes, asymptomatic CAD or a normal variation. But, this group were asymptomatic, life-long nonsmokers with no other major CAD risk factors. Each had a normal chest x-ray, resting and treadmill exercise ECG and were presumed to have normal hearts. The study is open to criticism as coronary arteriography was not performed in order to exclude CAD. In our institution the main indication for coronary arteriography is the preoperative assessment of patients with angina pectoris and invasive investigation of our control group was not felt to be ethically justifiable.

Several studies have assessed the value of CPT in detecting CAD. In studies comparing it with dynamic exercise Manyari et al (225), and others (218,240,243) have found it to be an inferior discriminator although possibly useful in subjects who are unable to perform dynamic exercise.

In the present study CPT was found to have a different discriminatory effect if used in subjects with lower ejection fractions (Group 2), where the sensitivity of RNV at rest in detecting CAD was 55% and this increased to 75% with CPT, but in subjects with normal or near normal resting EF's, the sensitivity was only 50%. It seems inappropriate to compare a group of normals with a group with a low mean EF. Thus the results of those with normal EF's at rest (> 50% : Group 3), may be more relevant.

Despite greater increases in heart rate and blood pressure compared to CPT, SIHG was only successful in detecting five subjects in group 3 (EF > 50%), giving a sensitivity of 25%, although specificity was more acceptable. Several studies (179,266,267) comparing SIHG and dynamic exercise have shown that it is of limited value in the detection of CAD. In contrast, Bodenheimer et al (219,231), using RNV found a sensitivity of 86% and specificity of 87% - however, these findings are of limited value as most of their subjects had abnormalities at rest, in a similar way to the results of group 2 (low mean EF), in the present study.

Conclusions.

This study has demonstrated satisfactory reproducibiliy of resting RNV in a control group and of CPT and SIHG in a group with CAD. Significant heart rate and blood pressure responses were observed in both normals and those with CAD, although elevations were higher with SIHG.

Both CPT and SIHG are useful when serial comparisons of myocardial performance are to be made. A specific area of application would be the serial assessment of drugs on the myocardium as described in the preceding section of this thesis. The detection of CAD is less reliable although a review of the literature suggests they may be alternatives to dynamic exercise, when this is not possible. In our laboratory inadequate sensitivity and specificity

was achieved in patients with CAD who had normal or near normal resting EF. When studying subjects with CAD, adequate exercise may not be possible because of the precipitation of angina pectoris - this did not occur with CPT or SIHG. One major advantage of CPT and SIHG is their ease of application without risk of patient movement or excessive use of camera-time. These factors are of obvious importance when serial evaluations are necessary.

SECTION 4.2. ASSESSMENT OF THE HITACHI HME-20 PULSE AND BLOOD PRESSURE MONITOR

Introduction.

All the heart rate and blood pressure recordings reported in this thesis were made using a Hitachi HME-20 pulse and blood pressure monitor. This instrument has therefore been evaluated for the purpose of this thesis.

In recent years, increasing reliance has been placed on automated or semi-automated devices to measure blood-pressure (BP) indirectly. (268) These measurements are believed to be free of observer error, and thus provide a more reliable estimate of BP when compared to the traditional mercury column sphygmomanometer. Reports on the conventional sphygmomanometer show that as many as half of those used in hospital are inaccurate (269) and that hospitals usually have no policy for maintaining sphygmomanometers. For these reasons a number of new techniques for measurement of BP have been developed. (270,271) In addition, by providing a device permitting self-recording of blood-pressure, BP can be measured by the patient at home, thereby minimizing error induced by the anxiety of a hospital visit. These BP recordings may be more representative. (272,273) Serial measurement of BP in this way also allows for the assessment of new antihypertensive or vasoactive agents outside a hospital.

Despite their widespread use, however, the performance characteristics of such devices are often poorly documented. It is important, if these machines are to be used in screening programmes or in population studies, to determine the accuracy and variability of the recordings obtained. A number of automatic instruments have been developed. Some have depended on the application of ultrasound reflectance for the detection of arterial blood flow. Others depend on detection of Korotkoff sounds. Some of these devices have the facility of automatic control over inflation and deflation. (274,275)

The Hitachi HME-20 blood-pressure and pulse monitor is one of the more recently introduced devices based on Korotkoff sound detection. This a low-cost device which has been used for research purposes, in intensive-care units and in rural general practice. I am not aware of any critical assessment of the device in the medical literature.

Material and Methods.

The Hitachi HME-20 pulse and blood-pressure monitor is a fully automatic unit which can operate from mains or battery. An electronic microphone, shielded from extraneous noise in the pressure cuff, is employed to detect Korotkoff sounds. Phase V of the Korotkoff sounds is taken as the diastolic end-point. Automatic inflation and deflation is performed and results are displayed on a fluorescent digital display. The

measuring range is from 0-300 mmHg. and 30-200 bpm. In operation, the cuff is positioned so that the microphone overlies the maximal pulsation of the brachial artery. If an inadequate signal is detected, the instrument fails to produce a result and indicates an error on the display screen, thus minimizing possible error when used by an unskilled individual.

Supine blood-pressure was recorded from the left arm and the results compared with simultaneously recorded intra-arterial measurements. The procedure was performed towards the end of left heart catheterisation for coronary arteriography in eight subjects: all of whom consented to the study. In each case the catheter tip was positioned in the arch of the aorta to approximate to the innominate artery. Thereafter, 10 successive simultaneous measurements of blood-pressure were recorded. Catheter patency was maintained between readings by continuous flushing with a normal saline and heparin mixture. Intra-arterial pressure was charted continuously and calculated as a mean of 15 complexes immediately prior to cuff inflation and heart-rate was calculated from a simultaneous electrocardiogram using the mean of five R-R intervals preceding cuff inflation.

Intra-arterial BP was measured using a Bentley Trantec Physiological Pressure Transducer (Model 800) and a Siemens electromanometer with a Mingograph 81 six-channel recorder, calibration being carried out prior to each procedure with a mercury manometer. Direct

calibration of the system was carried out before each recording against a mercury column, 100 mmHg. being equivalent to a 5 cm deflection on the recording paper. One hundred and fifty cm long manometer connecting lines were used, manufactured by Portex. Zero reference level was taken as mid-thorax in the supine position. Although this technique has been accepted by others to provide an adequate standard (271), the author appreciates that such a system may have a tendency to over-estimate true arterial systolic blood-pressure. The blood-pressure cuff was applied to the left arm, and American Heart Association recommendations for cuff size were fulfilled. (276) Intra-arterial pressures were read by the author, unaware of the cuff readings.

Statistical Analysis.

Comparisons between direct and indirect readings were made using Student's paired t-test (two tailed) and Armitage's test for trend. (277) Correlation coefficients and regression lines were calculated, together with a between-method frequency histogram for the difference in recordings.

Results.

In general, the device underestimated systolic blood-pressure, but reproduced an accurate assessment of diastolic pressure. There was a highly significant ($p < 0.001$) correlation with direct readings for both

systolic and diastolic recordings (Figure 4.7) and also for heart-rate (Figure 4.8). Systolic pressure was underestimated by a mean of -12 mmHg. ($p < 0.001$). Gross underestimation of systolic pressure tended to occur with a systolic pressure over 180 mmHg., where in two patients the device underestimated by more than 30 mmHg. on a number of occasions. Table 4.12 shows that no significant difference could be demonstrated between the mean values for diastolic BP, or the mean heart-rate between the two methods. The mean and standard deviation of each parameter and results of paired t-tests is also shown in the table. For each comparison, a histogram of between-method difference has been constructed (Figures 4.9 and 4.10), only 31% of systolic recordings fell within ± 10 mmHg. of the intra-arterial readings, although 62% of the readings are within 10 mmHg. of the line of identity in the region of 100-150 mmHg. 80% of diastolic recordings also fell in this range. 63.9% of heart-rate measurements fell within 5 beats per minute of those calculated from the electrocardiogram. Variability of measurements was not significantly different for systolic blood-pressure when comparing IA against the Hitachi monitor ($p > 0.1$). However, there was a significant difference in variability for diastolic pressure ($0.02 > p > 0.01$).

Heart-rate measurement variability did not differ significantly ($p > 0.1$) when compared to the ECG recordings. The scatter diagrams for systolic and diastolic blood-pressure indicate a trend away from the line of identity. To determine if this trend is signifi-

TABLE 4.12 HITACHI HME-20 (cuff) RECORDED BLOOD-PRESSURE COMPARED WITH SIMULTANEOUS INTRA-ARTERIAL BLOOD PRESSURE (pressures in mmHg.), USING STUDENT'S PAIRED T TEST (two-tailed).

	Mean	S.D.	No	Mean Difference Between Values	S.D. of Differences	t	p
Systolic							
Intra-arterial	145	30)					
		)	71	-13	15.6	7.02	<0.001
Cuff	133	17)					
Diastolic							
Intra-arterial	81	13)					
		)	71	-0.2	7.9	0.21	>0.9
Cuff	80	10)					
E.C.G.	65	11)					
		)	60	1.6	7.31	1.69	>0.05
Heart Rate Cuff	66	11)					

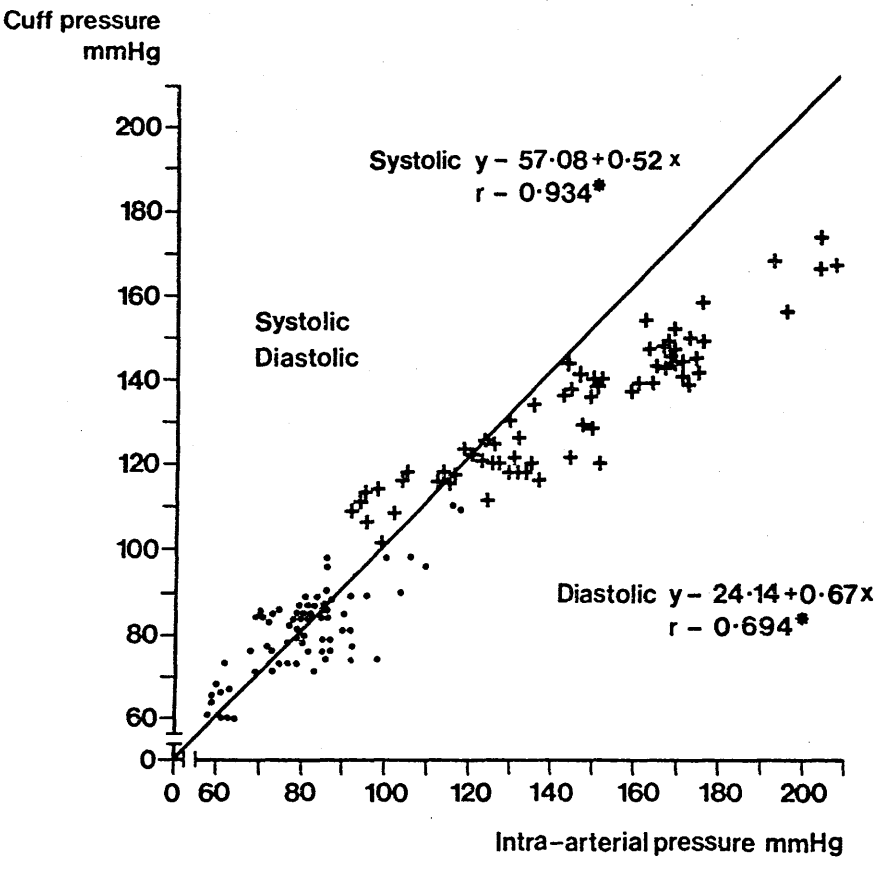


FIGURE 4.7

Scatter plot of intra-arterial blood-pressure versus cuff-recorded pressures. Line shown is line of identity. (* $p < 0.001$).

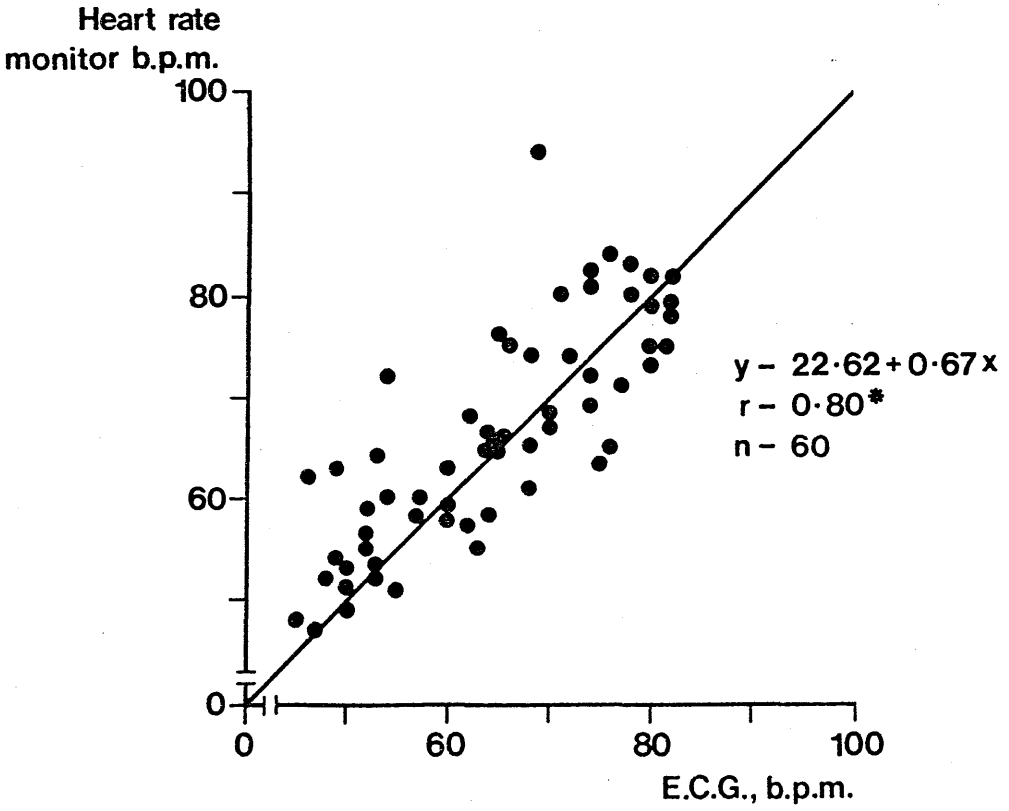
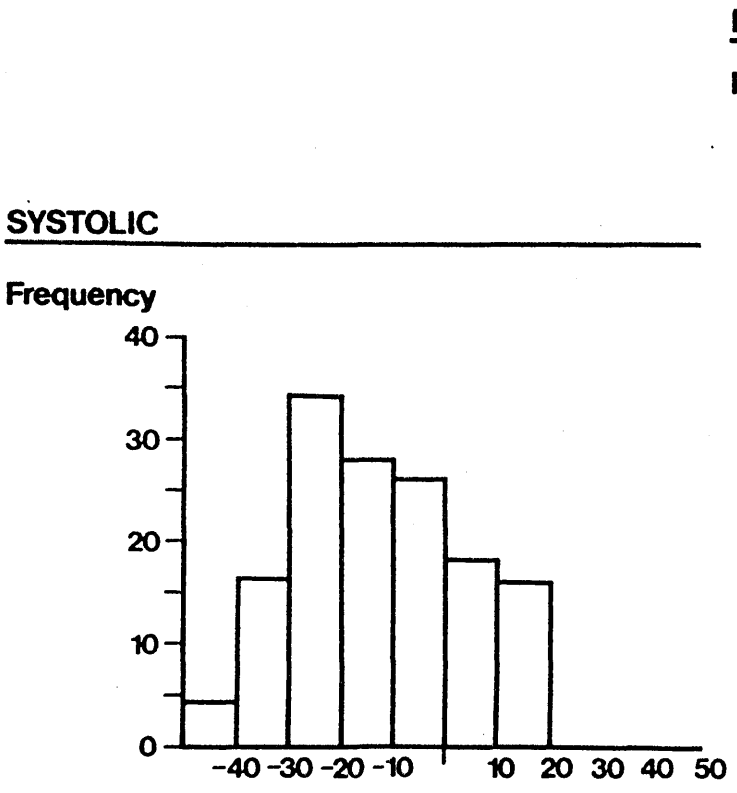


FIGURE 4.8

Scatter plot of heart-rate obtained from electrocardiogram and simultaneously recorded by Hitachi HME-20.
(* $p < 0.001$; b.p.m. = beats per minute; ECG = Electrocardiogram).



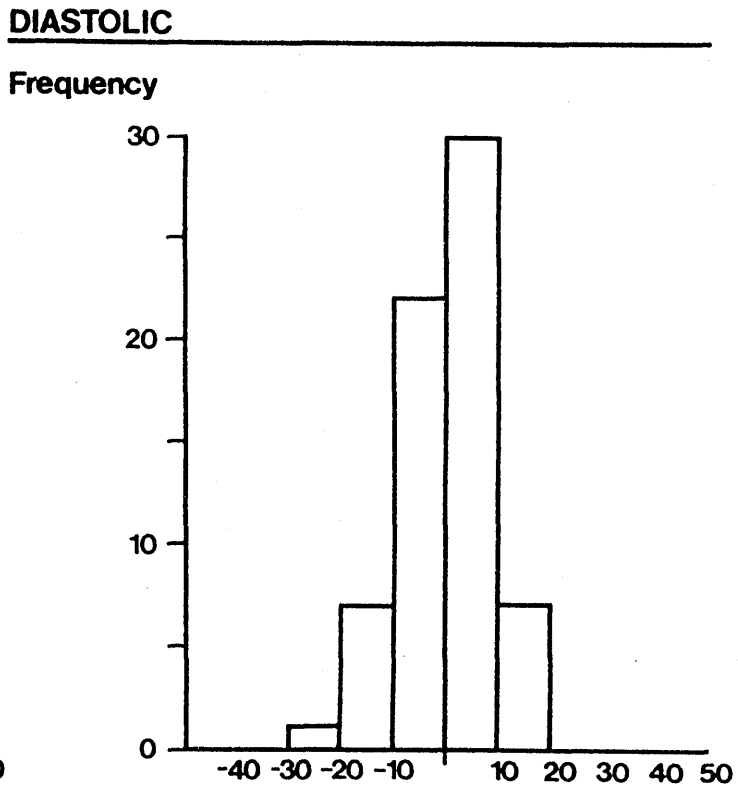


FIGURE 4.9

(a) Frequency histogram of between method difference for systolic pressure, 31% of monitor readings with ± 10mmHg. of intra-arterial pressure, 62% within ± 20mmHg.

(b) Frequency histogram of between-method difference for diastolic pressure. 80% of monitor radings within ± 10mmHg. of intra-arterial pressure.

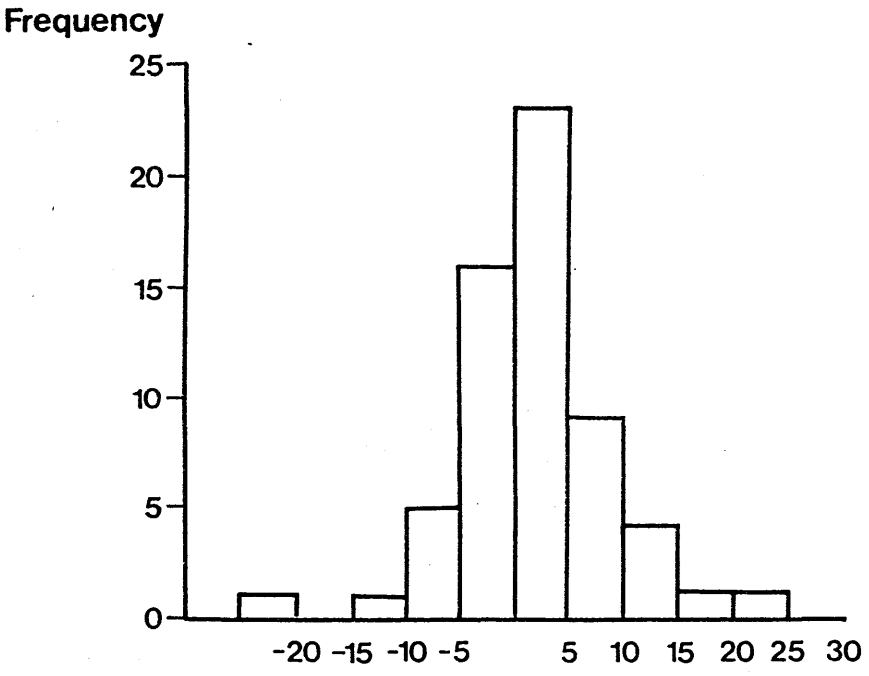


FIGURE 4.10

Frequency histogram of between-method difference for heart-rate. 63.9% of monitor readings within 5 beats per minute (b.p.m.) of electro-cardiographically recorded rate, 86.8% of readings within 10 b.p.m.

cant for a given range of blood-pressures a Chi-squared value was calculated for successive ranges of blood pressures (viz. for systolic BP: <100, 100-109, 110-119, >120 mmHg). Thus χ^2 can be split into a component due to linear regression (ie. trend) and a component due to departures from linear regression. The procedure is as detailed by Armitage. (277) The results for systolic blood-pressure are shown in Table 4.13, which shows a highly significant trend which results in erroneous measurement as the blood-pressure increases. Similar results (overall χ^2 < 0.001) are apparent for diastolic blood-pressure. When heart rate is subjected to this analysis, no significant trend was demonstrated, and thus it can be accepted that the relationship between ECG and Hitachi HME-20 recorded heart-rate follows the line of identity.

I assessed the value of this device in a number of situations. It was of particular use for home and ambulant BP recording. The machine is light (2.6 kg with batteries) and portable, and requires little maintenance. Patient operation is simple and the cuff is designed so that it is easy to apply. In addition, very little time is required for patient education, unlike the conventional sphygmomanometer. (278) Unfortunately, the device is not suitable for recording blood-pressure during patient movement, for example exercise electrocardiography, as even slight additional noise created by movement is detected by the microphone and results in erroneous measurement.

TABLE 4.13 ARMITAGE'S TEST FOR TREND, APPLIED TO RANGES OF SYSTOLIC BLOOD PRESSURE, INDICATING A HIGHLY SIGNIFICANT TREND.

Group	<100	100-109	110-119	⩾120	Total
Success	7	3	4	2	16
Failure	0	0	1	54	55
Total	7	3	5	56	71
Expected success	1.58	0.68	1.13	12.62	
Expected failure	5.42	2.32	3.87	43.38	
Score	-2	-1	0	1	

verall (1) χ^2 = 55.2 : 3 degrees of freedom : ($p < 0.001$)

(2) χ^2 due to linear regression = 49.4 : 1 degree of freedom ($p < 0.001$)

(3) χ^2 due to departures from linear regression = $^{(1)}\chi^2 - {}^{(2)}\chi^2$ = 5.8 with 2 degrees of freedom ($p > 0.05$)

Discussion.

In general, the Hitachi HME-20 pulse and BP monitor provides a satisfactory estimate of diastolic pressure and heart-rate. There is a tendency to underestimate systolic pressure, however, and this is most marked when intra-arterial pressure is more than 150 mmHg. (Figure 4.8): recordings in this range account for the skewed distribution of differences in Figure 4.9(a), which indicates that only 31% of measurements were within ±10 mmHg of IA recordings. There is an acceptable standard of measurement, however, between 100 and 150 mmHg. Highly significant correlation coefficients for heart-rate and both systolic and diastolic BP indicate that, when changes in a parameter are of prime importance (for example when evaluating anti-hypertensive medication), the device will reproduce an accurate record of these changes. Because of the additional noise created by exercise, which is detected by the cuff microphone, I did not find the instrument valuable as a means of assessing BP during exercise.

Systolic pressure was underestimated by a mean of -12 mmHg. This is comparable with the standard sphygmomanometer, which has been shown to underestimate systolic pressure by -10 mmHg. (271), and also the random zero sphygmomanometer which records clinic blood-pressures significantly lower than simultaneous IA pressures (mean -13/-1 mmHg.) (278) In a previous study evaluating BP recorders (269), all seven devices assessed gave signifi-

cantly different values compared to IA recordings for systolic BP and in five cases significantly underestimated diastolic BP. None of these alternative recorders are capable of measuring heart-rate. Labarathe et al (270), evaluated seven instruments, but used indirect means only. I considered that an intra-arterial standard was necessary for evaluation of this more recent device. Many workers have found a wide range of differences when comparing IA and indirect cuff BP measurements. (279,280) Indirect BP is subject to considerable variability (281), and to minimize the effect of this variability, serial simultaneous measurements were taken in this study.

Thus, the Hitachi HME-20 compared favourably with currently available devices, and may be superior when measuring diastolic pressure. Its main shortcoming is underestimation of systolic BP, and this failing is shared by other devices of this sort. (271) While occasional large individual differences in systolic pressure did occur ($>$ 150 mmHg), the meaned recordings from eight patients compared favourably, suggesting that a satisfactory estimate of blood-pressure patterns can be obtained with this instrument. Although the intra-arterial measurement may itself overestimate systolic blood-pressure, I do not feel that this could account for the gross differences in systolic pressure outlined above. However, I demonstrated a trend away from the line of identity for both systolic and diastolic blood-pressure. In addition, the technical reliability of the device over extended periods of operation has been found to be excellent, both during

hospital and domestic use. The number of innovations in techniques and devices for measuring blood-pressure is surprisingly small (270,271,282-284) and the reports are often lacking in detail. This position possibly reflects the gap between medical and engineering interests. I have evaluated a monitor, which, because of its low price and ease of operation, may prove attractive to both the clinician and patient and can be relied upon to provide a comparable performance to many more expensive devices.

Conclusions.

Highly significant ($p < 0.001$) correlations were found between intra-arterial systolic and diastolic pressures and pressures recorded by the Hitachi monitor. Similarly, the electrocardiographically computed heart-rate, and that given by the Hitachi monitor were significantly correlated ($p < 0.001$). Systolic blood-pressure was underestimated by a mean of -12 mmHg. and tended to become more erroneous when intra-arterial pressure was > 150 mmHg. These results are comparable to more expensive pulse and blood-pressure monitors. I conclude that the instrument can reproduce a satisfactory estimate of heart-rate and blood-pressure and may be of particular use when a change of blood-pressure is of prime importance, rather than an absolute measurement.

SECTION 5.

THE INFLUENCE OF INTRINSIC SYMPATHOMIMETIC ACTIVITY ON THE LIPOPROTEIN PROFILE DURING CHRONIC BETA-ADRENOCEPTOR BLOCKADE.

This study was carried out in collaboration with the Department of Pathological Biochemistry, The Royal Infirmary, Glasgow.

5.1. INTRODUCTION.

Together with methyldopa, prazosin, phenytoin and oral contraceptives (285), beta-adrenoceptor blockers have been shown to have an adverse effect on serum lipids. It is postulated that any agent which adversely affects lipoproteins, may exacerbate coronary atherosclerosis and thus diminish the benefit of treatment. The possibility that the benefits of treating hypertension with beta blockers may be negated by the increase in risk associated with changes in serum lipoproteins has been suggested by both Shaw (286) and Helgeland. (287)

It is hoped that by reducing blood pressure with beta blockers the medium and long-term risk of CAD is reduced. Although the Veterans Administration Co-operative Group (288) provided clear evidence of an effect on cerebro-vascular disease morbidity and mortality, no reduction in cardiac events was demonstrated. This failure to show a reduction in CAD mortality has been reported in several large studies investigating hypertensive individuals. (289-291) These negative results have raised the possibility that metabolic adverse effects may be negating the benefits of blood pressure reduction. The effect of at least eight commercially available beta blockers have been investigated with respect to plasma lipids and the literature concerning their effect on lipids is conflicting. No apparent consistent differences result from the presence of ISA or cardioselectivity. As few studies have lasted more than six months, and since these drugs are usually

prescribed on a long-term basis, it is important to investigate these drugs over a longer period of time. In addition since some earlier studies suggested that drugs with ISA might have less harmful effects on plasma lipids than pure beta blockers (286,292,293), it is appropriate to examine the influence of ISA in chronic treatment with beta blockers.

The following, is a brief summary of lipoprotein composition and their association with CAD.

Lipoprotein Composition.

Plasma lipoproteins are macromolecular aggregates consisting of an apoprotein shell with a lipid core, the predominant lipids in plasma being triglycerides, phospholipids and cholesterol esters, all of which are esters of long-chain fatty acids. The chief function of plasma lipoprotein is to transport lipids from sites of absorption or synthesis to sites of utilisation.

Triglycerides are mixed fatty acid esters of glycerol and are chiefly synthesized in the liver from circulating nonesterified fatty acids and glycerol phosphate. Cholesterol is a sterol which is an essential component of cell membranes. Virtually all the newly synthesized cholesterol in plasma originates from the liver and distal small intestine, while dietary cholesterol is predominantly absorbed from the proximal small intestine.

Lipoproteins can be classified according to their flotation rate (Svendberg Flotation Units: Sf) on analytical ultracentrifugation; hydrated density; electrophoretic mobility or immunochemical behaviour. I have used the former for the purposes of this thesis. The chief characteristics of the lipoproteins are shown in Table 5.1.

Chylomicrons are the largest of the lipoproteins and are the form in which dietary triglyceride is transported after its absorption from the small intestine. Triglyceride, together with small amounts of cholesterol ester, is enclosed within a spherical shell of phospholipid, free cholesterol and apoprotein.

Very low density lipoprotein (VLDL) is also relatively triglyceride rich, the particles resembling small chylomicrons, but containing proportionately more cholesterol, phospholipid and protein. They are synthesized mainly in the liver and act as the main carrier of endogenous triglyceride. VLDL synthesis is enhanced by an increased flux of nonesterified fatty acids to the liver by factors which stimulate hepatic fatty acid synthesis, such as a high carbohydrate intake.

Most of the cholesterol in plasma is transported in the form of low density lipoprotein (LDL). Each LDL particle contains the same amount of apo B as VLDL but has much less triglyceride, no apo C and a higher ratio of sphingomyelin to lecithin. LDL consists of one

TABLE 5.1 CHIEF CHARACTERISTICS OF PLASMA LIPOPROTEINS.

	Density g/ml.	Lipids % of total lipid		
		TG	TC	PL
Chylomicrous	0.95	88	3	9
VLDL.	1.006	56	17	19
LDL.	1.091-1.063	7	59	28
HDL_2.	1.063-1.125	6	43	42
HDL_3.	1.125-1.21	38	41	55

ABBREVIATIONS:
TG = Triglyceride.
TC = Total Cholesterol.
PL = Phospholipid.
VLDL = Very Low Density Lipoprotein.
LDL = Low Density Lipoprotein.
HDL = High Density Lipoprotein.

quantitatively major component (LDL_2) and two minor components (LDL_1,LDL_3).It is probable that LDL is normally derived exclusively from VLDL - this conversion generating an intermediate density lipoprotein (IDL).

High density lipoprotein (HDL) although precipitating as a single component, separates further on ultracentrifugation into minor and major subfractions HDL_2 and HDL_3, which have different properties and functions. Newly synthesized HDL contains mainly protein, phospholipid and free cholesterol.

Apolipoproteins.

Apoproteins are proteins which form the capsule or shell around the lipoproteins. Depending on molecular variations the apoproteins are subdivided, the major subdivisions being apoprotein A, B, C, and E.

The lipid composition of lipoproteins can vary greatly and it has been suggested that measurement of the apoprotein concentration provides a better index of the number of particles than does determination of their cholesterol or triglyceride content.

Apoproteins have three main functions:

1. They help solubilise cholesterol and triglycerides by interacting with phospholipids.

2. They regulate the reaction of lipids with enzymes such as lecithin cholesterol acyl transferase (LCAT) or lipoprotein lipase.

3. They bind to cell surface receptors and thus determine the sites of uptake.

The predominant apoprotein constituents of the major lipoprotein subfractions are shown in Table 5.2. It has been suggested that measurement of the apoproteins may be a more powerful indicator of atherosclerotic risk, compared to determination of the amount of cholesterol these particles carry. (294,295). At present, however, it is accepted that analysis of apo A-I and Apo B provides additional information to that obtained by measuring serum lipids, but has not replaced the latter as criteria of CAD risk.

Association of Lipoprotein Changes with Coronary Heart Disease.

After hypertension and cigarette smoking, it has been established that disturbances in serum lipoproteins are associated with an increased risk of CAD. Hypercholesterolaemia is generally considered a major risk factor for CAD. (296-298) Some (296), but not all (297,298) studies indicate that hypertriglyceridaemia may also be a risk factor irrespective of the cholesterol concentration, but it is unlikely that small increases in serum triglycerides contribute to vascular morbidity. In

TABLE 5.2 APOLIPOPROTEIN COMPONENTS OF THE MAJOR LIPOPROTEIN SUBFRACTIONS.

Lipoprotein	Apolipoprotein Composition	
	Major Component	Minor Component
Chylomicrons	Apo C	Apo B
	Apo A	Apo E
VLDL.	Apo B	Apo E
	Apo C	
LDL.	Apo B	Apo A
HDL_2.	Apo A-I)	Apo C,E
HDL_3.	Apo A-II)	

Abbreviations: Apo - Apolipoprotein.

addition there is still no evidence that reducing the triglyceride concentration to within the normal range results in a reduced incidence of cardiovascular disease. Epidemiological data (299) suggests that a combined hyperlipidaemia (increased level of cholesterol and triglycerides) may represent a more significant risk for premature CAD than hypertriglyceridaemia alone.

An elevation of LDL and reduction of HDL are associated with an increased risk of CAD (89,90). HDL_2 is significantly reduced in CAD and is the lipoprotein subfraction which correlates best with the severity of CAD (300), but there is no significant change in HDL_3. Whether an increase in VLDL is associated with an increased atherosclerotic risk, is still a subject of controversy. (301) As suggested above apoproteins may be better discriminators for atherosclerosis. (302-304) However, Ishikama (303) considered Apo A-I to be a less powerful predictor of CAD than HDL cholesterol. Avogaro (304) in a large series of MI survivors and controls, concluded that Apo A-I and Apo B were as effective discriminators as either cholesterol, triglycerides or HDL cholesterol in subjects less than 50 years and superior discriminators in older subjects. Whayne et al (305) have confirmed that Apo B concentration correlates better than cholesterol with angiographic evidence of CAD.

As beta-adrenoceptor blockers are capable of altering the lipoprotein profile it is important to examine the effects which ISA may have as even small

changes in the lipoproteins may result in a significantly increased or decreased risk of CAD.

5.2. PATIENTS AND METHODS.

Patients.

Male subjects referred to a Cardiology Clinic with a diagnosis of chronic stable angina were considered for the study if they were untreated or inadequately controlled on their previous therapy. If the patients were in the latter category, therapy was tailed off over two weeks and the subjects were given no therapy for a further two weeks, before entering into the study. Written informed consent was received from each patient before entry to the study and the protocol was approved by the Research Ethics Committee. Forty subjects were recruited with a mean age of 53.4 years (SD ± 7.9) and a range of 38-68 years. No patient was admitted to the study if there was any evidence of, or a previous history of diabetes mellitus; renal failure; chronic obstructive airways disease or asthma; valvular or congenital heart disease or unstable angina. As numerous environmental factors are known influence the serum lipoproteins (90,306), participants were instructed not to change their dietary, smoking, exercise habits or their alcohol consumption for the duration of the investigation. In addition, as metabolic events surrounding a myocardial infarction are known to cause disturbances or the lipoprotein profile (307), no subject was included in the study who had had a myocardial infarction in the previous year. Other than glyceryl trinitrate, no other drug therapy was permitted during the study.

Dietary Assessment.

Particular attention was paid to diet and each patient underwent dietary assessment by a qualified Dietician at two stages separated by six months during the study. Of the various methods of dietary assessment available the seven day diet history was the method of choice in this study (308). This method was chosen in preference to other methods which involved the weighing of food before meals as this technique is impractical for working men. Each subject was asked which foods would normally be eaten in the course of a week and to estimate quantity of food eaten at each mealtime using approximate household measures such as tablespoons and cups. There then follows a breakdown list which rechecks with the patients the accuracy of the diet recall. The dietary assessment relies on the accuracy of the patient's memory and detailed questioning by the Dietician. It is stressed that the resulting food analysis is an estimate of the food eaten. The dietary intakes were then analysed for protein, energy and kilocalories, total fat, saturated fat, polyunsaturated fat and cholesterol, as described elsewhere. (309,310)

Study Protocol.

On attendance at the clinic, weight and height was measured and the Quetelet Index (306) (weight/height^2) was calculated. Subjects were randomly allocated to

treatment with either Pindolol 2.5 mgs. t.d.s. or Propranolol 40 mgs. t.d.s. on a single-blind basis. After two weeks treatment the dose of each drug was doubled and held constant for one year. During this time patients were seen on six occasions - 2,6,12,26, and 52 weeks following commencement of therapy. At each visit heart rate and blood pressure were recorded after five minutes supine rest, 70 ml. of blood was withdrawn in a sitting position for analysis of haematocrit, serum lipoproteins and apolipoproteins. HDL subfractions were measured at 0,12,26 and 52 weeks only. All blood samples were taken at the same time of day (usually 09.00 hours to 11.00 hours) after an overnight fast (at least 14 hours) and the patient was instructed to take the last dose of medication at 08.00 hours on the day of each hospital visit and also to refrain from smoking for at least 14 hours beforehand. Compliance with drug therapy was assessed and is described elsewhere in this thesis. (Section 2)

5.3. LIPOPROTEIN ANALYSIS.

The major lipoprotein classes may be separated and quantified in a number of different ways. In this study the technique of ultracentrifugation was used. This involves preparative ultracentrifugation of serum samples followed by lipid analysis of the resultant fractions, and is an accepted technique which has been used previously in studies examining the effects of beta blockers on lipoprotein profiles (83,311), and is the accepted reference technique. Separation of lipoprotein classes may be effected by sequential ultracentrifugation (312), but a modified procedure combining single ultra-centrifugation followed by precipitation (313) of LDL to separate it from HDL is now widely used and was the technique used in this study.

After venepuncture, blood was withdrawn into tubes containing potassium EDTA for measurement of plasma lipids and lipoproteins. Plasma total triglycerides were estimated by a fully enzymatic method on a Technicon Autoanalyzer (2nd generation) according to the fluorometric procedure of Kessler and Lederer. (314) Plasma total cholesterol was estimated by an enzymatic colorimetric method (315) using a modified Lieberman-Burchard reaction. (316) Five mls. of plasma was transferred to a 6.5 ml. Beckman Cellulose Nitrate Ultracentrifuge tube, which was then filled by layering saline of density 1.006 on top of the plasma. After ultracentrifugation at 105,000 g (39,000 rpm.) for 16 hours, at a temperature of 4°C.,

three zones can be seen in the tube, a narrow top layer which is opalescent, a clear middle layer and a yellow bottom layer. The top layer (Figure 5.1a) contains the VLDL which is separated from the rest (Figure 5.1b) by slicing the tube. Both fractions, A and B, are quantitatively transferred to separate volumetric flasks. A heparin - manganous chloride reagent is added to Fraction B (ie. the infranatant containing LDL and HDL and mixed by vortexing. (317) The tube is then stoppered and left overnight at 4°C. The following day it is centrifuged for 30 minutes at 10,000 rpm. at 4°C. Thus precipitating LDL which is packed at the bottom of the tube with HDL in the supernatant. The cholesterol concentrations of fractions A(VLDL), B (LDL and HDL) and of HDL were measured. The concentration of LDL was obtained by subtracting the HDL cholesterol concentration from that in fraction B.

HDL was further subfractionated into it's components HDL_2 and HDL_3 by rate zonal ultracentrifugation. (318,319) The sample for analysis is prepared by increasing the density of a 2 ml. aliquot of plasma to 1.216 Kg./1. by the addition of 4 mls. of a sodium bromide solution of density 1.31 Kg./1. The preparation is then subjected to ultracentrifugation for 30 hours at 40,000 rpm. and at 18°C. One millilitre (containing total plasma lipoproteins) is harvested from the top of the tube into a graduated volumetric cylinder and used for analytical ultracentrifugation. Prior to analysis the sample is diluted with 1.20 Kg./1. of sodium bromide solution so

SERUM LIPOPROTEIN ANALYSIS :- ULTRACENTRIFUGATION + PRECIPITATION

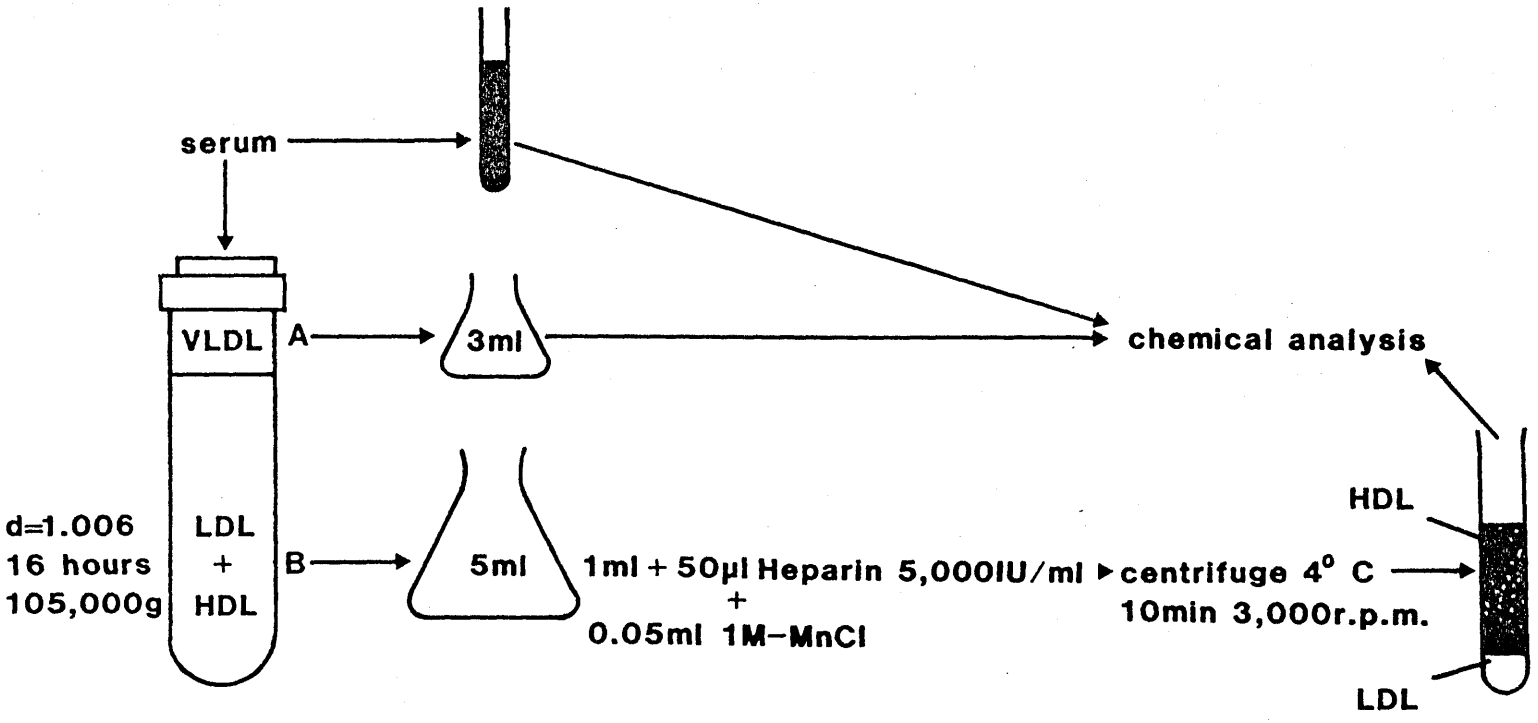


FIGURE 5.1

Analysis of serum lipoproteins by ultracentrifugation and precipitation. The lipid concentrations in serum, A(VLDL) and HDL are measured directly. The concentrations in LDL are obtained by subtracting the lipid concentrations in HDL from B(LDL + HDL).

that during centrifugation the total light absorbance at a wavelength of 280 nm. does not exceed 1.0. An aliquot of the diluted sample is then injected into the sample side of a double sectored cell of a Beckman AN-F rotor for ultra-violet scanning. This technique is fully automatic.

Apoprotein Analysis.

These analyses were carried out using an Encore Centrifugal Analyser (Baker Instruments). The analysis depends on a specific protein reaction between the apoprotein (antigen) and an anti-apolipoprotein antibody in the serum which is raised in sheep. A similar process is described by Austin and Mazuicki. (320) A precipitation reaction occurs causing formation of 3-dimensional complexes which cause the sample to become turbid and to be capable of scattering and absorbing light. Light, with a wavelength of 292nm. is shone into the sample and the complexes will absorb a proportion of this. There is a direct relationship between the amount of light absorbed and the quantity of apoprotein. Using test standard with a known concentration of apoprotein it is possible to calculate the concentration in a test sample and to construct a calibration curve. The reaction between antibody and apoprotein is carried out in the rotor of the Encore Centrifugal Analyser. Complexes are detected spectrophotometrically as the reaction proceeds. Prior to loading the sample onto the machine, to achieve rapid formation of antigen - antibody complexes it is

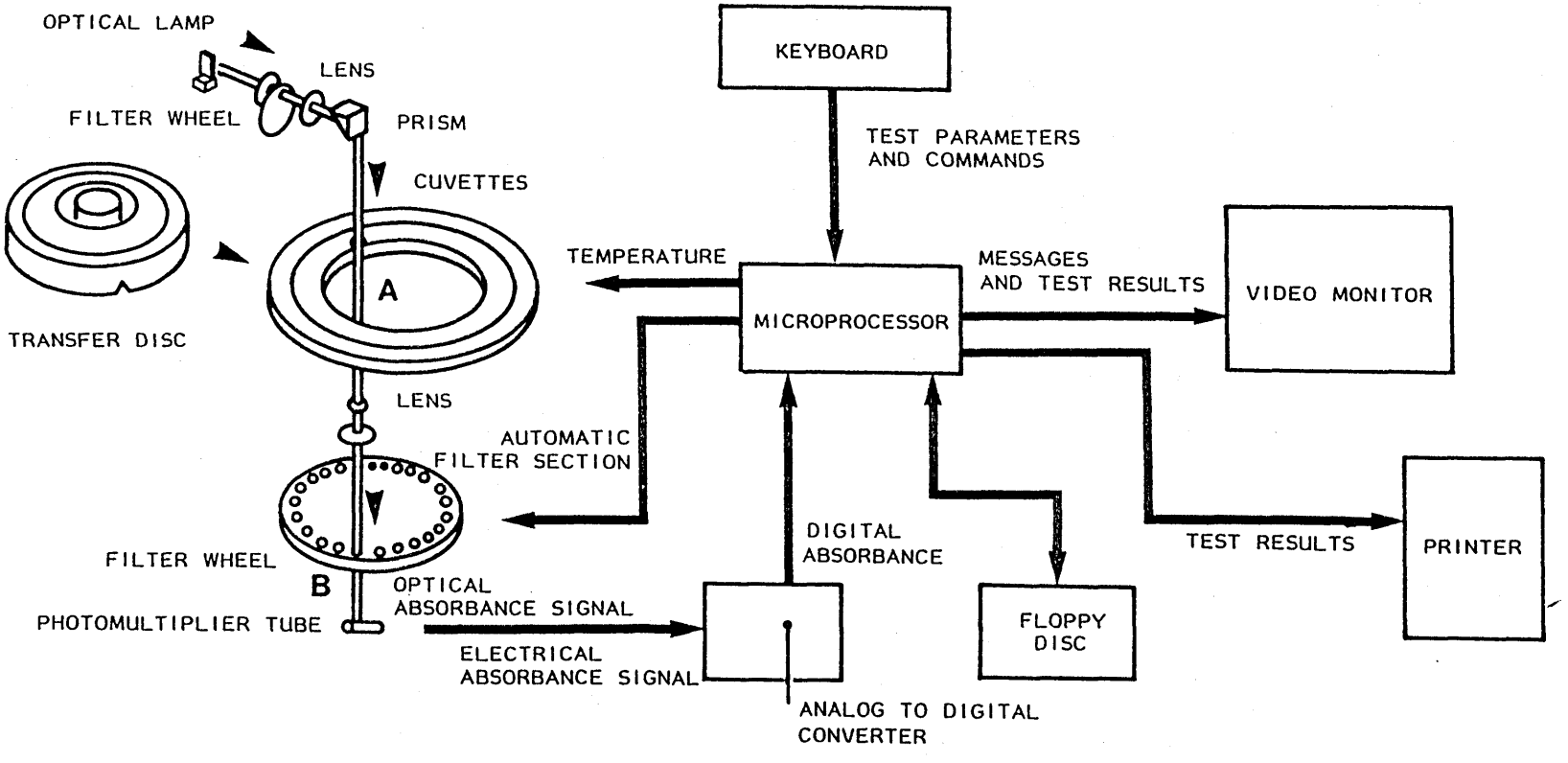


FIGURE 5.2

Functional diagram of Encore autoanalyser. The transfer disc contains both the patient's serum and the specific antibody when placed within the machine as indicated. The centripetal effect exerted by rotation causes mixing of the antigen and antibody and a resultant turbidity of the solution to occur.

necessary to accelerate complex formation by adding a 4% polyethylene glycol and isotonic saline mixture. After 7.5 minutes, to allow for equilibration, the solution is then passed through a 0.22 m. millipore filter to remove any debris. After mixing this diluted sample with 250 ml. of 1/40 diluted antiserum, mixing then occurs on the analyser and the reaction proceeds.

A schematic representation of the procedure from this stage is shown in Figure 5.2.

Statistical Analysis.

Two-way analysis of variance was carried out initially. Where this indicated a significant effect due to treatment then parametric statistical analyses (paired Student's t test) were performed. In addition to a Wilcoxon rank sum test to test for between group differences. The significance levels reported are the most conservative obtained. Linear regression analysis was applied to the change from initial values of HDL concentrations to identify any relation between the magnitude of changes after treatment and the initial value.

5.4. RESULTS.

There were no significant differences in the pre-treatment characteristics of the two groups of subjects (Table 3.1), in terms of age, body mass index, resting heart rate or blood pressure. Dietary assessment revealed a similar weekly intake of protein, kilocalories, total fat, saturated fat and polyunsaturated fat between the two groups. Dietary intake between the two assessments was similar (Table 5.3) with the exception of saturated fat and cholesterol of which more was consummed by those on Propranolol at the second dietary assessment ($p < 0.05$). Haematocrit, as a crude assessment of plasma volume, did not change significantly in either treatment group throughout the investigation (Table 5.4). The effect of each drug on resting heart rate and blood pressure is shown in Figure 5.3. There was a significant fall in heart rate in those receiving propranolol after two weeks (71 ± 10 to 55 ± 7 bpm; $p < 0.01$), but not with pindolol and this pattern was maintained throughout. Likewise those treated with propranolol showed a significant reduction in resting systolic blood pressure (134 ± 29 to 112 ± 14 mmHg., $p < 0.01$), but subjects receiving pindolol did not have a reduction in blood pressure.

The concentrations of the major lipoproteins and apolipoproteins at each assessment period are shown in Table 5.5 (Pindolol Group) and Table 5.6 (Propranolol Group). No significant change in any parameter occurred in those treated with pindolol. However there were

TABLE 5.3 RESULTS OF DIETARY ASSESSMENT. (Expressed as estimated weekly consumption, mean ± standard deviation) AT FIRST AND SECOND ASSESSMENTS.

	PROTEIN (g)		KILOCALORIES		TOTAL FAT (g)		SATURATED FAT (g)		POLYUNSAT. FAT (g)		CHOLESTER
	1	2	1	2	1	2	1	2	1	2	1
PINDOLOL GROUP	531 ± 139	535 ± 144	11065 ± 917	11643 ± 3132	492 ± 186	536 ± 158	207 ± 84	231 ± 103	52 ± 27	48 ± 19	2265 ± 877
P VALUE	NS		NS		NS		NS		NS		NS
PROPRANOLOL GROUP	530 ± 114	574 ± 84	11794 ± 2803	12462 ± 3368	489 ± 195	565 ± 165	208 ± 93	238 ± 87	57 ± 19	57 ± 20	1803* ± 707
P VALUE (within group)	NS		NS		NS		$p < 0.05$		NS		NS

* $p < 0.05$ (between group)

TABLE 5.4 HAEMATOCRIT VALUES THROUGHOUT THE STUDY.

Week No.	0	2	6	12	26	52
Pindolol Group	0.458	0.448	0.460	0.457	0.449	0.456
	±	±	±	±	±	±
NS	0.024	0.021	0.028	0.026	0.040	0.031
Propranolol Group	0.459	0.466	0.459	0.456	0.453	0.455
	±	±	±	±	±	±
NS	0.026	0.032	0.039	0.036	0.038	0.041

Abbreviation : NS = No significant change throughout.

TABLE 5.5 EFFECT OF PINDOLOL ON SERUM LIPID CONCENTRATIONS. Values are expressed as mean ± 1 S.D.and are expressed mmols/l. apart from HDL subfractions and apoproteins which are in mg/100ml.

	Basal	2 weeks	6 weeks	12 weeks	26 weeks	52 weeks
Serum Cholesterol Concentration.						
Total	7.08 ± 1.419	6.80 ± 1.127	7.13 ± 1.323	6.88 ± 0.955	6.84 ± 1.109	6.86 ± 1.011
LDL	4.97 ± 1.285	4.77 ± 1.117	4.99 ± 1.165	4.80 ± 0.995	4.73 ± 1.211	4.85 ± 0.896
VLDL	0.83 ± 0.383	0.78 ± 0.395	0.84 ± 0.343	0.79 ± 0.283	0.85 ± 0.417	0.78 ± 0.346
HDL.	1.27 ± 0.192	1.24 ± 0.174	1.29 ± 0.195	1.29 ± 0.204	1.24 ± 0.158	1.23 ± 0.172
HDL_2.	27.26 ± 16.336	–	–	27.53 ± 15.097	31.32 ± 18,388	32.42 ± 13.829
HDL_3.	224.37 ± 42.642	–	–	215.16 ± 39.939	218.05 ± 37.944	212.00 ± 32.118
HDL/Total Cholesterol	0.188 ± 0.0557	0.188 ± 0.0457	0.187 ± 0.0452	0.191 ± 0.0382	0.186 ± 0.0414	0.182 ± 0.0320
HDL_2/HDL_3.	0.124 ± 0.0849	–	–	0.133 ± 0.080	0.139 ± 0.886	0.155 ± 0.0657
Total Triglyceride Concentration.	1.94 ± 0.654	2.06 ± 0.983	2.17 ± 0.882	2.05 ± 0.631	2.16 ± 0.794	1.94 ± 0.681
Apoprotein A-1	124.59 ± 15.444	125.83 ± 11.185	128.98 ± 13.223	127.85 ± 23.446	125.89 ± 20.238	130.18 ± 23.660
Apoprotein A-II	29.02 ± 3.884	28.11 ± 3.580	28.19 ± 4.274	28.97 ± 3.410	28.68 ± 6.090	28.67 ± 3.829
Apoprotein B	168.57 ± 51.767	177.87 ± 33.770	179.28 ± 35.73	175.35 ± 29.615	180.18 ± 41.616	185.79 ± 30.402

Abbreviations : LDL - Low Density Lioporoteins; VLDL - Very Low Density Lipoprotein; HDL - High Density Lipoprotein.

FIGURE 5.3

Resting blood pressure and heart rate response at intervals throughout one years treatment with
a. Pindolol (n = 19) and
b. Propranolol (n = 21).
Values are mean ± standard deviation.

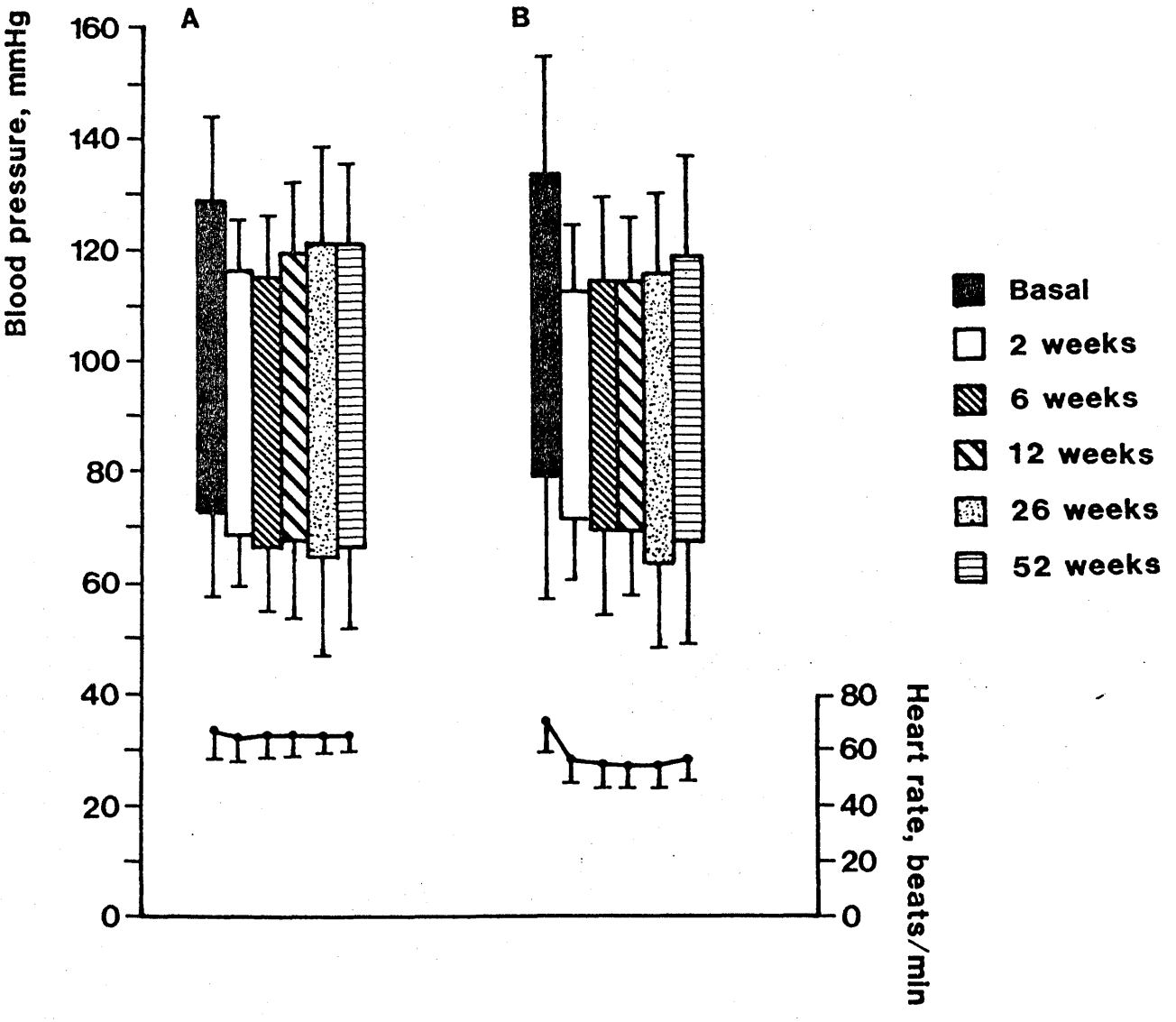


TABLE 5.6 EFFECT OF PROPRANOLOL ON SERUM LIPID CONCENTRATIONS. Values are expressed as mean ± 1 S.D. and are expressed in mmol/l. apart from HDL subfractions and apoproteins which are in mg/100ml.

	Basal	2 weeks	6 weeks	12 weeks	26 weeks	52 weeks
Serum Cholesterol Concentration.						
Total.	6.73 ± 1.061	6.84 ± 1.257	6.72 ± 1.111	6.94 ± 1.281	6.71 ± 1.249	6.83 ± 1.352
LDL.	4.69 ± 1.062	4.67 ± 0.982	4.61 ± 0.963	4.54 ± 1.065	4.54 ± 1.198	4.51 ± 1.188
VLDL.	0.80 ± 0.541	0.93 ± 0.722	0.88 ± 0.428	1.05 ± 0.846	1.01 ± 0.926	1.11 ± 0.952*
HDL.	1.31 ± 0.305	1.25 ± 0.206	1.23 ± 0.206	1.27 ± 0.203	1.18 ± 0.208**	1.17 ± 0.234*
HDL_2.	33.09 ± 22.558	–	–	32.29 ± 24.319	27.43 ± 21.495*	39.00 ± 22.190*
HDL_3.	219.29 ± 42.816	–	–	220.14 ± 35.879	193.95 ± 36.314***	199.05 ± 54.396*
HDL/Total Cholesterol.	0.199 ± 0.0610	0.188 ± 0.446	0.187 ± 0.0410	0.188 ± 0.0425	0.181 ± 0.0480	0.178 ± 0.0515*
HDL_2/HDL_3.	0.155 ± 0.0980	–	–	0.146 ± 0.1082	0.140 ± 0.0888	0.195 ± 0.0982*
Total Triglyceride Concentration.	2.48 ± 1.595	2.60 ± 1.722	2.51 ± 1.094	2.85 ± 1.972	2.78 ± 1.840	2.62 ± 2.079
Apoprotein A-I.	127.15 ± 17.039	134.73 ± 21.430*	136.27 ± 31.595	128.05 ± 11.655	127.40 ± 10.074	128.49 ± 13.000
Apoprotein A-II.	30.42 ± 4.633	29.82 ± 3.433	29.66 ± 4.082	30.11 ± 3.635	29.17 ± 2.929	28.82 ± 2.989
Apoprotein B.	171.09 ± 38.458	187.87 ± 49.412*	178.51 ± 36.063	177.00 ± 37.424	171.51 ± 36.397	181.35 ± 44.290*

Abbreviations : LDL - Low Density Lipoprotein; VLDL - Very Low Density Lipoprotein; HDL - High Density Lipoprotein.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

significant rises in total triglyceride (↑13.5%) and in HDL_2 at 52 weeks (↑18%) (Figure 5.4), despite there being little change in total HDL or HDL_3. This is reflected in a sequential rise in the HDL_2 to HDL_3 ratio from a basal value of 0.124 ± 0.0849 to 0.155 ± 0.0657 at 52 weeks. Although no change occurred in apoprotein A-II, both apoprotein A-I and apoprotein B rose throughout the study, but these changes failed to reach significant levels.

As with pindolol, propranolol produced a non-significant rise in triglyceride (↑14.2%). No significant change in total cholesterol or low density lipoprotein occurred. Very low density lipoprotein rose progressively to a level 38.5% higher than the basal value at 52 weeks ($p < 0.05$). Although the level of total HDL fell by up to 12.5% at 26 and 52 weeks ($p < 0.01$ and $p < 0.05$ respectively), the level of HDL_2 rose significantly by 17.5% at 52 weeks ($p < 0.05$). This followed a fall in HDL_2 at 26 weeks of 20.5% ($p < 0.05$). HDL_3 fell by up to 13.2% at 26 weeks ($p < 0.001$). These changes resulted in a rise in the HDL_2 to HDL_3 ratio from 0.155 ± 0.0980 to 0.195 ± 0.0982 ($p < 0.01$) at 52 weeks.

Apoprotein A-I rose from 127 ± 17.0 to 135 ± 21.4 ($p < 0.05$) at two weeks, but after six weeks began to fall back to pre-treatment levels. No significant change in apoprotein A-II occurred, but apoprotein B rose significantly at two weeks ($p < 0.05$) and 52 weeks ($p < 0.05$).

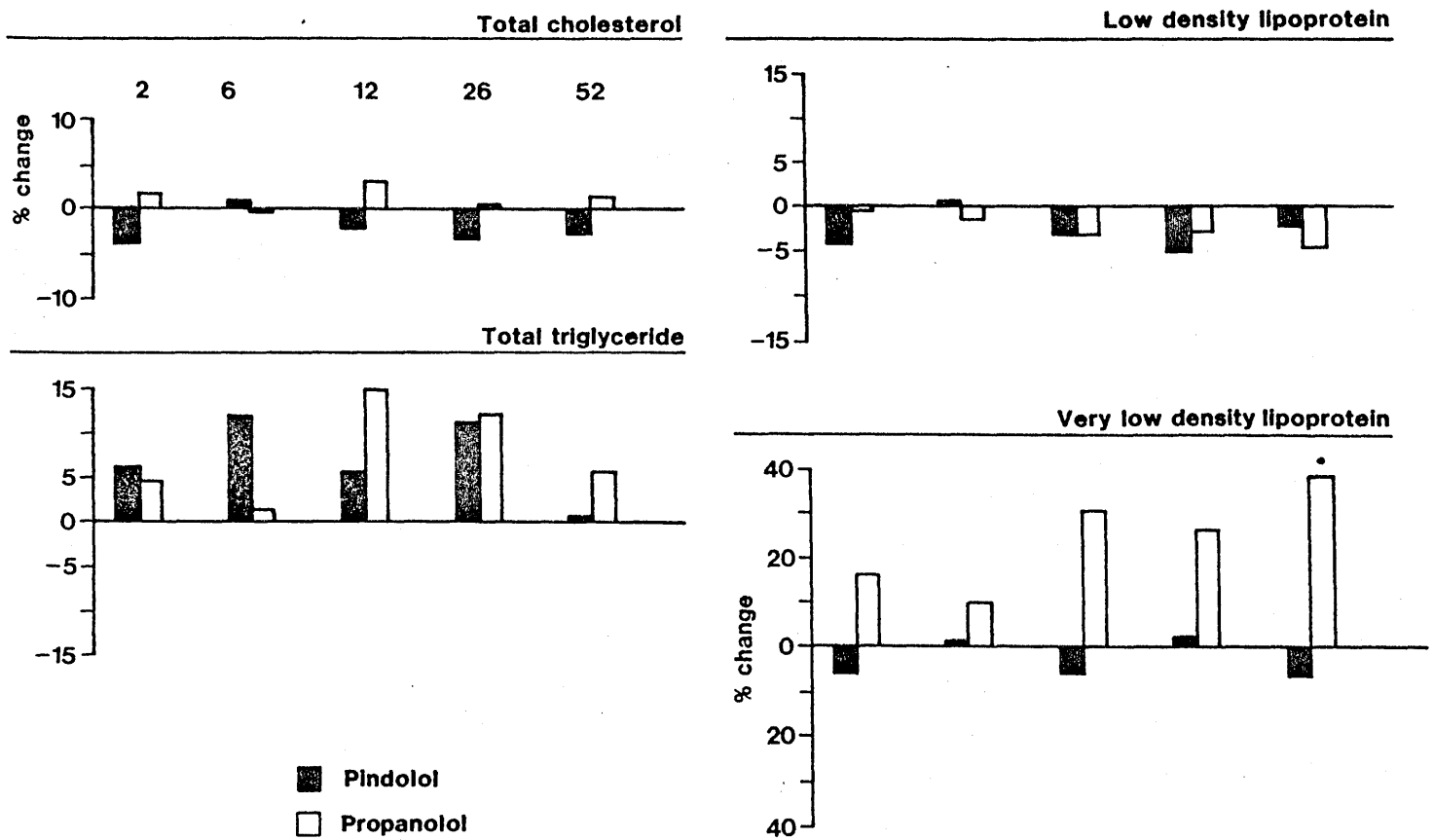


FIGURE 5.4

Mean percentage changes in serum lipid concentrations at 2, 6, 12, 16, and 52 weeks relative to basal levels.

• $p < 0.05$.

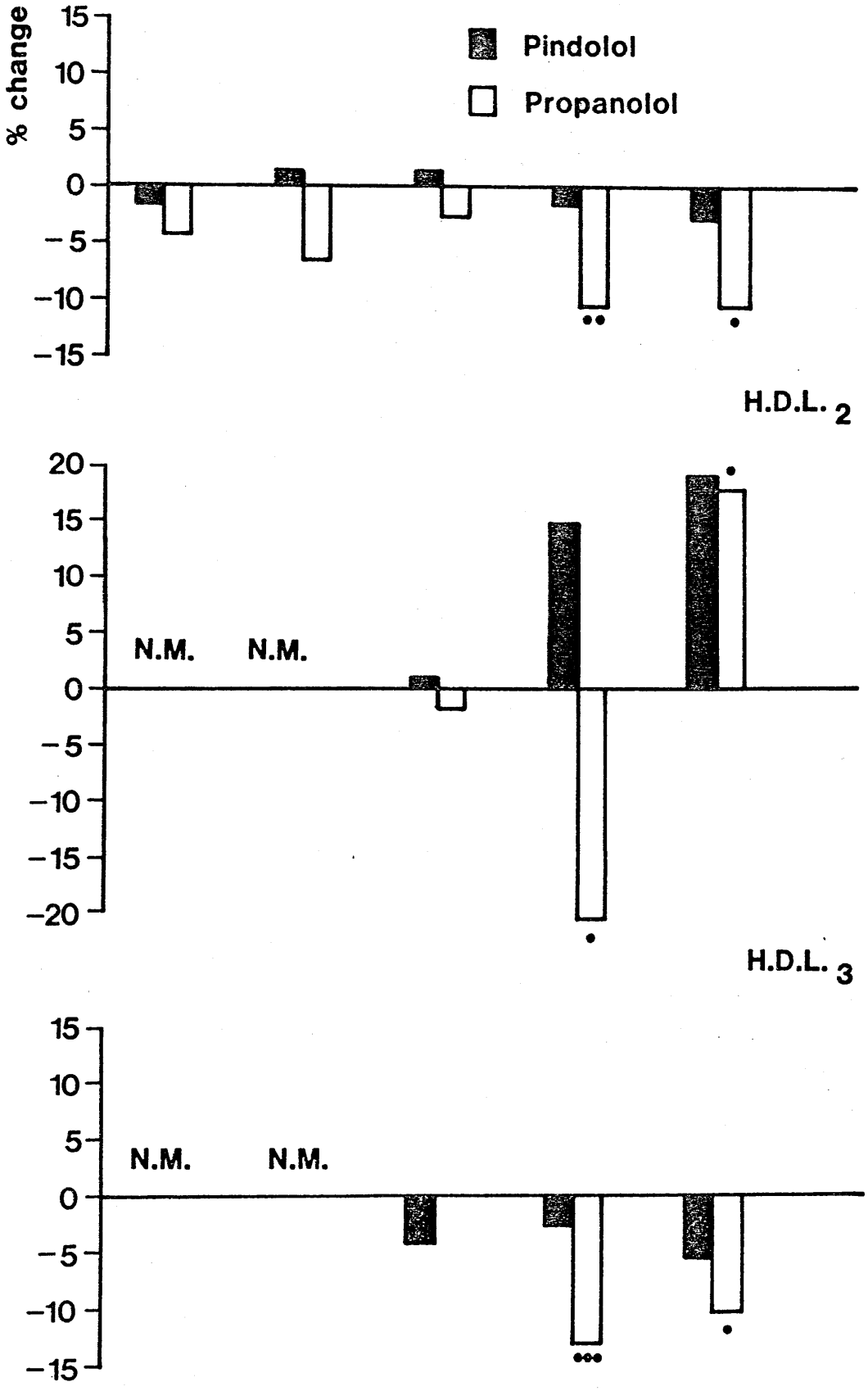


FIGURE 5.5

Mean percentage changes in serum HDL subfractions at 2, 6, 12, 26 and 52 weeks relative to basal levels.

• $p < 0.05$; •• $p < 0.01$; ••• $p < 0.001$.

Abbreviations: HDL - High Density Lipoprotein.
N.M.- Not measured.

In order to assess whether subjects with pre-treatment normal or elevated values of total cholesterol, triglycerides, and HDL cholesterol responded differently to each drug the participants were divided into groups according to basal values of these parameters. The results of this analysis are shown in Table 5.7. In the pindolol group total cholesterol rose slightly if the initial value was low or normal, but fell significantly at 2, 12 and 52 weeks ($p < 0.01$) if the value was high initially. A less consistent response occured with total triglyceride which tended to rise by a maximum of 26% in those with basal values <2.,00 mmols/l., but fell again at 52 weeks. In those with basal values >2.00 mmols/l., the levels tended to fluctuate more with rises and falls observed throughout treatment. Total HDL cholesterol rose by up to 11% in those with initial values <1.2 mmols/l. ($p < 0.05$), but fell by up to 11% if basal values were >1.2 mmols/l. ($p < 0.05$ at 26 weeks).

In the propranolol group, those with initially high total cholesterol levels showed a small increase, in distinction to the response with pindolol, and those with total triglyceride <2 mmols/l. showed a significant increase of up to 40% at the 26 week stage ($p < 0.05$ at 26 weeks), although no substantial change occurred if the initial value was >2 mmols/l. Total HDL cholesterol fell slightly in those with initially low levels, but fell significantly by as much as 17% at 52 weeks in those with basal values >1.2 mmols/l. ($p < 0.05$ at 2, 26 and 52 weeks).

TABLE 5.7 RESPONSE OF TOTAL CHOLESTEROL, TRIGLYCERIDES AND HDL-CHOLESTEROL TO EACH DRUG, ACCORDING TO BASAL LEVELS.

	Week No.	Basal Total Cholesterol <7.0mmol/l.	Basal Total Cholesterol >7.0mmol/l.	Basal Total Triglyceride <2.0mmol/l.	Basal Total Triglyceride >2.0mmol/l.	Basal HDL-Cholesterol <1.2mmol/l.	Basal HDL-Cholesterol > 1.2mmol/l.
Pindolol Group		n = 10	n = 9	n = 10	n = 9	n = 8	n = 11
	0	5.90 ± 0.637	8.38 ± 0.633	1.49 ± 0.373	2.45 ± 0.510	1.09 ± 0.106	1.40 ± 0.110
	2	6.00 ± 0.801	7.69 ± 0.728**	1.83 ± 1.044	2.31 ± 0.904	1.09 ± 0.099	1.35 ± 0.121
	6	6.24 ± 1.170	8.12 ± 0.561	1.88 ± 0.895	2.49 ± 0.794	1.19 ± 0.115*	1.36 ± 0.171
	12	6.21 ± 0.723	7.63 ± 0.533**	1.79 ± 0.601	2.33 ± 0.567	1.17 ± 0.084	1.38 ± 0.224
	26	5.89 ± 0.642	7.90 ± 0.799*	1.72 ± 0.361	2.64 ± 0.878	1.21 ± 0.168	1.26 ± 0.152*
	52	6.13 ± 0.740	7.67 ± 0.523	1.59 ± 0.238	2.33 ± 0.808	1.15 ± 0.128	1.29 ± 0.163
Propranolol Group		n = 13	n = 8	n = 11	n = 10	n = 10	n = 11
	0	6.10 ± 0.595	7.87 ± 0.0630	1.35 ± 0.448	3.73 ± 1.456	1.10 ± 0.095	1.5 ± 0.311
	2	6.16 ± 0.993	7.95 ± 0.743	1.61 ± 0.719	3.69 ± 1.872	1.10 ± 0.076	1.37 ± 0.208*
	6	6.17 ± 0.789	7.62 ± 0.985	1.79 ± 0.786	3.30 ± 0.799	1.06 ± 0.137	1.33 ± 0.123
	12	6.31 ± 1.055	7.95 ± 0.943	1.69 ± 0.766	4.13 ± 2.179	1.16 ± 0.182	1.38 ± 0.168
	26	6.20 ± 1.03	7.71 ± 0.858	1.89 ± 0.747*	3.76 ± 2.205	1.03 ± 0.162	1.31 ± 0.148*
	52	6.08 ± 0.917	8.06 ± 1.010	1.56 ± 0.599	3.78 ± 2.515	1.05 ± 0.239	1.28 ± 0.172*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Linear regression analysis was applied to the change in HDL_2 levels compared with the initial values. Significantly positive relationships were shown for the pindolol group at 12 weeks ($p < 0.05$) and 52 weeks ($p < 0.001$), indicating that those with the lowest initial concentration showed the least change. No such relationship was shown for those taking Propranolol. The results of this analysis is shown in Table 5.8.

TABLE 5.8 RESULTS OF LINEAR REGRESSION ANALYSIS BETWEEN BASAL HDL_2 CONCENTRATIONS AND THE CHANGE IN CONCENTRATION AT THE TIME INTERVALS STUDIED.

	0 vs 12 weeks	0 vs 26 weeks	0 vs 52 weeks
Pindolol Group	$y = -9.339 + 0.347x$ $r = 0.452^*$	$y = -5.985 + 0.0888x$ $r = 0.110$	$y = -27.359 + 0.814x$ $r = 0.702^{**}$
Propranolol Group.	$y = -2.94 + 0.113x$ $r = 0.182$	$y = -0.734 + 0.197x$ $r = 0.367$	$y = -11.87 + 0.179x$ $r = 0.315$

* $p < 0.005$; ** $p < 0.001$.

5.5. DISCUSSION.

The major findings of this investigation included a sequential rise in VLDL cholesterol in the group treated with propranolol ($p < 0.05$ at 52 weeks). In this group also, although total HDL fell significantly at 26 and 52 weeks the level of HDL_2 rose significantly at 52 weeks ($p < 0.05$), despite a significant fall in this parameter at 26 weeks ($p < 0.05$). Only one other investigation of this sort has examined the effect of beta blockers on HDL subfractions (321) and this found a reduction of total HDL cholesterol after 6 and 12 weeks ($p < 0.05$), and small insignificant reductions in HDL_2 , in those taking propranolol. It is possible that this difference is due to the length of treatment periods between the present investigation and that of Murphy et al (321). Also, in contrast to the latter report no change occurred in HDL_3 in the propranolol treated group until 26 weeks when there was a highly significant fall ($p < 0.01$) which was maintained to the 52 week stage ($p < 0.05$). The gross effect of these changes in HDL_2 and HDL_3 was a favourable and highly significant increase ($p < 0.01$) in the HDL_2 to HDL_3 ratio at 52 weeks only, despite there being a fall of 11% (p = NS) at 26 weeks. This finding alone indicates that long-term effects of beta blockers on serum lipoproteins may differ from short-term effects. Since patients are usually prescribed beta blockers on a long-term basis, it is important that the long-term effects be assessed. I have been unable to find any long-term studies involving propranolol in the

literature. Total HDL cholesterol concentration correlates strongly and inversely with the risk of atherosclerosis, but HDL_2 has the strongest negative correlation with the extent of CAD in angiographic studies. (300) Although no epidemiological evidence has been forthcoming, this may be because this would be technically demanding to achieve and because measurement of these substances is a relatively recent undertaking. This suggests that the long-term effect of propranolol on HDL_2 is beneficial although short-term effects may be harmful in terms of atherosclerotic risk. It is possible that this effect is negated by long-term benefit, although this change will require confirmation.

Like Murphy et al (321), I found a small sequential fall in LDL cholesterol, but this was not significant.

Other positive findings in the propranolol group include a rise in both apoprotein A-I and apoprotein B at two weeks ($p < 0.05$) with the latter also significantly elevated at 52 weeks ($p < 0.05$). As pronounced variation can occur in the lipid composition of lipoproteins and plasma, it is possible that measurement of apoprotein concentration provides a better index of the number of particles than does determination of their cholesterol or triglyceride content. (322) Apo B-100 can be regarded as a marker for LDL and Apo A for HDL. However, in this study a rise in Apo B ($p < 0.05$ at 2 and 52 weeks) occurred at the time of a fall in the LDL cholesterol (although this was insignificant). It is possible that

the cholesterol content of these particles falls, but the number of particles rises. A level of Apo B may be a better indicator of atherosclerotic risk than a rise in LDL cholesterol. (294,295) No correlation was demonstrated between changes in Apo A-I or HDL.

Using multivariate analysis, Whayne et al (305) confirmed that apo B concentration correlated better with angiographically confirmed CAD than did serum cholesterol. This indicates that the rise in Apo B experienced in those treated with propranolol may be harmful despite the possible beneficial effects on total HDL cholesterol and HDL_2, although the latter changes were not reflected by a favourable change in Apo A-I. Opinions are divided concerning Apo A-I as a better index of CAD than HDL or HDL_2 (294,303,304), therefore the changes in HDL are probably more reliable at present until more information becomes available. The rise in Apo B in this study may also reflect the significant rise in VLDL at 52 weeks ($p < 0.05$) in the propranolol group as VLDL also contains Apo B although in small quantities. It is possible that if LDL Apo B and VLDL Apo B could be separated, the former would be a better index of atherosclerotic risk (301) and this is currently under investigation.

A rise in total triglyceride concentration was confirmed with both drugs in this study. Although these changes were not significant, the rise of around 14.% at 12 weeks for propranolol is similar to that found in other investigations (77,321,323), and the rise of 12% at

12 weeks (p = NS) in those treated with pindolol has been the experience of some (286,321,324), but not all workers (325) who have investigated pindolol.

By relating changes in lipoprotein concentration to the basal values, additional information was obtained. The most important of which is a highly significant fall in total cholesterol in response to pindolol treatment for those with initial values of >7.00 mmols/1. ($p < 0.01$ at 2, 12, 52 weeks). Although the numbers in this subdivision are small (n = 9) and caution must be exercised in the interpretation of this result, there is a clear difference with those treated with propranolol who had initial values >7 mmols/1. as no consistent or significant changes were demonstrated at any of the sampling intervals. The finding of a significant change in cholesterol concentration in response to beta blockade is rare. Using propranolol two reports suggest a significant fall (321,326), while using sotalol (pure beta receptor antagonist with no ISA), Lehtonen and Viikari (82) found a significant increase. Of the studies which have examined the effects of beta blockers with ISA on plasma lipids, only two found a significant fall, using oxprenolol (86) (weak ISA) and pindolol (88) (potent ISA), with Ballantyne et al showing a significant increase with oxprenolol. (87) Few of these studies have been controlled however, and with the exception of Lehtonen and Viikari (82) have been over short treatment periods. Although the present investigation failed to show any difference in cholesterol concentration in response to propranolol or

pindolol in all the participants there would appear to be an advantage for those with pre-treatment elevation of serum cholesterol who are treated with pindolol rather than propranolol.

Further theoretical disadvantages of propranolol over pindolol may include the rise in total triglyceride ($p < 0.05$ at 26 weeks) in those with initially low or normal values (< 2.0mmols/1.) This change resulted in a number of individuals becoming hypertriglyceridaemic (> 2 mmols/1.) and as this may be a CAD risk factor (327), even small changes may enhance the atherosclerotic risk. In addition, total HDL rises in those taking pindolol if the initial value is less than 1.2 mmols/1. ($p < 0.05$ at 6 weeks), although in those treated with propranolol no significant change occurs, and a further reduction of approximately 7% occurs at 26 weeks. If the initial HDL concentration is >1.2 mmols/1. significant reductions were noted for both drugs.

Thus, using this form of analysis, previously "hidden" advantages of pindolol have been demonstrated, but the interpretation of this information must be tempered by the small numbers available for each sub-division. These data prompt the further long-term investigation of pindolol in hyperlipidaemic individuals in whom a beta blocker with ISA may be more appropriate.

5.6. REVIEW OF CURRENT LITERATURE.

No fewer than 31 investigations have taken place examining the effects of beta blockers on plasma lipoproteins in the last 12 years, and the results are often inconsistent and have led to confusion. The principle findings of these investigations are detailed in Table 5.9. Criteria used for inclusion in this table included a minimum duration of treatment 4 weeks, a minimum of 10 patients completing the study and the beta blocker being given as monotherapy.

The most consistent findings include a significant increase in triglycerides and reduction in total HDL in individuals treated with non-cardioselective agents without ISA although several studies have failed to find any change in these parameters.

Cardioselectivity does not appear to affect these changes, although the number of studies reporting changes in HDL cholesterol is much smaller. The effects of non-cardioselective agents with ISA do not appear to be as great with only two short-term studies showing an increase in triglycerides. (321,328) Two studies have found significant increases in total HDL using pindolol which was not confirmed in the present investigation. (88,329)

In general it appears that the lipoprotein profile has less tendency to change in groups treated with agents possessing ISA and these agents have been

TABLE 5.9a EFFECT OF THERAPY WITH BETA ADRENOCEPTOR BLOCKING AGENTS ON PLASMA LIPOPROTEINS.

Type of Beta adrenoceptor Blocking Drug Study.	Number	Plasma Lipids		Lipoprotein			Duration (weeks)	Drug
		TG	Chol.	VLDL	LDL	HDL		
Non-Cardioselective Agents without ISA.								
Barboriak and Friedberg, 1973 (335)	8	NS	NS	–	–	–	2	Propranolol
Tanaka et al, 1976 (77)	10	NS	NS	↑TG	↓TG	↓LIP	8	Propranolol
Stretja and Mynin, 1978 (86)	37	NS	NS	–	–	↓	not given	Propranolol
Day et al, 1979 (79)	16	↑	NS	–	–	–	24	Propranolol
Lehtonen and Viikari, 1979 (82)	12	↑	↑	↑	↑	↓	52	Sotalol
Leren et al, 1980 (81)	23	↑	NS	NS	NS	↓	8	Propranolol
Schauer, 1980 (326)	25	↑	↓	NS	NS	↓	6	Propranolol
Sommers et al, 1981 (86)	80	NS	↓	–	–	NS	3	Labetolol
Bauer et al, 1981 (78)	10	NS	NS	NS	NS	NS	4	Propranolol
Gemma et al, 1982 (336)	11	↑	NS	↑	NS	NS	8	Propranolol
Leren et al, 1982 (328)	23	↑	NS	NS	NS	↓	8	Propranolol
Murphy et al, 1984 (321)	9	↑	↓	NS	NS	NS	12	Propranolol

Abbreviations: TG = Triglyceride; Chol. = Cholesterol; VLDL = Very Low Density Lipoprotein; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; – = Not Analysed; NS = No Significant Difference; ↑ = Significantly Increased; ↓ = Significantly Decreased.

TABLE 5.9b EFFECT OF THERAPY WITH BETA ADRENOCEPTOR BLOCKING AGENTS ON PLASMA LIPOPROTEINS.

Type of Beta adrenoceptor Blocking Drug Study.	Number	Plasma Lipids		Lipoprotein			Duration (weeks)	Drug
		TG	Chol.	VLDL	LDL	HDL		
Cardioselective Agents without ISA.								
Waal-Manning, 1976 (335).	14	↑	NS	–	–	–	12	Metoprolol
Nillson et al, 1977 (84).	9	NS	NS	–	–	–	12	Metoprolol
Day et al, 1979 (79).	14	↑	NS	–	–	–	24	Atenolol
Beinart et al, 1979 (356).	12	NS	NS	–	–	–	12	Metoprolol
Leren et al, 1980 (81).	34	↑	NS	–	–	↓	12	Metoprolol
England et al, 1980 (85).	34	NS	NS	–	–	↓	12	Atenolol/Metoprolol
Waal-Manning, 1980 (355).	10	NS	NS	–	–	–	8	Atenolol
Eliasson et al, 1981 (83)	15	NS	NS	↑TG	↑TG	NS	32	Atenolol
Leren et al, 1982 (328).	20	–	–	NS	↓	–	5	Atenolol
Pasotti et al, 1982 (329).	16	NS	NS	NS	NS	NS	12	Metoprolol

ABBREVIATIONS: TG = Triglyceride; Chol. = Cholesterol; VLDL = Very Low Density Lipoprotein; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; – = Not Analysed; NS = No Significant Difference; ↑ = Significantly Increased; ↓ = Significantly Decreased.

TABLE 5.9c EFFECT OF THERAPY WITH BETA ADRENOCEPTOR BLOCKING AGENTS ON PLASMA LIPOPROTEINS.

Type of Beta adrenoceptor Blocking Drug Study.	Number	Plasma Lipids		Lipoprotein			Duration (weeks)	Drug
		TG	Chol.	VLDL	LDL	HDL		
Non-Cardioselective Agents with ISA.								
Ballantyne et al, 1981 (87)	9	NS	↑	NS	↑	NS	16	Oxprenolol
Sommers et al, 1981 (86)	80	NS	↓	-	-	NS	3	Oxprenolol
Lehtonen et al, 1982 (88)	20	NS	↓	-	-	↑	26	Pindolol
Leren et al, 1982 (328)	10	NS	NS	NS	NS	NS	10	Pindolol
Leren et al, 1982 (292)	20	↑	NS	NS	NS	NS	5	Oxprenolol
Pasotti et al, 1982 (329)	16	NS	NS	NS	NS	↑	12	Pindolol
Karmakoski et al, 1983 (325)	13	NS	NS	NS	NS	NS	16-26	Pindolol
Murphy et al, 1984 (321)	8	↑	NS	NS	NS	NS	12	Pindolol
Cardioselective Agents with ISA.								
Ghosh et al, 1975 (340)	20	NS	NS	-	-	-	52	Practolol

Abbreviations: TG = Triglyceride; Chol. = Cholesterol; VLDL = Very Low Density Lipoprotein; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; - = Not Analysed; NS = No Significant Difference; ↑ = Significantly Increased; ↓ = Significantly Decreased.

found to show the smallest mean increase in triglycerides and a more favourable lipid profile in a recent review. (330) This would support the findings of the present study. (Table 5.5 and 5.6). Likewise, this review also reported a mean reduction in total HDL of 19 ± 7% for nonselective beta blockers without ISA, 5 ± 7% for cardioselective agents without ISA, but an increase of 3 ± 11% for those possessing ISA. This finding was not confirmed in this study.

Beta Blocking Agents with ISA and Lipoproteins.

In a three week investigation of oxprenolol, Sommers et al (86) reported a significant decrease in plasma total cholesterol with no change in plasma triglyceride or total HDL (VLDL and LDL concentrations were not measured). In contrast Ballantyne et al (87), found significant rises in plasma total and LDL cholesterol after 16 weeks of therapy. No change was found in plasma triglyceride, VLDL cholesterol or HDL cholesterol. It has been suggested by Lehtonen et al (88,324) in a 52 week study, that pindolol significantly lowers plasma total cholesterol and raises HDL cholesterol. However, the rise in HDL was only significant at one month and, even then, only at the 5% level. In addition this was an uncontrolled study with a rather heterogeneous group of patients (11 males and 9 females). In an earlier study England et al (331) examined the effect of pindolol, atenolol, metoprolol and propranolol in combination with chlorothiazide. They demonstrated a small but significant

increase in triglycerides for all beta blockers. However, their findings are probably less meaningful than other studies as the therapy was complicated by the concomitant administration of a diuretic, and the triglyceride changes cannot be directly related to beta blockers, but may result from an interaction of the diuretic with the beta blocker.

Karmokoski et al (325) studied the effect of pindolol on 13 patients after myocardial infarction and 11 control subjects. Baseline samples were taken within two hours of admission to hospital with chest pain, despite the fact that the patient had not been fasting. It is probable that a reliable baseline was not acheived. The results showed a slight, but not significant increase in HDL cholesterol and reduction in total triglyceride. In a cross-over study of metoprolol versus pindolol, Pasotti et al (329) measured lipoproteins over a 12 week treatment period. The only significant change was an increase in the HDL cholesterol after 6 and 12 weeks treatment with pindolol, which was significantly different from the effect of metoprolol. Leren et al (292) found no change in total cholesterol, triglyceride or HDL in a 10 week study of 20 patients taking pindolol. In another publication from the Oslo study, Leren et al (328) studied the effect of pindolol, atenolol, oxprenolol and propranolol on serum lipids and found that pindolol was again neutral in its effects in comparison to other beta blockers - but since treatment regimes varied from 5-10 weeks for each drug direct comparisons are not appropriate.

The most recent report concerning pindolol is that of Murphy et al (321) who compared propranolol and pindolol in a double-blind trial. Unlike the present study they examined exclusively normolipidaemic subjects with hypertension or angina and found that both drugs had similar effects on lipoproteins with no change in total cholesterol and transient increases in triglycerides. That study was the first to measure HDL subfractions and although small reductions in HDL_2 were found, these were insignificant. Intravenous intralipid clearance studies were also performed, and these confirmed an enhanced rate of clearance during treatment with pindolol.

Two studies have examined the effect of alprenolol on lipoproteins. Bjontorp (332), found no change in plasma cholesterol or triglycerides, and this was confirmed by Jurgensen (333) who examined alprenolol's effect on 33 post-myocardial infarction patients over a 52 week period.

Effects of Other Beta Blockers on Lipoproteins.

Several uncontrolled population studies have suggested an adverse effect of beta blockers on the lipoprotein profile. The Lipid Research Clinics Program monitored the effects of 8 medications in 10 study populations in the USA, and found that females taking propranolol had a lower mean HDL cholesterol than non users. (311) Similarly, the Oslo Heart Study Group

reported that propranolol reduced HDL cholesterol by 13% and also increased triglycerides by 24%, (81) and a population sample of Swedish women were found to have higher triglyceride levels when taking beta blockers, compared to other women. (334) No specific conclusions can be drawn from these studies as a variety of beta blockers with different properties were involved.

Barboriak and Friedberg (335) showed an enhanced lipaemic response to a 60G. fat meal after a three week period of treatment with propranolol in eight subjects with initially elevated triglyceride levels. The data also show a small, but not statistically significant increase in fasting plasma triglyceride levels after only two weeks exposure to the drug. This rise in plasma triglyceride was not confirmed by Tanaka et al (77), who gave propranolol for eight weeks to 10 patients who had suffered cerebrovascular accidents. However, despite the lack of a significant change in total triglycerides, there was a significant rise in VLDL triglyceride which was accompanied by falls in the LDL triglyceride and in HDL cholesterol concentrations. Post heparin lipolytic activity was significantly suppressed by propranolol and the authors considered that inhibition of lipoprotein lipase by propranolol might have played a role in the reciprocal changes in lipoproteins.

There have been seven more recent studies of the effect of propranolol therapy (see Table 5.9a). The duration of treatment ranged from four (335) to 26 weeks.

(79) In one study, however, the length of treatment was not reported. (80) In four of these studies (79,81,326, 333) a significant increase in plasma triglyceride occurred, but no significant change in plasma total cholesterol. One study which failed to show any significant change in triglyceride level (337) had treatment regimes of propranolol ranging from 30 - 120mgs. per day which is not desirable when trying to demonstrate consistent effects of drugs on lipid concentrations. Four of the 11 studies analysed HDL cholesterol (78,80,81,337), but in only two were significant falls in HDL recorded. (80,81)

In contrast to the report by Tanaka et al (77), VLDL and LDL concentrations were unchanged in the studies of Leren et al (81) and Bauer et al (78).

Only one study examining the effect of propranolol on lipids measured apoproteins (336) and found no significant change in Apo A-I or Apo B, unlike the present study which showed a significant increase in both these parameters. It is possible that these differences may be due to the methodology involved in measuring the apo-proteins as Gemma et al (336) relied on electroimmuno-diffusion which is regarded as a less accurate and reproducable form of analysis than the method described here.

Propranolol is a non-cardioselective beta-adrenoceptor blocking agent without ISA. One might

therefore expect other drugs with this property to cause similar changes in lipoproteins. Sotalol is one such agent which was investigated by Lehtonen and Viikari (82) which is the only study, with the exception of the present one, to have lasted more than 26 weeks. They found significant rises in plasma total triglyceride and cholesterol and accompanying increase in VLDL and LDL cholesterol and a fall in HDL. It is not clear why this study differs from others of similar design and in view of the fact that it demonstrated such a departure from other published findings, I repeated the study and the results follow this discussion. As might have been predicted on reviewing other investigations of non-selective beta blockers without ISA, I was unable to reproduce Lehtonen and Viikari's findings.

Labetolol is also a non-cardioselective agent without ISA, but which possesses significant alpha blocking activity. In a three week study, Sommers et al (86) found that labetolol produced a significant fall in plasma total cholesterol without significantly altering plasma triglyceride or HDL cholesterol.

Thus, a review of the literature concerning the non-cardioselective beta blockers without ISA does not reveal a consistent effect although the most frequently positive finding is an elevation of plasma total triglyceride and fall in total HDL cholesterol.

The cardioselective agents atenolol and metoprolol have been extensively studied. Six reports concerning metoprolol and five of atenolol have been reviewed (Table 5.9b). Only the study of Eliasson et al (83) lasted for longer than six months. Two groups reported an increase in plasma triglyceride. Five found no significant change. (83-85,329,338) In none of these studies was a rise in plasma total cholesterol found. England et al (85) who investigated both metoprolol and atenolol over 12 weeks found that they produced a fall in HDL cholesterol but 3/4 of the study population were taking concurrent diuretic therapy which makes these results difficult to interpret. In addition only a ten day washout period was allowed between metoprolol and atenolol which is probably not sufficient. This was also the fault of another cross-over study by Kristensen (339), but in this study a range of treatment periods between 8 - 79 months was used, and 80% of the group also received concurrent thiazide diuretic therapy. Eliasson et al (83), found no change in HDL cholesterol after 32 weeks of atenolol therapy. The latter authors, however, reported increased VLDL and LDL triglyceride concentrations. England (85) also measured apoproteins by electroimmuno-diffusion and found no change in Apo B, but a fall in Apo A.

The presence of cardioselectivity therefore, does not seem to produce more consistent changes than those found with non-selective beta blockers. Where significant changes were found, they were similar to those

reported with non selective agents ie. a rise in plasma triglyceride and a fall in total HDL cholesterol. As with nonselective drugs, there is a paucity of long-term studies, only one being conducted for more than six months.

In summary the literature concerning the effect of beta blockers and plasma lipoproteins is conflicting. No consistent differences arise from the presence of cardioselectivity or ISA. In this regard it is relevant that the one study involving the cardioselective drug practolol, (which also possesses ISA) (340), showed no significant changes in plasma lipids following 12 months treatment.

5.7. POSSIBLE MECHANISMS OF CHANGES IN LIPOPROTEIN PROFILE IN RESPONSE TO BETA BLOCKERS.

The most consistent changes in serum lipoproteins induced by beta blockers are an elevation of total triglyceride and reduction in total HDL cholesterol (Table 5.9). The reasons for these changes are speculative with several hypotheses suggested. The increased levels of triglyceride must be due to increased synthesis or reduced catabolism. Day et al (341), proposed that unopposed alpha stimulation in the face of beta blockade inhibits lipoprotein lipase with a subsequent rise in plasma triglyceride and fall in HDL concentration. Their finding of a reduction in free fatty acid concentration during therapy argues against there being an increased rate of synthesis of triglycerides. In response to this suggestion, Lehtonen (342) pointed out that this would not be consistent with his own findings of no change in adipose tissue lipoprotein lipase activity (88) during treatment with beta blockers. However, the latter report did observe a significant increase in lecithin cholesterol acetyl transferase activity during treatment with pindolol and a decrease when pindolol was discontinued. This enzyme, catalyzes the transfer of fatty acids from HDL lecithin to HDL cholesterol during HDL formation. (343) This finding may explain changes in HDL concentrations experienced by Lehtonen (82,88) and others. (81,85,326,328)

The stimulating effect of catecholamines on lipolysis is probably mediated by their beta receptor

stimulating property. Their importance in regulating lipolysis is evidenced by the fact that beta blockers will reduce plasma free fatty acid concentrations during different lipolysis conditions such as fasting, exercise and following hypoglycaemia. (344) Pindolol has not been found to reduce concentrations of free fatty acids under resting conditions (88), and is therefore probably not antilipolytic. The resultant lipoprotein effects reflecting the balance between partial stimulation of the beta receptor and beta blockade.

However, the hypothesis that increases in triglyceride may be linked to a reduction in lipoprotein lipase activity also finds favour with Tanaka (77), who noted a 40% reduction in post heparin lipase during treatment with propranolol although a reduction of only 7% was observed by Schauer. (326) This would cause a reduced rate of removal of circulatory triglyceride. Such a change could explain the previously described elevation of triglyceride and the reduction in total HDL cholesterol as this enzyme is also involved with HDL cholesterol metabolism. (345) Inhibition of lipoprotein lipase could be mediated through a direct inhibitory action by the beta-adrenergic blockers or secondary to unopposed alpha adrenergic stimulation. During adrenergic blockade, plasma catecholamine concentrations may be increased and in vitro catecholamines appear to inactivate lipoprotein lipase. (346) Alpha adrenergic stimulation may have an important role in suppressing adipose tissue lipoprotein lipase, with a secondary reduction in plasma

HDL cholesterol and rise of triglyceride concentrations. Both Beta$_1$ and$_2$ adrenoceptor stimulation activates lipolysis (347), by stimulating adenylate cyclase activity. Thus, if propranolol is a powerful inhibitor of lipolysis then a reduction in total triglyceride (rather than the frequently reported increase) would be expected - similar to that produced by nicotinic acid and other antilipolytic agents. (348) Therefore beta blockers by inhibiting both lipolysis and lipoprotein lipase have "divergent activity", with the resultant change in the lipoprotein profile being related to the pharmacological properties of the agent used. This may help explain the differences in response noted with beta blockers possessing ISA (88,329), as one could argue that stimulation of the adrenoceptor is maintained, and thus, despite a reduction in lipoprotein lipase activity, lipolysis is maintained, sufficient to prevent a significant increase in plasma triglyceride.

Day et al (341) suggested that individuals with low basal concentrations of HDL cholesterol were liable to excessive alpha stimulation which impaired the production of HDL cholesterol but the present study was not able to confirm this and in fact showed a significant rise in HDL cholesterol after six weeks treatment with pindolol, but not propranolol when the initial value was <1.2 mmols/l. The cause of this discrepancy is speculative, but is probably related to the ISA effect of pindolol on lipolysis.

Alternative, but less likely mechanisms liable to cause disturbance in the lipoprotein profile include a direct effect on hepatic triglyceride synthesis which may be increased - this aspect has not so far been the subject of investigation. In addition, as most studies have been performed in hypertension it is possible that the hypotensive action of the beta blocker in some way causes lipoprotein disturbances. This unfashionable suggestion was presented in an earlier study of a thiazide diuretic (349), but could not be substantiated by Day et al. (79)

In summary, the changes in lipoproteins caused by beta blockers are not fully understood but are probably related to activity of lipoprotein lipase and intracellular lipolysis - it is probable that the more stable lipoprotein profiles experienced when using pindolol, are the result of a balance between increased lipolysis and diminished lipoprotein lipase activity.

In the present study the highly significant fall in cholesterol experienced in those taking Pindolol with basal values >7mmols/l., cannot be explained by the foregoing hypotheses and must remain a matter for speculation. Likewise, the cause of a significant increase in HDL_2 after 52 weeks of treatment with propranolol following a significant reduction at 26 weeks is unknown.

5.8. CONCLUSIONS.

The results of the present study suggest that pindolol is less likely to upset the lipoprotein profile compared to propranolol, but not all changes associated with the latter drug are potentially harmful ie. the rise in HDL_2 after 52 weeks treatment, in association with a rise in VLDL and Apo B and fall in total HDL cholesterol over the same time scale.

Further useful information was derived from the data by separating the subjects into groups according to their initial lipoprotein concentrations. In this way, a highly significant reduction in total serum cholesterol was observed during therapy with pindolol in those with initially elevated levels (> 7.0 mmols/1.). No such benefit was observed with propranolol. Total HDL cholesterol also fell significantly with both drugs for those with initial values >1.2 mmols/1. Although elevation of total triglyceride is the most frequent change noted in other investigations. I was unable to show significant increases using either drug although a 13.5% increase occurred after 12 weeks treatment with propranolol, this deviation gradually declined thereafter. The only significant change in triglyceride was observed in those with initial values of <2.0 mmols/1., treated with propranolol, but not pindolol.

In conclusion I would suggest that pindolol is less likely to upset lipoprotein metabolism and in those

in whom this occurs there is a favourable change in comparison to propranolol apart from the latters ability to raise HDL_2 levels significantly after a year of treatment.

It is not immediately clear why there is such inconsistency in reported findings of beta blocker therapy and serum lipoproteins. It is possible that different characteristics of study population are important. Most studies reporting an increase in serum triglycerides or other significant change in lipoproteins were performed in patients with hypertension (78,81,82,88,328,329,338) although some have been performed in those recovering from a cerebrovascular accident (350) or myocardial infarction. (325) No significant changes in plasma cholesterol or triglycerides have been demonstrated in a group requiring beta blockade exclusively for CAD, either because of angina or as part of secondary prevention (351,352), although Murphy et al (321) studied a group containing some subjects with angina pectoris.

Another reason for discrepancy in results is the methodology of lipoprotein analysis and quality assurance in individual laboratories and differing experimental conditions in relation to diet, smoking, levels of exertion, changes in plasma volume which may be important in long-term studies (353), drug compliance, duration of treatment period and concurrent drug therapy. In the present study strenuous efforts were made to ensure that all these variables remained constant and that no other

drug therapy was administered.

It is possible that an elevation of plasma total triglyceride induced by beta blockers will enhance the risk of CAD. (296) Similarly a reduction in HDL cholesterol (300) and Apo B concentration (322) may result in an increased risk. Hypercholesterolaemia has long been recognised as having a role in the genesis of atherosclerosis (354) and in this respect the fall in cholesterol observed in those with elevated levels taking pindolol in this study is potentially beneficial. It is possible that even subtle changes in the lipoprotein profile may substantially influence atherosclerotic risk in the large population taking beta blockers for long periods of time. With this view, it would seem prudent to use drugs with the least effect on lipoprotein metabolism, and current evidence suggests that pindolol may be the safest drug in this respect. However, where beta-adrenoceptor blockade is necessary in the presence of established atherosclerosis it is possible that small changes in lipoproteins are of less importance than effective beta blockade.

5.9. THE EFFECT OF SOTALOL ON PLASMA LIPOPROTEINS.

Introduction.

Lehtonen and Viikari (82) examined the effect of sotalol on plasma lipids in hypertensive subjects over a one year period. The authors found a significant elevation of plasma total triglycerides and cholesterol and LDL with a fall in total HDL cholesterol. All of these changes reaching statistical significance after six months of treatment. These results are in conflict with similar investigations on non-cardioselective beta blockers without ISA, as described previously in this thesis, but none have observed a significant change in total cholesterol. Likewise, VLDL and LDL concentrations do not change, although studies have shown an increase in VLDL. (77,336)

Sotalol is a non-cardioselective beta-adrenoceptor blocking agent without ISA, and one might expect it to influence plasma lipids in a similar way to propranolol. This study was undertaken in view of the discrepancy in results between studies investigating propranolol (78-81, 321,326,328,335) and sotalol (82) (Table 5.9a). As this drug is a frequently prescribed B-blocker, it is important to confirm any adverse influence on plasma lipids, which may exert an atherogenic effect.

Methods and Subjects.

Thirteen previously untreated hypertensive subjects were commenced on sotalol hydrochloride 80 mg.bd increasing to 160 mg.bd after two weeks. Three subjects developed intolerance to the drug and were removed from the study (two subjects developed a metallic taste and one developed mild left ventricular failure). The remaning ten patients had a mean age of 51 ± 11.2 years (mean ± SD) and an initial supine blood pressure of $\frac{180 \pm 25.9}{107 \pm 7.5}$ (mean of three readings). The study protocol was designed to reproduce that of Lehtonen and Viikari (82), and blood sampling was timed to coincide with the times at which Lehtonen and Viikari (82) found significant lipoprotein changes. Blood pressure, haematocrit and fasting plasma lipoproteins were recorded following an overnight fast before treatment commenced and then six weeks and six months later. All patients were normolipaemic at the beginning of the study, and did not alter their diets or mean body weight significantly during the study period.

Lipoproteins and apolipoproteins were analysed as described previously.

Statistical Analysis.

Comparison of results was made using a two-way analysis of variance followed by a Student's paired t-test and Wilcoxan signed rank test. The most conservative significance values are reported.

Results.

Heart rate fell sequentially throughout the study, reaching a highly significant difference between basal and six month visits ($p < 0.01$). There was a similar fall in blood pressure, but this did not reach statistical significance for either systolic or diatolic values. Throughout the study there was no significant change in the haematocrit. Changes in serum lpoproteins are shown in Table 5.10. There was a sequential rise in plasma triglyceride from a basal value of 1.87 ± 1.064 to 2.5 ± 0.877 ($p < 0.005$) at six months. There was no significant change in total plasma cholesterol and although there was a rise of VLDL cholesterol this did not reach statistical significance. An insignificant fall in HDL cholesterol also occurred. There was no significant change in plasma apolipoproteins.

Discussion.

As previously discussed, many conflicting reports have been published concerning the effect of beta-adrenoceptor blocking agents on plasma lipoproteins. Of particular relevance to this study is the report by Lehtonen and Viikari (82) which demonstrated significant increases in plasma total cholesterol and LDL cholesterol while at the same time causing a fall in HDL cholesterol. All of these changes could be regarded as detrimental in terms of CAD. (89,90) That study contrasts with others on

TABLE 5.10 PLASMA LIPOPROTEINS DURING TREATMENT WITH SOTALOL (Mean ± S.D.)

	Concentration (mmol/l)		
	Basal Value	6 Weeks	6 Months
Triglycerides	1.87 ± 1.064	2.02 ± 0.590*	2.50 ± 0.877**
Cholesterol	6.68 ± 0.886	6.46 ± 1.053	6.76 ± 1.204
VLDL-Cholesterol	0.58 ± 0.466	0.64 ± 0.346	0.73 ± 0.392
LDL-Cholesterol	4.55 ± 0.813	4.30 ± 0.943	4.64 ± 1.081
HDL-Cholesterol	1.55 ± 0.362	1.52 ± 0.299	1.39 ± 0.365
$\frac{\text{HDL-Cholesterol}}{\text{Total Cholesterol}}$	0.24 ± 0.066	0.23 ± 0.047	0.20 ± 0.046
APO A-I	169.7 ± 36.58	164.9 ± 32.05	174 ± 34.8
APO A-II	27.4 ± 3.29	26.7 ± 0.95	27.3 ± 2.68
APO B	119.8 ± 19.54	125.7 ± 29.58	123.4 ± 26.69

ABBREVIATIONS: * $p < 0.02$; ** $p < 0.005$.

non-selective B-blockers in which the predominant, but not consistent findings have been an increase in plasma triglycerides and fall in HDL cholesterol (Table 5.9a). Lehtonen and Viikari (82) used a precipitation method to analyse HDL cholesterol and (VLDL + LDL) cholesterol concentrations. The present study, used the more generally accepted combination of ultra-centrifugation and precipitation to separate the individual lipoprotein classes. In addition, the mean dose of sotalol used by Lehtonen and Viikari was 80 mg. per day higher than the present investigation. Other possible causes of discrepancy between such studies may be difficulties with quality assurance or in differences with patient compliance.

Apolipoproteins are now thought to be useful discriminators in determining risk for future coronary events (304), and it was felt relevant to estimate these substances inthis study, although I found no significant change.

The fact that this was an uncontrolled study detracts from it's merit. However, the objective was to reproduce the circumstances of the study by Lehtonen and Viikari. (82) Thus, I conclude that sotalol has similar effects on serum triglycerides as other non-cardioselective beta blockers without ISA and is not likely to exert an increased atherogenic influence as previously suggested when compared to other beta blockers. (82)

Conclusions.

Plasma lipoproteins were estimated in ten hypertensive subjects (mean age 51 ± 11.2 years), before and six weeks and six months following treatment with sotalol 320 mg. per day. Heart rate fell sequentially throughout the study ($p < 0.01$) and although there was a sequential fall in mean blood pressure this did not reach statistical significance. There was a significant increase in plasma triglyceride concentration from a basal value of 1.87 ± 1.064 to 2.50 ± 0.877 mmol/l. ($p < 0.005$) at six months. No significant change was found in VLDL, LDL and HDL cholesterol or apolipoprotein concentrations (Apo-I, ApoA-II, ApoB). I conclude that sotalol exerts a similar influence on plasma lipoproteins as other non-cardioseletive beta-adrenoceptor blockers without ISA and its use does not constitute an increased risk of developing atherosclerosis, when compared with other B-blockers

SECTION 6.

THE INFLUENCE OF BETA-BLOCKADE ON HEART RATE, ARRHYTHMIAS AND ST SEGMENTS: COMPARISON OF PROPRANOLOL AND PINDOLOL IN PATIENTS WITH CHRONIC STABLE ANGINA PECTORIS.

6.1. INTRODUCTION.

Beta blockers are now established for the symptomatic relief of angina pectoris (66), and their beneficial effects are well described. (357-359) Their effect on asymptomatic myocardial ischaemia has only recently come under scrutiny.

Beta blockers were introduced to antagonise the cardiac effects of sympathetic stimulation (360), which can, through it's beta adrenergic actions cause markedly increased myocardial oxygen requirements by increasing heart rate and enhancing myocardial contractility. There appear to be four main factors which influence myocardial oxygen demand. (361) The most important of these are heart rate and ventricular systolic pressure, but the rate of rise of left ventricular pressure and left ventricular size are also of importance. Beta blockers reduce myocardial oxygen requirements mainly by reducing heart rate and blood pressure increments with exercise, and therefore allowing a longer time for diastolic filling of the coronary arteries. In addition there is a reduction in the velocity of contraction and oxygen consumption at a given workload. (359,362) Other possible metabolic effects and effects on platelet aggregation may also contribute to the anti-anginal action. (363,364)

The anti-anginal efficacy of pindolol has been confirmed in several reports (8,32,58,365-367), and comparative studies have failed to find any significant

difference with beta blockers not possessing ISA. (365,367) However, because of ISA, pindolol produces little or no reduction in resting heart rate (5) and it's antagonistic effects only become apparent during periods of increased sympathetic activity (eg. during exercise). This effect is potentially harmful in those with rest or nocturnal angina who are dependant on a reduction in resting heart rate for relief of symptoms. Quyyumi et al (65) have recently compared the effect of pindolol and atenolol in 15 patients with severe angina pectoris (including rest or nocturnal angina) on symptoms and ambulatory ST segment responses. They found that heart rate, frequency of angina, and the frequency and magnitude of episodes of ST depression were reduced significantly more by atenolol than by pindolol. They conclude that a reduction in resting heart rate is important in the treatment of rest angina, and therefore pindolol is not a suitable agent in this group. This was the first report to utilise the technique of ambulatory electrocardiography to assess the efficacy of beta blockers, in terms of ST segment changes.

The present study was undertaken to assess the effect of pindolol on heart rate, arrhythmias, and ST segments in a group of middle aged men with stable exertional angina pectoris in comparison to propranolol, and was already in progress when Quyyumi's paper was published.

Improvements in the recording and reproduction of low frequency signals by ambulatory electrocardiography

systems have provided an opportunity to study ST changes. (368) and this has now provided a useful aid in the detection of painful and painless ST segment deviation in several recent studies of patients with CAD. (65,369,370)

6.2. PATIENTS AND METHODS.

Study Group.

Seventeen males with a mean age of 54 ± 9.1 years (range 38-68 years), were recruited into the study. Their characteristics are summarised in Table 6.1. All the patients had a diagnosis of chronic stable angina pectoris - describing typical exertional symptoms and having an abnormal exercise electrocardiogram. Each subject underwent a maximal symptom limited treadmill exercise test in the run-in period using a modified Bruce Protocol. (125) In all cases, ST segment depression of >1 mm. for 0.08 seconds after the J point developed and persisted for at least three consecutive complexes. Patients who showed some ST segment depression before exercise were included only if the ST segment depression became deeper by >1 mm. at peak exercise and if a previously normal lead showed ST segment depression. The subjects had a mean duration of symptoms of 30 ± 28.6 months (range 6-84 months), and seven had a previous history of myocardial infarction. Written informed consent was obtained from all patients and the protocol was approved by the local Ethical Committee.

Study Protocol.

After a diagnosis of chronic stable angina pectoris was made, characterised by a typical history of exertional chest pain and positive exercise electro-

TABLE 6.1 PRETREATMENT CHARACTERISTICS OF STUDY GROUP (n = 17).

Mean Age	:	54 ± 9.09 years (Range 38 - 68)
Previous Myocardial Infarction	:	7
Quetelet Index ($Kg./cm^2 \times 10^3$)	:	2.43 ± 0.247
Mean Resting Heart Rate (bpm)	:	70.7 ± 10.09
Mean Resting Blood Pressure (mmHg.)	:	$^{134}/_{74} \pm {}^{21}/_{15}$

b.p.m. = beats per minute.

Results are expressed as mean ± SD.

cardiogram, all anti-anginal medication was withdrawn for at least two weeks before investigation. Glyceryl trinitrate was permitted for pain. Patients were randomised to treatment with propranolol 80 mg. t.i.d. or pindolol 5 mg. t.i.d. for a period of 14 days each, then cross-over took place onto the alternative medication for a further period of 14 days (Double Blind). During the last 48 hours of each treatment period, ambulatory electrocardiography was performed.

Ambulatory Electrocardiography.

The Medilog 4000 (MARS) ambulatory ECG recorder (Oxford Medical Systems Ltd., Oxford) was used to perform ECG recording. This apparatus performs real-time ECG analysis and includes cassette tape storage of the resultant ECG and analysis results. Previous systems have analysed ECG recordings at replay time, but such an analyser needs to be able to work at high speeds to make this practicable. This limits the processing capacity available to analyse each beat. In addition, several systems employ an audio-visual playback of the recording with a human operator identifying abnormalities on an ECG running at X60 normal speed. Thus, over or under reporting of abnormalities is liable to occur. In the present study, ECG analysis data was retrieved from the cassette tape by the Medilog MARS replay system (Oxford Medical Systems Ltd., Oxford).

The importance of real-time ECG analysis using this system lies in the ability of the system to analyse each

beat more thoroughly than systems dependent on analysis at replay time. Thus the processing capacity is greater.

To permit subsequent verification of the analysis the system stores both the ECG and results which can be reproduced in full disclosure form.

In all, four channels are recorded on the cassette - two for analogue ECG, one for the results of the analysis in digital form on a beat-by-beat basis and one for time code.

Analysis is performed by recorder based electronics, which compares each beat against a template and records the template number and the timing of the beat on a digital track. The templates are classified by the replay system. Arrhythmia sequences are identified during high speed scanning through the recorded digital information.

The timing and the template number of each beat are recorded in digital form, together with ST information averaged over 30 second periods. At the end of the recording, a data dump consisting of each template shape is recorded digitally with a number indicating how many matches were obtained.

On replay, the data dump is read and each template is classified by feature or extraction measurements, as dominant, supraventricular, ventricular or artefact. This information is used to build up a table of arrhythmia

combinations with times and durations of each episode. The times of occurence are listed in the report and searches are made to provide analogue examples of each type. The report also includes trends of heart rate, ST level and ventricular ectopy, as well as examples of each template. The templates may be edited manually if required and a further report generated, based on this classification.

The ST segment is defined 100 ms after the peak of the R wave and the system calculates the differences between this segment and the isoelectric line, as defined 60 ms before the peak of the R wave. The ability of the apparatus to measure changes in the ST segment has previously been compared to a standard ECG during an exercise test. (371) Mean sensitivity was 87%, specificity was 95% for detection of ST-shift, and correlation coefficient for ST segment level was 0.94. Thus, this system provides a valid means of recording ST segment changes.

The system provides a report including maximum and minimum HR and ST level and mean ST level. For each of these results, a corresponding section of ECG is produced at the precise time when these events occurred. This allowed the author to verify all individual results and reject any which were artefactual. From the ST segment level trend, ST segment elevation (< 1 mm. over baseline) or depression (> 1 mm. under baseline) could be measured in terms of frequency, duration and depth. These changes were verified by correlating the ST segment changes produced by the full disclosure. Thus any potential for artefact to

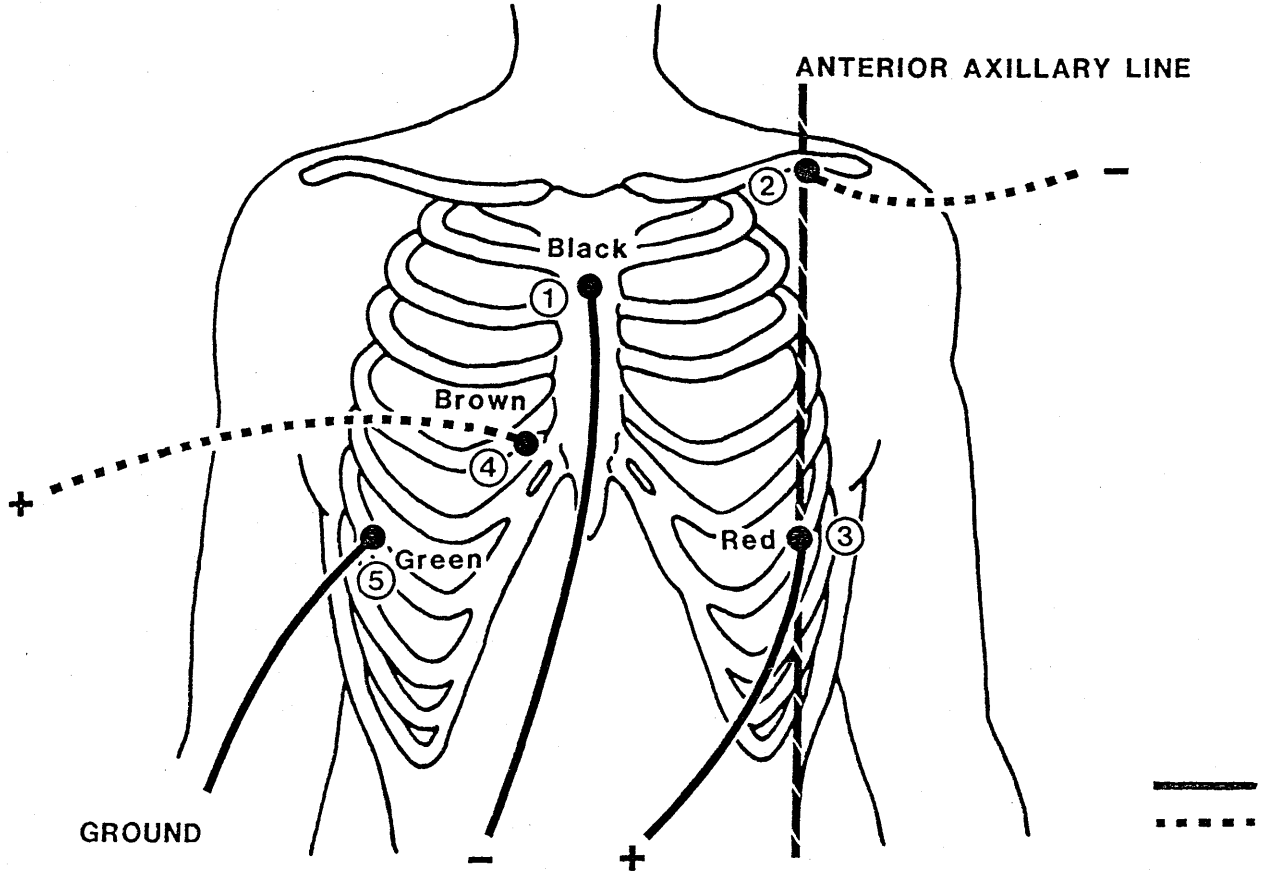


FIGURE 6.1

Placement of electrodes on the chest wall.
Electrodes 1 and 3 provides CM5 recording and
electrodes 2 and 4 record lead I.

influence the results was removed.

to ensure optimum performance of the equipment the recording head and tape transport mechanism were cleaned before each recording, a new set of batteries was used for each 24 hour recording and the cassette tapes were demagnetised using a bulk demagnetiser (Oxford Medical Systems Limited, Type 26). After careful skin preparation using an abrasive paste and shaving if necessary, five electrodes (Medicotest) were applied to the chest wall as shown in Figure 6.1, thus producing a recording of lead CM5 and a modified lead II. Careful skin preparation and siting of the electrodes helps minimise baseline instability. An impedence meter was then used to ensure that the resistance between each electrode was <5 kilohms, and surgical tape was used to attach the leads to the patient incorporating stress loops to reduce artefact caused by electrode movement. The recorder was worn at the patient's side and supported by a belt. A 1 mv. calibration test signal was then recorded and was subsequently used by the system to calibrate analysed data. The patient was instructed to follow his normal daily habits and to record any symptoms or activities in a diary, particular attention was paid to the occurance of any chest pain. Before leaving the laboratory the ECG waveform and magnitude being recorded was checked on a conventional ECG writer to ensure a satisfactory recording.

Mean nocturnal heart rate was derived from the

mean of the hourly heart rates between 24.00 - 06.00 hours when the patients were in bed. Significant ST segment depression was defined as planar or downsloping shift of the ST segment of >1 mm. in magnitude measured 100 milliseconds after the peak of the R wave and persisting for at least 30 seconds.

Maximum and minimum heart rates refer to rates recorded over the average R-R interval over four complexes. A sinus pause is defined as asystole greater than 1.5 seconds and 1.9 times greater than the average R-R interval of the four previous complexes. Ventricular tachycardia is regarded as three or more consecutive premature ventricular contractions (PVC's) during which two R-R intervals exceed 110 bpm and if less than 110 bpm this is regarded as idioventricular rhythm.

At the end of each recording the cassette was transferred to the Medilog Mars replay system which generates a comprehensive report and offers a search or full 24 hour disclosure, via a Microdot Printer, for verification of the analysis.

Statistical Analysis.

Results are expressed as mean $\pm$ standard deviation. Data was analysed using Student's paired t-test and Wilcoxon's signed rank test for paired observations. The most conservative significance values obtained are reported.

6.3. RESULTS.

Heart Rate.

The 24 hour trend of mean heart rate per hour is shown in Figure 6.2, for each drug. Propranolol resulted in a significantly lower mean hourly ($p < 0.001$), mean 24 hour, ($p < 0.001$), minimum ($p < 0.001$) and lower maximum heart rate (p = NS). Likewise, propranolol caused a lower mean daytime ($p < 0.001$) and nocturnal heart rate ($p < 0.025$). These results are shown in Table 6.2.

Frequency of Angina and ST Changes.

Fifteen episodes of angina occurred during the last 48 hours of treatment with pindolol compared to 12 with propranolol (p = NS), and although the mean number of attacks rose from 1.79 ± 3.94 per 48 hours (range 0-14) on propranolol to 2.12 ± 4.74 (range 0-20), this was also not significant. In all, five patients developed pain during the treatment periods, and with the exception of one case, all of these subjects noted more frequent angina during treatment with pindolol. The remaining 12 patients were symptom free on both drugs. During ambulatory electrocardiography the total number of episodes of ST segment depression increased from 59 on propranolol to 85 on pindolol (p = NS). Both the mean 24 hour ST level and the mean maximum ST segment depression were lower during treatment with pindolol, but this failed to reach statistical significance. (See Table 6.3)

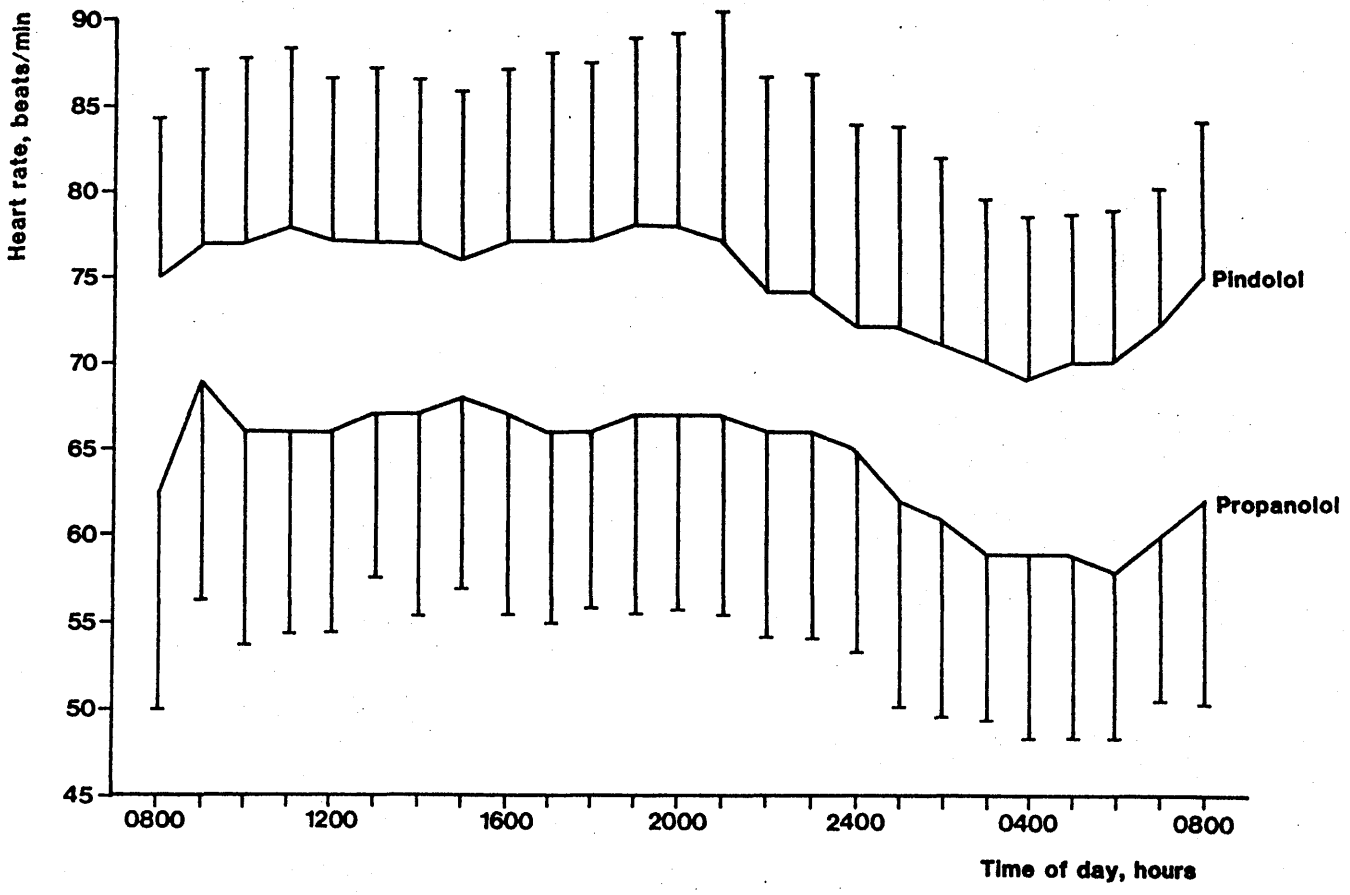


FIGURE 6.2

Mean heart rate over 24 hours during treatment with pindolol and propranolol (± standard deviation).

TABLE 6.2 HEART RATE RESPONSE TO BETA BLOCKADE. RESULTS ARE EXPRESSED AS BEATS PER MINUTE (MEAN ± STANDARD DEVIATION AND REPRESENT FINDINGS OVER 48 HOURS CONTINUOUS E.C.G. MONITORING.

	PROPRANOLOL	PINDOLOL	P
24 Hour Heart Rate	62 ± 11.9 (45-79)	73 ± 8.4 (55-88)	< 0.001
Minimum Heart Rate	43 ± 8.1 (28-57)	52 ± 7.1 (29-63)	< 0.001
Maximum Heart Rate	118 ± 24.3 (83-186)	130 ± 23.1 (103-189)	NS
Daytime Heart Rate	66 ± 2.1 (60-69)	76 ± 1.9 (72-78)	< 0.001
Nocturnal Heart Rate	60 ± 1.5 (58-62)	70 ± 1.0 (69-72)	< 0.025

TABLE 6.3 FREQUENCY OF ANGINA AND - NUMBER, DURATION AND MAGNITUDE OF S-T SEGMENT CHANGES DURING 48 HOURS CONTINUOUS E.C.G. MONITORING.

	PROPRANOLOL	PINDOLOL	P
No. of Episodes of Pain.	12	15	NS
ST Level (mm). (median with range)	-0.10 (-1.76-1.08)	-0.20 (-2.24-1.08)	NS
Maximum ST Level (mm). (median with range)	0.78 (-0.28-1.92)	0.76 (-0.68-1.96)	NS
ST - SEGMENT DEPRESSION:			
Total No. of Episodes.	59	85	NS
Mean No. of Episodes.	1.79 ± 3.94	2.12 ± 4.74	NS
Total Duration (minutes).	1155	2630	NS
Maximum Magnitude (mm). (median with range)	-0.82 (-4.96-0.28)	-0.94 (-4.96-0.56)	NS

Heart Rhythm.

During 48 hour ambulatory electrocardiography a total of 117 nocturnal pauses or episodes of asystole occurred in three patients during treatment with propranolol, ranging in length from 1.5 - 2.8 seconds. (See Figure 6.3a) During treatment with Pindolol no pause was noted in these patients, although one other patient had one episode lasting 1.7 seconds.

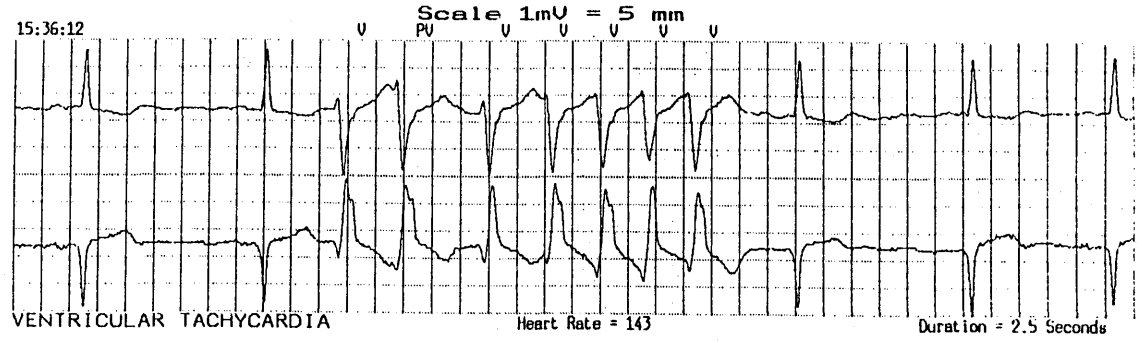
All patients exhibited PVC's during treatment with both propranolol and pindolol although only six had more than 100 PVC's in any one 24 hour period. The total number of PVC's occurring during treatment with pindolol (1316 beats) was less than on propranolol (2010 beats) and the mean hourly frequency of PVC's was significantly lower during pindolol administration ($p < 0.02$). (Figure 6.4)

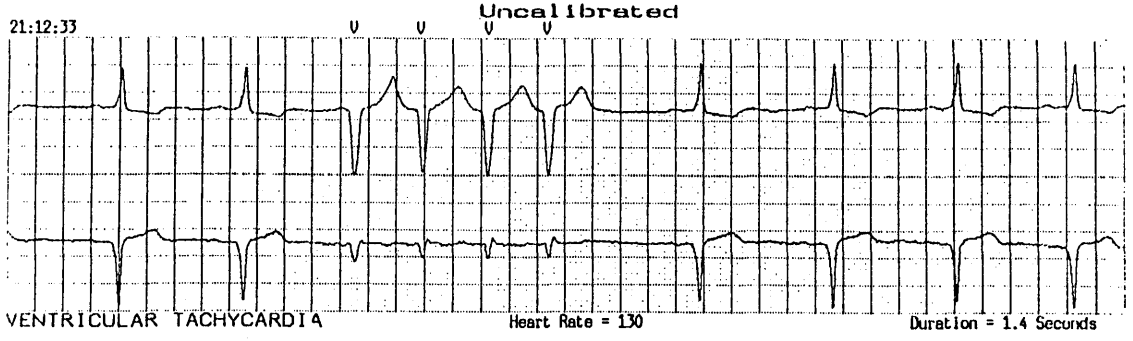
One subject (A.S.) developed one episode of ventricular tachycardia while on propranolol and pindolol (Figure 6.3b), and one subject (J.M.) had 42 episodes of ventricular bigemeny while taking propranolol, but only five episodes occurred in the last 48 hours of treatment with pindolol. (Figure 6.3c)

In general, the VPC's were unifocal in origin, but in two subjects (A.S. and J.M.), multifocal VPC's were identified together with occurrence of couplets.

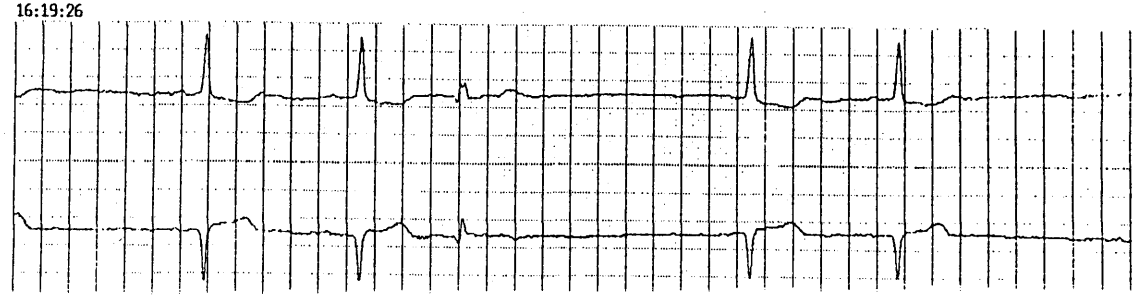
FIGURE 6.3

a. Ventricular tachycardia (7 complexes plus 4 complexes) during treatment with propranolol.





b. Period of asystole lasting 2.8 seconds at 16.19 hours during treatment with propranolol.



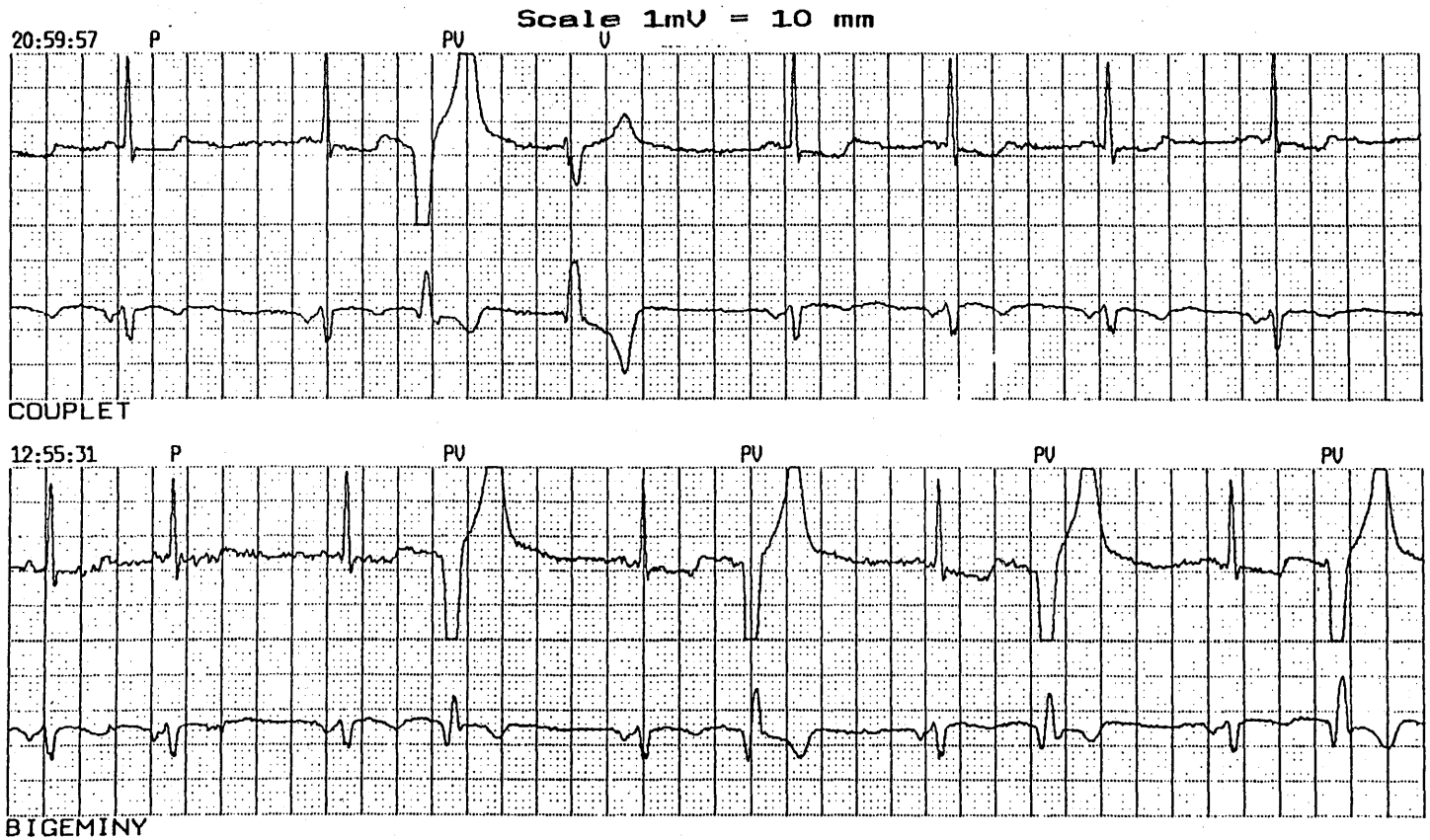


FIGURE 6.3

c. Ventricular bigeminy and couplets recorded in a patient with an average of 25 VPCs per hour. (J.M.)

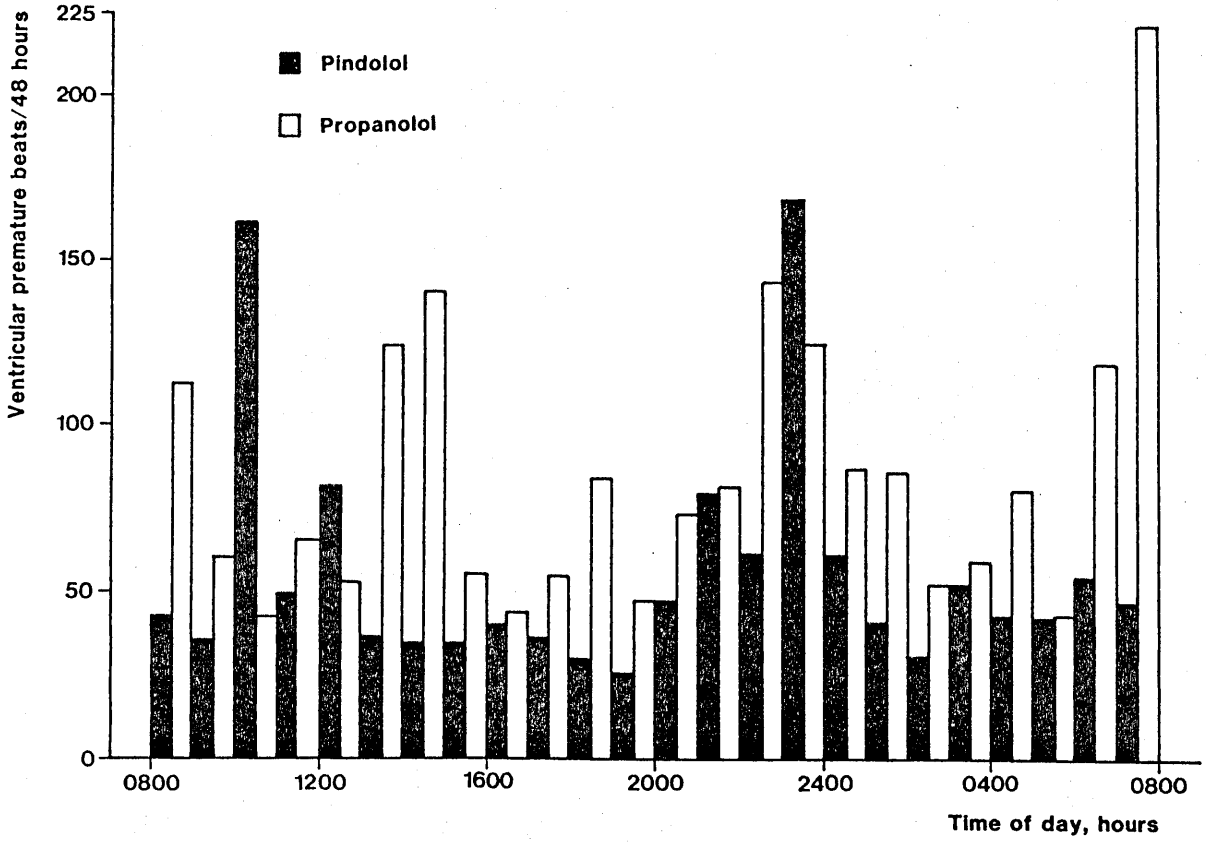


FIGURE 6.4

Frequency histogram of ventricular premature contractions occurring during 48 hours of continuous E.C.G. monitoring. Propranolol vs Pindolol : p = NS.

6.4 DISCUSSION

Previous studies evaluating the use of pindolol in the treatment of angina pectoris have confirmed its efficacy in reducing anginal symptoms in 42-85% of patients and increasing exercise tolerance by 12-21%. A greater improvement being observed in short-term or uncontrolled studies. (See Table 6.4) However, in a double blind cross-over comparative study with atenolol Quyyumi et al (65) drew attention to the deliterious effects of pindolol in subjects with severe effort angina and nocturnal angina. They studied 15 subjects with documented CAD and severe symptoms and randomised them to treatment with pindolol 5 mgs. t.i.d. or atenolol 100 mgs. daily in a cross-over study of five days treatment with each drug. They found that atenolol caused a greater reduction in the frequency and magnitude of day-time and nocturnal episodes of ST depression and attributed this to the ability of atenolol to reduce resting heart rate more than pindolol. Their study differed substantially from the present in several ways: the patients investigated had more severe CAD; there was a very short withdrawal period for patients already on beta blockers before entry into the study, which could have resulted in rebound effects in the first treatment phase and the method of analysis of ambulant ECGs was different. It is difficult to place their findings in clinical perspective as it is unlikely that the subject with severe rest or nocturnal angina would be treated with beta blockers alone - being liable to require additional therapy such as nitrates or

TABLE 6.4 PREVIOUS STUDIES OF PINDOLOL IN ANGINA PECTORIS.

STUDY	PATIENTS (n)	STUDY DESIGN	DURATION (weeks)	DAILY DOSE (mg)	% PATIENTS WITH DECREASED ANGINA	% REDUCTION IN ANGINA PECTORIS	% IMPROVEMENT IN EXERCISE TOLERANC
Harston and Friesinger (366)	12	A	15	20	42	32	13
Arstila et al (365)	20	B	24	20	50	23	12
Frishman et al (58)	23	C	12	40	NR	53	21
Thorpe (390)	16	A	10	20	75	NR	NR
Nair (391)	30	D	6	10	80	NR	NR
Sainani and Mukherjee (367)	25	D	6	10	72	*	+
Arvanis and Michaelides (392)	48	E	4-40	7.5-4.0	85	NR	NR
Saner (393)	14	E	NR	15	71	NR	NR
Magnani et al (394)	20	C	12	15	NR	38	14

Abbreviations: * = 56% of patients had a greater than 25% reduction in angina pectoris. + = Ten of 25 patients improve 50%; 7 of 25 showed no change or had decreased exercise tolerance. A = Double blind crossover comparison with placebo. B = Double blind crossover comparison with propranolol and placebo. C = Double blind comparison with propranolol or atenolol. D = Double blind comparison with placebo. E = Not controlled. NR = Not reported.

calcium antagonists. As this group will probably have more marked deterioration in cardiac contractility than those with chronic stable angina, it is possible that the benefits of a beta blocker with ISA will outweigh the disadvantages. I chose to study patients with stable angina who had been observed for at least one year, and compare the effects of pindolol with another nonselective beta blocker which does not possess ISA (propranolol). The withdrawal phase before entry into the study was longer, as were the treatment periods. Ambulatory electrocardiography was performed using recently introduced automatic equipment, thus removing any possiblity of observor error which could have been a factor in Quyyumi's study (65), as they utilised a visual playback system at 60 times normal speed to analyse the ECGs. This method is fraught with difficulty and may lead to under or over reporting of abnoralities.

Using cruder methods of assessment, other workers have reported variable findings using pindolol in angina. In a randomised control study, Harston and Friesinger (366) reported a reduction in the HR x BP product and increased exercise tolerance in 12 patients treated with pindolol. However, in the long-term, pindolol did not cause a significant reduction in attacks of angina or an enhanced exercise tolerance in comparison to placebo. Erikssen et al (372), in a study comparing pindolol with atenolol and metoprolol noted that pindolol was more effective in suppressing heart rate and blood pressure in a group of males aged 19-25 years, but extrapolation of this finding

to the diseased patient is not appropriate. Using high doses of pindolol (40 mgs) against moderate daily doses of propranolol (160 mgs) in patients with angina, Frishman et al (58) demonstrated a significant reduction in the frequency of angina and increased exercise tolerance with both drugs, but did not compare the difference in effect. In the present study a daily dose of 15 mg. per day in three divided doses was administered. This is the dose most frequently used in clinical practice, and previous studies have shown adequate beta blockade using this dosage with no additional haemodynamic benefit being observed with higher doses. (32) In another cross-over comparative study in stable angina pectoris with atenolol, lasting six weeks with each drug, both drugs reduced anginal attacks and increased exercise tolerance. But, atenolol was superior to pindolol in both these effects. (5)

It appears, that although pindolol is effective in terms of suppression of anginal symptoms, it is possibly inferior to other agents without ISA. During exercise, several investigators including Quyyumi (65) have observed effective beta blockade with pindolol suggesting that patients with effort angina will derive sufficient benefit from this drug. In the present study, although frequency of angina was greater during treatment with pindolol, this failed to reach significance.

Heart Rate.

The present study confirmed that pindolol suppresses resting heart rate to a lesser extent than propranolol (figure 6.2), but maximum heart rate achieved during treatment with these drugs was not significantly different, suggesting a similar beta blocking effect during periods of increased sympathetic tone. Pindolol protected the individual from severe bradycardia with a significantly higher minimum heart rate ($p < 0.001$). Three subjects exhibited asystolic episodes of 1.5-2.8 seconds during sleep while taking propranolol, but not pindolol. These findings are similar to those observed with atenolol vs pindolol previously. (65) However, in this study, the circadian rhythm of heart rate was maintained, there being no significant difference between each drugs effect on daytime and nocturnal heart rates. These results are virtually identical to another study examining circadian heart rate. (44) The failure of beta-blockers with ISA to effectively reduce resting heart rate has been noted by others (58,9,65), but in stable effort angina pectoris, it is probably more important to suppress exercise induced tachycardia than reduce resting heart rate. The relative impact of pindolol on resting heart rate is probably dependant on the pretreatment level of sympathetic tone as it has been found to reduce heart rate in subjects with pretreatment heart rates of greater than 80 bpm and increase heart rate in those with initial rates less than 80 bpm. (373) Thus, at rest, when sympathetic tone is low, beta blockers

with ISA will cause little change in heart rate, but during exercise an attenuation of heart rate will occur which is probably of equal potency to beta blockers without ISA, as shown by Finch et al (374) in a comparison with propranolol.

Ambulatory Electrocardiography.

The equipment used in the present study is one of a new generation of systems which are capable of faithfully reproducing the ST segment. This is an improvement on the form of analysis used by Quyyumi et al (19) and several other investigators who have studied ST segments using the audio-visual superimposed electrocardiographic presentation (AVSEP) method at 60 times normal speed. A recent review has suggested that these older systems are essentially outmoded. (375) The newer systems now incorporate analogue to digital convertors and electronic memories allowing real time ECG strip analysis and printout that can provide a real time, trend, graph or digital display of data. These systems have been shown to provide reproducible results and have removed observor error or bias from analysis of continuous ECG recordings.

In addition the poor low range frequency response of older monitoring equipment rendered assessment of ST changes unreliable. (376,377).

ST Segment Analysis.

This study found that 59 episodes of significant ST segment depression occurred during 48 hours monitoring while the patients were taking propranolol, and 85 episodes while taking pindolol. Only 12 and 15 episodes respectively were accompanied by pain. This is a similar proportion to that described by Quyyumi et al (65), but in this study no significant difference was observed between the number, duration or magnitude of ST depressions comparing the two drugs, although ST segment depression was more frequent, longer in duration and deeper during treatment with pindolol. It is possible that the episodes of painless ST depression do not represent ischaemia, but other influences which can disturb the ST segment such as changes in patient posture. (378) In addition, ST segment depression has been shown to occur in healthy individuals. (379) However, recently, Deanfield et al (380) have shown that planar ST depression during ambulatory electrocardiography, in patients with normal coronary arteriograms is rare, and in a separate report (381) they have correlated the results of positron tomography and ST segment recording and conclude that ST segment depression during continuous monitoring is a useful and reliable method of assessing the activity of CAD, but only in those with typical angina and proved CAD. Similarly, symptomatic and asymptomatic attacks of ST depression have been correlated with the results of stress testing (371,382), and there seems to be a concensus that asymptomatic ST depression is a more

frequent phenomenon than ST segment depression with angina and does in fact represent myocardial ischaemia in these patients. In this study, many of the ST segment depressions occurred at times when the heart rate was not significantly elevated. It has previously been suggested by Quyyumi et al (383) that ST depression is usually preceded by elevation of heart rate. Under resting conditions, in those with severe CAD, nocturnal resting ischaemia would be more liable to occur as myocardial oxygen demand may still be high. However, this hypothesis has recently been refuted by Chierchia et al (384) who demonstrated that ST depression could occur irrespective of resting heart rate, and further, that tachycardia could occur in the absence of ST depression. They suggest that myocardial oxygen demand is not the only, or the most common cause of acute ischaemia in chronic stable angina. These findings suggest that a suppression of heart rate alone need not indicate an advantage to a beta blocker without ISA, in chronic stable effort angina.

It is possible that future therapy aimed at morbidity and mortality in CAD may have to relieve asymptomatic as well as symptomatic ST depression, to have a desirable result.

Arrhythmias.

In this study, the mean hourly frequency of PVCs in the last 48 hours of monitoring during treatment with pindolol was significantly lower than during treatment

with propranolol ($p < 0.02$). The reason for such a difference is not clear. It has previously been shown that a diurnal variation of VPC frequency occurs in patients with CAD - with a fall in frequency during sleep. (385) This suggests that PVCs are more common at times of increased neural activity with resultant high sympathetic tone. If this were true, one would expect fewer VPCs to occur during treatment with propranolol. It is possible that the sustained, but suboptimal stimulation of B-receptors by pindolol is capable of suppressing ventricular ectopic foci already present and if a pure beta blocker is administered, this control is lost and ectopic foci are "released" from sympathetic influence. A number of studies have supported the hypothesis that the presence of VPCs in patients with CAD is a risk indicator of sudden death. (386,387) Thus, the 35% reduction in VPC frequency observed during pindolol treatment may be of some importance. However, according to Morganroth (388), a reduction of more than 65% would be required for 95% confidence of a drug effect and even then, 72 hour periods of monitoring would be required because of the spontaneous variability in frequency of VPCs.

In one study examining the electrophysiological effects of beta blockade (389), both propranolol and oxprenolol increased the threshold for ventricular fibrillation by 42 and 56% respectively, but pindolol resulted in an elevation of only 25%, suggesting that ISA alters myocardial excitability. Thus, the reason for my finding of a fall in VPCs during treatment

with pindolol is not consistent with previous findings and may be related to spontaneous variability of frequency alone, although no formal investigation using the techniques utilised in this study has been performed.

6.5. CONCLUSIONS.

Treatment with propranolol (80 mg. t.d.s.) and pindolol (5 mg. t.d.s.) resulted in significantly lower mean 24 hour, minimal, maximal, nocturnal and daytime heart rates with propranolol in patients with chronic stable effort angina. Although the number, duration and magnitude of both symptomatic and asymptomatic ST depression was greater during treatment with pindolol, none of these differences reached statistical significance. The mean hourly frequency of VPCs fell by 35% ($p < 0.02$) during treatment with pindolol compared to propranolol, the cause of this is unclear. Pindolol is a useful drug in the treatment of chronic stable angina pectoris and was not shown to be significantly inferior to propranolol, but may have less benefit in the treatment of severe or rest angina.

SECTION 7.

THE EFFECT OF CHRONIC BETA BLOCKER THERAPY ON RESPIRATORY FUNCTION: INFLUENCE OF ISA.

7.1. INTRODUCTION.

Soon after their introduction, it was appreciated that B-blockers could have a deliterious effect on respiratory function. This was due to blockade of the beta-adrenoceptors in the lung which are responsible for bronchomotor tone. Stimulation of the B_2 receptors results in bronchodilation - a situation which occurs when a sympathomimetic (or B_2 agonist) is administered eg. salbutamol. Blockade of these receptors may result in significant bronchoconstriction in susceptible individuals, such as those with pre-existing chronic obstructive airways disease (COAD), in whom the use of beta blockers may be restricted (395,396), or in ashtmatics in whom beta blockers are contra-indicated because of the risk of bronchospasm (397), and even acute asthmatic attacks. (396,398) In patients with fixed irreversible bronchial obstruction this is thought to be less likely (397,399), but has nevertheless been reported. (400) Further, it is recognised that acute bronchospasm can occur in some with no previous history of asthma, COAD or allergic disorders, following case reports by Froley et al (401) and Schwarz et al. (402) In healthy subjects some beta blockers have been shown to cause an increase in airways resistance in a proportion of individuals. (403) Using the body plethysmograph MacDonald et al (404) and McNeill and Ingram (405) have shown that a single dose of intravenous propranolol can increase airway resistance although Singh et al (406) failed to confirm these findings in normal subjects following a single oral dose of

propranolol (80 mg). The beta blocker most frequently incriminated in such respiratory effects is propranolol (396,398) (non-selective, without ISA). With the introduction of $Beta_1$ selective blockers such as atenolol and metoprolol it was hoped that the risk of bronchospasm would be reduced and although these agents are also known to produce a broncho-constrictive effect (407), studies comparing the effect of oral metoprolol with propranolol have shown that the former agent has less adverse effects on pulmonary function than equivalent doses of propranolol. (408-410) The fact that relatively selective beta blockers can cause bronchoconstriction, is probably because they are not exclusively selective and that besides $beta_2$ receptors, $beta_1$ receptors may also be present in the bronchi. (411)

Beta blockers possessing ISA are also thought to result in a less detrimental effect on ventilation compared to "pure" beta blockers, such as propranolol. However, it has not been established whether these agents can be safely administered to patients with COAD. Few studies report the effect of propranolol on patients with nonasthmatic COAD and the results are often conflicting. (399,412,413) This may be due to differences in methodology and study population involved. The results of most controlled studies are based on single doses of beta blocker of either the intravenous or oral formulation. (414-416) Data for chronic administration has usually resulted from open, uncontrolled investigations (417,418), and so the effect of chronic therapy in subjects with hypertension or angina pectoris has not been established.

In addition, the role of ISA in moderating beta blocker induced bronchoconstriction is not clear (419), although both oxprenolol and pindolol were found by Kumana et al (420) to have less effect on airways resistance when compared to propranolol in normal volunteers.

Since beta blockers are commonly prescribed to patients with angina pectoris or hypertension who may suffer from a degree of COAD, this study was undertaken to establish the effect of chronic oral beta blocker administration on respiratory function in a group of patients with angina pectoris, and to assess the potential benefits of ISA in this respect.

7.2. PATIENTS AND METHODS

Forty male patients with chronic stable angina were recruited to the study. Prior to inclusion these subjects were either untreated or responding inadequately to previous therapy. After at least two weeks without any medication the subjects were randomly allocated to treatment with propranolol 40 mgs. t.i.d. (n = 21) or pindolol 2.5 mgs. t.i.d. (n = 19) for two weeks, thereafter increasing to 80 mgs. and 5 mgs. t.i.d. respectively as described in previous sections of this thesis. Respiratory function was assessed at intervals of 2, 6, 12, 26 and 52 weeks following commencement of therapy. No subject was admitted to the study who suffered from reversible airways obstruction, a known allergic disorder, diabetes mellitus, heart block or renal failure, and glyceryl trinitrate was the only other routine medication permitted throughout the study. Indirect estimation of airways diameter was made by measuring Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV_1). Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV) and Inspiratory Capacity (IC) were also measured using a Morgan Rolling Seal Dry Spirometer (Model b), which has a reproducibility better than 2%. The calculation of these parameters is demonstrated in Figure 7.1. All measurements were taken after three minutes rest in the seated position after an overnight fast. Measurements were taken approximately 2-3 hours after the last oral dose of beta blocker at between 09.30 - 11.00 hours, as peak blood levels have

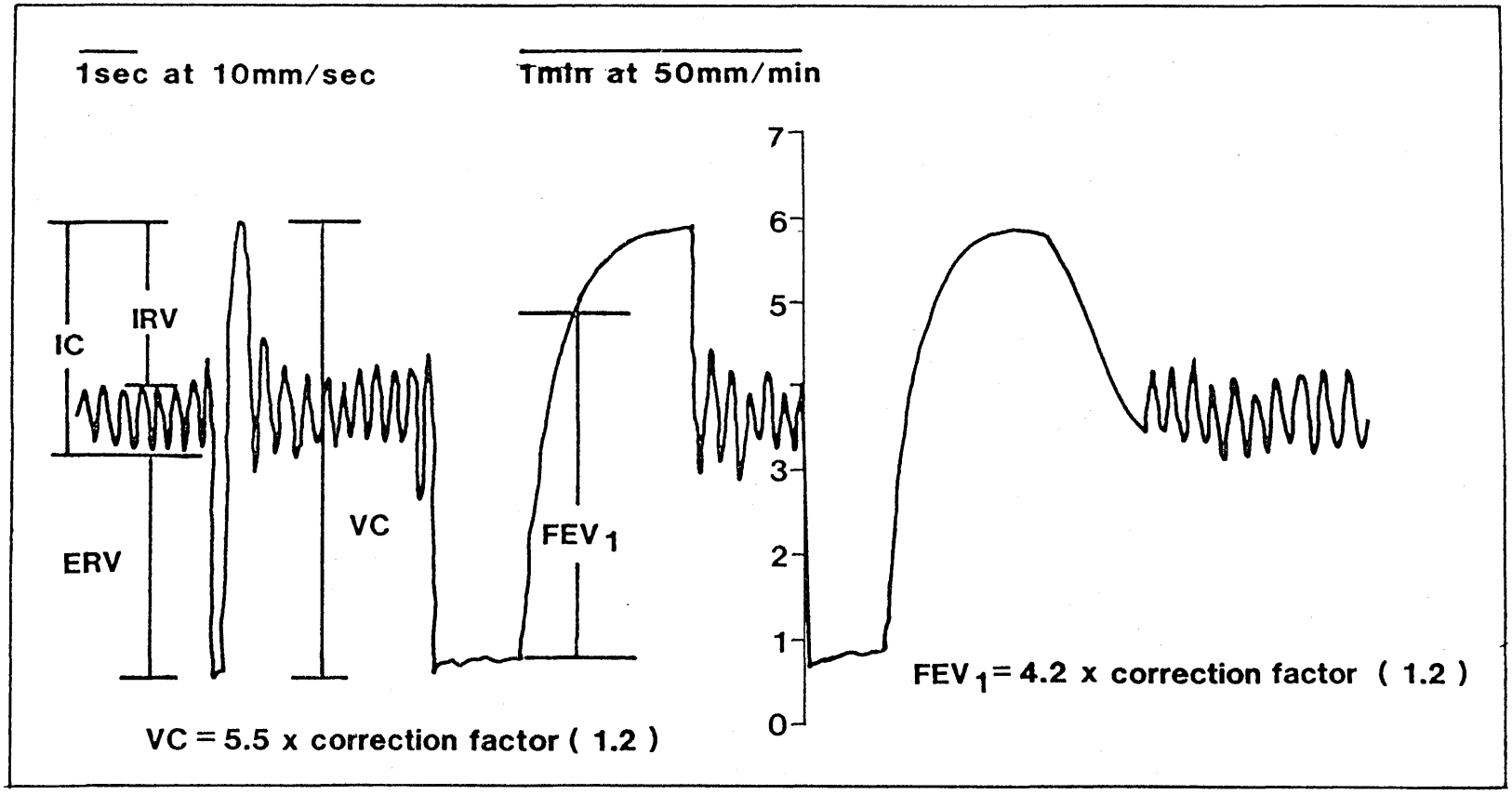


FIGURE 7.1

Spirometer tracing demonstrating the measurement of vital capacity (VC), forced expiratory volume in one second (FEV_1), expiratory reserve volume (ERV), inspiratory reserve volume (IRV) and inspiratory capacity (IC) at an ambiant temperature of 22°C. (correction factor = 1.12).

been demonstrated at this time. (421) On each occasion the subject had been present in the laboratory for at least 45 minutes to allow for equilibration to occur. There is no concensus concerning the number of measurements of each parameter that need be taken when measuring respiratory function. (422) In the present study I used the mean of three satisfactory attempts after a single training attempt, each attempt being separated by a period of one minute. All testing and analysis was carried out by the author and the spirometer was calibrated daily, prior to any measurement. As a dry spirometer was used, the volumes indicated on the chart paper were corrected to standard temperature and pressure according to the ambient temperature.

Statistical Analysis.

Two way analysis of variance was carried out for each measurement, if this indicated a significant change, then Student's paired t-test and a Wilcoxan signed rank test (for non parametric data) was applied with each comparison to the basal measurment. The most conservative significance values from these tests are reported. Between drug differences were tested using a Student's paired t-test and Wilcoxan signed rank test.

7.3. RESULTS

The groups of patients were not significantly different in terms of age, body weight, height or mass index (Table 3.1). The results of respiratory function testing are shown in tables 7.1 (pindolol) and 7.2 (propranolol). Basal respiratory function was similar in the two groups, although those taking propranolol had a slightly lower FEV_1. Heart rate and blood pressure changes are recorded on Figure 5.3.

In those treated with pindolol there was a fall in the mean FEV_1 of 120 mls. after 52 weeks treatment ($p < 0.05$) and a fall of up to 270 mls. in IC. at 12 weeks ($p < 0.05$). If results are expressed as a percentage of that predicted for age (using nomograms of Kamburoff and Woitowitz (423)), there was a highly significant fall in the FEV_1 from a mean of 89.5% to 85.6% ($p < 0.01$) at 52 weeks. No significant changes occurred in other parameters, although a slight fall in the FEV_1/FVC ratio occurred which reflects the fall in FEV_1.

In those treated with propranolol there was a fall in FEV_1, first significant after two weeks ($p < 0.05$) and falling sequentially by 240 mls. at 52 weeks ($p < 0.001$) which was twice the fall recorded with pindolol (Figure 7.2). A similar reduction in percentage of predicted value of FEV_1 occurred. In addition, a significant fall in VC occurred at 52 weeks ($p < 0.05$), and although no

TABLE 7.1 RESPIRATORY FUNCTION TEST RESULTS: PINDOLOL GROUP. Results are expressed as Mean ± SD.

Week No. →	Basal	2	6	12	26	52
FEV_1 (L)	3.16 ± 0.830	3.11 ± 0.824	3.11 ± 0.831	3.06 ± 0.832	3.07 ± 0.826	3.04 ± 0.782*
FEV_1 (% Pred. Value)	89.5 ± 19.01	87.5 ± 18.80	87.7 ± 18.45	86.4 ± 19.43	86.8 ± 18.89	85.6 ± 17.88**
FVC (% Pred. Value)	4.6 ± 0.819	4.6 ± 0.876	4.66 ± 0.875	4.59 ± 0.856	4.6 ± 0.860	4.6 ± 0.874
FVC (L)	100.7 ± 14.16	99.5 ± 13.90	101.7 ± 12.92	100.3 ± 14.74	100.5 ± 14.08	100.5 ± 14.75
FEV_1/FVC	68.1 ± 9.79	67.6 ± 8,92	67.2 ± 9.06	67.0 ± 9.36	66.9 ± 9.50	66.7 ± 9.29
EXP. RES. VOL. (L)	1.64 ± 0.589	1.75 ± 0.498	1.82 ± 0.661	1.81 ± 0.533	1.83 ± 0.658	1.80 ± 0.627
INSP. RES. VOL. (L)	1.54 ± 0.614	1.47 ± 0.644	1.39 ± 0.495	1.37 ± 0.613	1.46 ± 0.654	1.45 ± 0.590
INSP. Capacity. (L)	2.98 ± 0.602	2.85 ± 0.715	2.82 ± 0.604	2.71 ± 0.634*	2.77 ± 0.626*	2.81 ± 0.674

* $p < 0.05$; ** $p < 0.01$.

Abbreviations: FEV_1 = Forced Expiratory Volume in one Second; FVC = Forced Vital Capacity; EXP. RES. VOL. = Expiratory Reserve Volume; INSP. Capacity = Inspiratory Capacity. INSP. RES. VOL. = Inspiratory Reserve Volume; FEV_1 (% Pred. Value) = Forced Expiratory Volume in one Second Expressed as a Percentage of Predicted Value (see text).

TABLE 7.2 RESPIRATORY FUNCTION TEST RESULTS: PROPRANOLOL GROUP. Results are expressed as Mean ± SD.

Week No. →	Basal	2	6	12	26	52
FEV_1(L)	3.07 ± 0.585	2.93 ± 0.590*	2.9 ± 0.579*	2.87 ± 0.579***	2.86 ± 0.570**	2.88 ± 0.612**
FEV_1 (% Pred. Value)	87.1 ± 14,84	83.5 ± 14.40	82.4 ± 14.98**	81.6 ± 14.89***	81.6 ± 14.44***	80.6 ± 14.98**
FVC (L)	4.42 ± 0.717	4.37 ± 0.746	4.38 ± 0.776	4.31 ± 0.739	4.27 ± 0.766	4.23 ± 0.772*
FVC (% Pred. Value)	97.9 ± 14.10	96.6 ± 14.20	97.0 ± 14.78	95.3 ± 14.31	94.4 ± 13.41	93.5 ± 13.58*
FEV_1/FVC	67.1 ± 9.02	67.1 ± 8.79	67.0 ± 8.70	66.9 ± 8.56	67.0 ± 8.61	66.8 ± 7.67
EXP. RES. VOL.(L)	1.82 ± 0.552	1.85 ± 0.660	1.96 ± 0.621	1.99 ± 0.626	2.08 ± 0.599*	2.10 ± 0.578**
INSP. RES. VOL.(L)	1.43 ± 0.515	1.37 ± 0.598	1.37 ± 0.629	1.17 ± 0.502**	1.17 ± 0.522*	1.13 ± 0.581*
INSP. Capacity (L)	2.52 0.500	2.49 ± 0.733	2.41 ± 0.705	2.36 ± 0.598	2.22 ± 0.584*	2.12 ± 0.632

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Abbreviations: FEV_1 = Forced Expiratory Volume in one Second; FVC = Forced Vital Capacity; EXP. RES. VOL. = Expirator Reserve Volume; INSP. Capacity = Inspiratory Capacity; INSP. RES. VOL. = Inspiratory Reserve Volume; FEV_1 (% Pred. Value) = Forced Expiratory Volume in one Second Expressed as a Percentage of Predicted Value (see test).

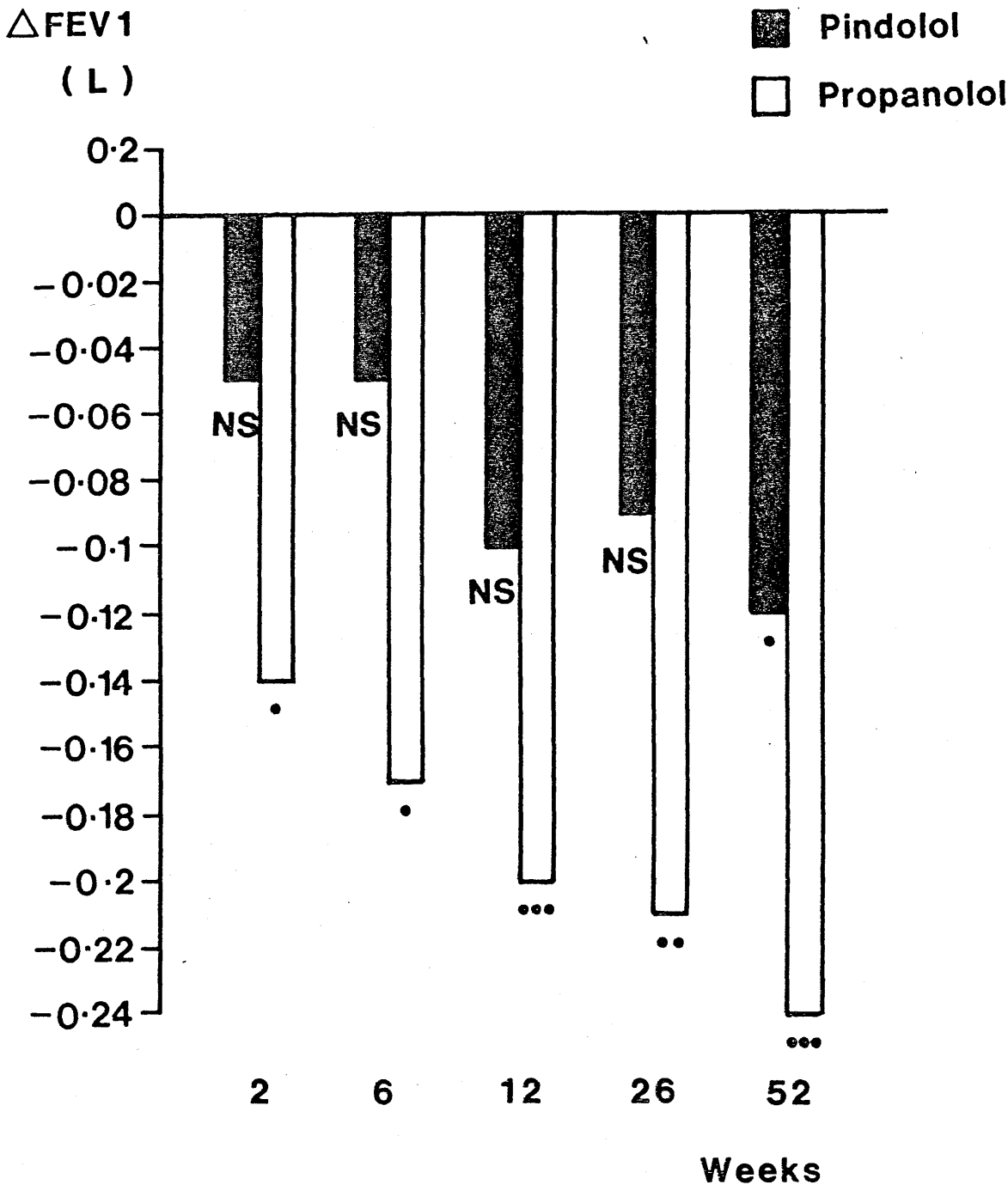


FIGURE 7.2

Changes in FEV_1 related to mean basal value.

Abbreviations: FEV_1 - Forced expiratory volume in one second.

• $p < 0.05$; •• $p < 0.01$; ••• $p < 0.001$.

change occurred in FEV_1/FVC ratio, this reflected a similar fall in FEV_1 and VC. A significant rise occurred in ERV and falls in IRV and IC were also recorded.

To determine whether those with chronic airflow obstruction reacted differently to each drug the subjects were subdivided according to a basal FEV_1/FVC ratio of less than, or greater than 70%.

Pindolol caused a significant reduction of FEV_1 and FEV_1/FVC at 52 weeks only when the basal FEV_1/FVC was greater than 70% (Table 7.3). Propranolol caused a similar reduction in FEV_1 regardless of the basal value although this became more significant at 12 and 52 weeks in those with basal ratios greater than 70% (Table 7.4), compared with those who had values less than 70%.

TABLE 7.3 RESPIRATORY FUNCTION TEST RESULTS CLASSIFIED ACCORDING TO BASAL VALUE (FEV_1/VC < > 70%): PINDOLOL GROUP.

	Week No. →	Basal	2	6	12	26	52
$\frac{FEV_1}{FVC}$ >70%	FEV_1 (L)	3.73 ± 0.56	3.71 ± 0.57	3.67 ± 0.63	3.64 ± 0.66	3.65 ± 0.55	3.54 ± 0.58*
	FEV_1 (% Pred. Value)	101.4 ± 13.35	99.9 ± 15.47	98.6 ± 15.12	98.0 ± 18.10	98.1 ± 12.55	95.3 ± 14.08
	FEV_1/VC	76.7 ± 3.62	73.6 ± 4.22	74.1 ± 3.92	75.7 ± 4.11	75.0 ± 3.31	72.3 ± 2.78*
$\frac{FEV_1}{FVC}$ <70%	FEV_1 (L)	2.63 ± 0.662	2.57 ± 0.620	2.61 ± 0.665	2.58 ± 0.619	2.55 ± 0.677	2.58 ± 0.663
	FEV_1 (% Pred. Value)	78.8 ± 17.19	76.4 ± 14.24	77.9 ± 15.87	75.9 ± 14.43	76.2 ± 15.93	77.0 ± 16.94
	FEV_1/VC	60.4 ± 6.28	61.1 ± 6.06	59.4 ± 7.32	58.6 ± 8.08	59.6 ± 8.08	59.4 ± 6.57

* $p < 0.05$.

Abbreviations: FEV_1 = Forced Expiratory Volume in one Second; FVC = Forced Vital Capacity; EXP. RES. VOL. = Expiratory Reserve Volume; INSP. Capacity = Inspiratory Capacity; INSP. RES. VOL. = Inspiratory Reserve Volume; FEV_1 (% Pred. Value) = Forced Expiratory Volume in one Second Expressed as a Percentage of Predicted Value (see text).

TABLE 7.4 RESPIRATORY FUNCTION TEST RESULTS CLASSIFIED ACCORDING TO BASAL VALUE (FEV_1/VC < > 70%): PROPRANOLOL GROUP.

	Week No. →	Basal	2	6	12	26	52
$\frac{FEV_1}{FVC}$ > 70%	FEV_1 (L)	3.35 ± 0.47	3.19 ± 0.58*	3.18 ± 0.52*	3.13 ± 0.49**	3.21 ± 0.49	3.14 ± 0.52**
	FEV_1 (% Pred. Value)	93.0 ± 10.70	88.3 ± 12.70*	88.6 ± 12.49*	86.9 ± 12.49**	89.3 ± 10.42	87.8 ± 11.41**
	FEV_1/VC	75.1 ± 3.98	71.8 ± 4.34*	72.0 ± 5.73*	72.1 ± 4.61*	72.6 ± 4.96	71.5 ± 5.02
$\frac{FEV_1}{FVC}$ < 70%	FEV_1 (L)	2.82 ± 0.582	2.71 ± 0.526	2.63 ± 0.559*	2.63 ± 0.567*	2.54 ± 0.445*	2.54 ± 0.564*
	FEV_1 (% Pred. Value)	81.6 ± 16.42	79.2 ± 15.03	76.7 ± 15.33*	76.7 ± 16.19*	74.7 ± 14.41*	74.0 ± 15.25*
	FEV_1 /VC	64.4 ± 5.16	63.1 ± 7.99	60.8 ± 6.01*	61.5 ± 5.78	62.8 ± 9.91	62.5 ± 7.20

* $p < 0.05$; ** $p < 0.01$.

Abbreviations: FEV_1 = Forced Expiratory Volume in one Second; FVC = Forced Vital Capacity; EXP. RES. VOL. = Expiratory Reserve Volume; INSP. Capacity = Inspiratory Capacity; INSP. RES. VOL. = Inspiratory Reserve Volume; FEV_1 (% Pred. Value) = Forced Expiratory Volume in one Second Expressed as a Percentage of Predicted Value (see text).

7.4 DISCUSSION

The most important finding of this study is the progressive deterioration in respiratory function during chronic beta blockade in subjects with no history of reversible airways disease. This phenomena was most marked with propranolol which had a significantly greater effect on FEV_1 than pindolol. In addition VC became progressively smaller during treatment with propranolol, but no change occurred during treatment with pindolol. There was no significant difference in an individuals response to each beta blocker according to basal values of FEV_1/FVC, propranolol being shown to have a consistently detrimental effect, while pindolol caused only small reductions in FEV_1 and the FEV_1/FVC ratio.

Although propranolol caused a progressive and highly significant reduction in FEV_1 (Figure 7.2), it is unclear whether a reduction of 240 mls. in FEV_1 (at 52 weeks) is of clinical significance as no subject reported increasing breathlessness or wheeze with this drug. It is also possible that the deterioration in respiratory function will progress beyond one year in a cummulative fashion, thus precipitating symptomatic deterioration. In addition the effect of chronic oral administration of propranolol to patients with COAD might have been an adverse progressive effect on pulmonary function which could lead to deterioration in a previously compensated patient. While the drug did not cause a rapid and

dramatic clinial exacerbation in these patients, it did cause a definite and sustained increase in airways obstruction compared to pindolol.

The significantly greater deterioration in respiratory function indices presumed to reflect changes in large airway calibre after propranolol administration compared to an agent with ISA, has been referred to by others. (407,424) However, Patakas et al (425), when studying respiratory function after single oral doses of propranolol (40 mgs.) and pindolol (2.5 mgs.)in asthmatics confirmed a bronchoconstrictive effect on large and small airways after propranolol, but pindolol, although causing no significant effect on large airway calibre, caused a significant bronchoconstriction of the small airways. They suggest that pindolol remains potentially dangerous in asthmatics because of the small airway effects.

7.5. PREVIOUS STUDIES

Most studies have examined the effect of single dose oral or intravenous administration of beta blockers. Usually these experiments have been carried out in subjects with reversible airways obstruction, and most have evaluated respiratory effects on the basis of FEV_1, peak expiratory flow rate (PEFR) or airways resistance (Raw). Studies evaluating the effect of beta blockers on respiratory function, in subjects being treated for hypertension or angina pectoris on a chronic basis, are rare. (426) Of the studies exclusively examining non-selective agents without ISA, Nordstrom et al (399) administered intravenous propranolol to 10 patients with COAD, and found an increase in airways resistance after only 10 minutes. In a similar study, using intravenous administration Ryo and Tomnley (427) found a significant reduction of FEV_1 after 3 mgs. propranolol. Using a single oral dose of propranolol (80 mgs.) Kumana and Ruffin (428) reported a reduction in FEV_1 and PEFR, and during chronic administration, Horvath et al (429) reported increased airways obstruction during chronic administration with propranolol (320 mgs./day).

In contrast, Trembath et al (430), found no change in FEV_1 or VC following a single oral dose of propranolol (80 mgs.), although only five patients were included in that study. In one of the few studies examining the effects of propranolol on respiratory function in non-

asthmatic subjects with angina pectoris, Jebavy et al (426), found a significant reduction in total ventilation and tidal volume after 10 mgs. intravenous propranolol, but no bronchoconstriction was observed. Other single dose studies have confirmed the finding of a minor, but significant reduction in FEV_1 following propranolol. (431.432) In healthy subjects, both Campbell et al (433) and Warren et al (434), failed to find any deterioration in respiratory function after oral propranolol, but in those with non-asthmatic COAD, Chester et al (435), in a double blind cross-over comparison of propranolol and placebo found a deterioration after propranolol only and concluded that this beta blocker may exacerbate symptoms in these individuals.

With the introduction of B_1 selective blockers, it was hoped that they would have a less damaging effect on respiratory function. Svedmyr and Thiringer (410) reported a slight and similar reduction in FEV_1 after oral administration of propranolol (40 mgs) and metoprolol (50 and 100 mgs.).

In healthy subjects, Singh et al (406), failed to show any significant effect on respiratory function after oral metoprolol (100 mg.), but this dose caused an increase in airways resistance in 12 asthmatic subjects although less pronounced than following propranolol. In contrast, Mue et al (436) observed no change in FEV_1 or VC in a placebo controlled study of metoprolol in 33 asthmatic patients. Skinner et al (437) have shown that although

8 mgs. intravenous metoprolol given to 12 stable asthmatics had a minimal effect on FEV_1, in two subjects, FEV_1 fell by more than 500 mls. and this was felt to be clinically significant. Again, using single dose iv. administration, Johnsson (438) found that an equipotent dose of metoprolol had less effect on FEV_1 than propranolol. In seven subjects with chronic, stable obstructive airways disease, Abraham et al (439) administered increasing doses of intravenous metoprolol until a reduction of FEV_1 occurred at 0.15 mg./kg. body weight - thus demonstrating that cardioselectivity was lost at high dosage, but might be useful in preventing bronchospasm if used in smaller doses. In more recent studies, Butland et al (440) found a reduction of FEV_1 and VC during therapy with metoprolol (intravenous and oral administration) in 10 patients with emphysema. During chronic administration of atenolol and metoprolol in a cross-over study in 14 hypertensive subjects with asthma, Lawrence et al (441) found that Atenolol caused significantly less bronchospasm ($p < 0.05$) in terms of fewer asthmatic attacks and less effect of PEFR. However, they also found that after a single dose, both atenolol and metoprolol caused similar, significant falls in FEV_1 and FVC.

A new B_1 adrenoceptor blocker, pafenolol, which is more selective for B_1 adrenoceptors than metoprolol, has been studied by Löfdahl et al (442), in eight asthmatic subjects in a cross-over study with metoprolol. There was no difference between the treatments on FEV_1, but following inhaled terbutaline (B_2 stimulant) it was found

that there was a greater response in those treated with pafenolol, thus indicating that less blockade of B_2 adrenoceptors had occurred with this drug.

Several studies have evaluated the role of ISA on respiratory function. Benson et al (408) carried out a study in 12 asthmatic subjects who received placebo, propranolol (100 mgs.), Pindolol (5 mgs.), acebutalol (300 mgs.) and atenolol (100 mgs.) and showed that propranolol caused the greatest reduction in FEV_1 and this was less marked with the other drugs. In eight normal subjects, Folgering and Braakhekke (443) carried out a double blind cross-over trial of propranolol, metoprolol and oxprenolol in normal subjects and found no effect with any drug on PEFR. England, however, found that only propranolol caused a significant reduction in FEV_1, in a study of 18 non-asthmatic hypertensives taking propranolol, atenolol and pindolol. (119) Using a different approach, Dorow (444), in a group of 10 asthmatics, determined the pretreatment histamine concentration necessary to produce a 20% fall in FEV_1. Histamine provocation was repeated after equipotent doses of propranolol, pindolol and metoprolol. Although the amount of histamine required to induce bronchospasm fell slightly following pindolol or metoprolol, this was not significant. After propranolol, however, very small quantities of histamine were required to produce a 20% reduction in FEV_1.

One disadvantage of agents with ISA compared to cardioselective drugs was demonstrated by Greefhorst (445), who studied the effect of metoprolol and acebutolol on eight asthmatic subjects. FEV_1 and PEFR were reduced significantly by both drugs, but following a terbutaline infusion a dose dependent increase in FEV_1 and PEFR occurred, although the increase in these indices was partly inhibited by acebutolol compared to atenolol. Thus, if airways obstruction does occur, it is less likely to be reversed by a B_2 agonist if the beta blocker is not relatively B_1 selective. Patakas et al (425) found that pindolol was more likely to cause bronchoconstriction in the small airways only compared to the broncho-constrictor effect of propranolol which affects both large and small airways, and they concluded that pindolol may still be potentially dangerous in asthmatic patients because of this.

Thus, there is agreement that non-selective agents without ISA cause potentially harmful changes in respiratory function in asthmatics and possibly also in those with irreversible chronic obstructive airways disease and even in healthy subjects. Cardioselectivity tends to reduce the bronchoconstrictive effect as does ISA, but if bronchoconstriction is induced it is less likely to be reversed by a B_2 agonist compared with a cardio-selective agent.

The present study is the first to evaluate the effect of chronic beta blocker therapy in individuals

being treated for angina pectoris and has shown a clear advantage of pindolol compared to propranolol.

The available evidence suggests that no beta blocker is entirely safe in patients with chronic obstructive airways disease. If possible, an alternative medication should first be considered. Bronchoconstriction following beta blocker administration is most marked in those with reversible bronchial obstruction and less pronounced in those with irreversible bronchial obstruction. Beta blockers with ISA or cardioselectivity have a less marked effect on pulmonary function and so should be considered in preference to those noncardioselective agents without ISA in situations where a beta blocker is felt desirable despite the presence of respiratory impairment. In such an instance in patients with angina pectoris requiring additional antianginal agents, the most appropriate drug could be nifedipine, which has been shown to have a slightly more beneficial effect on beta blocker induced bronchoconstriction than that achieved by nitrates. (446)

Ideally, it would be advantageous to develop a beta blocker with no adverse effects on respiratory function ie. a completely cardioselective agent. However, in view of present knowledge of beta receptors, this would not be possible, as it has been established that an absolute separation of B_1 and B_2 receptors in different organs, as postulated by Lands et al (447) is incorrect. Radioligand studies and pharmacodynamic experiments have

shown that the airways possess, besides mainly B_2, also B_1 receptors (411,448), and further, that stimulation of both of these receptors may cause bronchodilation. (449,450) This may explain why a B_1 selective beta blocker can induce a limited increase in bronchoconstriction which can be counteracted by a B_2 stimulant.

7.6. CONCLUSIONS

It is firmly established that beta blockers can have a bronchoconstrictive effect, especially in asthmatic subjects and possibly also in those with irreversible airways obstruction and those with normal respiratory function. Most studies evaluating the effect of beta blockers have used a single oral or intravenous dose of drug in small numbers of subjects, who usually have had a degree of obstructive airways disease. The present study evaluated the effect of chronic oral administration of propranolol and pindolol in subjects with angina pectoris. Propranolol caused a progressive and highly significant deterioration in respiratory function when compared to pindolol. It is suggested that pindolol may be a more suitable drug in subjects with respiratory disease in whom beta blockade is thought to be desirable although respiratory function should be monitored from time to time regardless of the beta blocker employed.

SECTION 8.

8.1. Final Commentary

8.2. References.

8.1. FINAL COMMENTARY.

The medical management of angina pectoris has been enhanced by beta-adrenoceptor blockers, with the result that many hundreds of thousands of individuals are currently being treated on a long-term basis with these drugs. Thus, it is vitally important to establish the chronic effects of beta blockers and the role of any inherent pharmacological property. Despite this, there is a paucity of long-term studies evaluating the use of beta blockers in angina pectoris. In addition, the effect of different pharmacological properties has not been fully established.

In this thesis the effects of beta blockers with and without ISA have been evaluated. The prototype of a beta blocker with ISA was pindolol and that of a pure beta blocker, propranolol.

Treatment with propranolol was associated with improved left ventricular function, both at rest and during exercise at intervals throughout treatment, but no significant improvement occurred during treatment with pindolol. This result contradicts the findings of short-term studies which have suggested improved left ventricular performance with beta blockers possessing ISA. However, there are no other long-term studies of either pure beta blockers or those with ISA with which to compare these results. Thus, the work in this thesis

indicates that ISA does not represent an advantage in terms of left ventricular performance. It is probable that propranolol reduced myocardial oxygen demand at rest and during exercise to a greater extent than pindolol, and by lowering heart rate by a greater degree, allowed more time for diastolic filling of the coronary arteries. This may result in improved left ventricular function, causing the possible inotropic effect of ISA to be undetectable over the long-term.

By assessing the effect of propranolol and pindolol in a short-term study using ambulatory electrocardiography, I found that there was no significant difference between the drugs in their ability to prevent symptomatic and asymptomatic myocardial ischaemia judged by changes in the ST-segment, although pindolol was associated with more episodes of ST-segment depression. This result, in chronic stable angina, differed from an earlier study which found pindolol to be less effective in controlling ischaemia, but in subjects with severe, or rest angina pectoris.

There are few long-term studies examining the effect of beta blockers on plasma lipids, despite several short-term studies suggesting possible harmful effects. In the present studies, I found that pindolol was less likely to upset the lipoprotein profile than propranolol, and if the pre-treatment total cholesterol level was elevated, only pindolol caused a significant fall.

However, the potentially harmful effects of propranolol observed in short-term studies were not confirmed. In particular, propranolol was found to increase HDL_2 after 12 months treatment, despite there being a fall in total HDL. This effect is potentially beneficial with respect to coronary artery disease risk. Pindolol also caused an increase in HDL_2. No other study has carried out such an analysis and the results require confirmation. It is possible that the failure to reduce cardiovascular mortality in several large antihypertension studies is a result of the detrimental effect of pure beta blockers on plasma lipids. If an alternative beta blocker were to prevent these changes, or minimise them, this would be of considerable value.

Respiratory function was found to deteriorate in a sequential manner during treatment with propranolol - this was significantly greater than during treatment with pindolol suggesting an advantage of ISA in subjects with obstructive airways disease when a beta blocker is felt desirable for treatment of angina pectoris.

Finally, the use of radionuclide ventriculography and the value of cold pressor testing and sustained isometric handgrip exercise were assessed as an integral part of this thesis. Previous work has shown inconsistent results using these techniques in the detection of coronary artery disease, and in our laboratory they proved to be of

only moderate sensitivity. However, their value in the serial assessment of left ventricular performance has not previously been assessed, and in this respect they were useful, easily applied and reproducible interventions.

In summary, although ISA has been found to be potentially useful in terms of respiratory function and, plasma lipoprotein responses to beta blockade, it is not a useful property in the long-term, when compared to pure beta blockade in the control of myocardial ischaemia and improvement in left ventricular performance.

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