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BORDERLINE HYPERTENSION IN YOUNG MEN

by

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THESIS CONTAINS
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SUMMARY

This study was concerned with the measurement of blood pressure and the assessment of its patterns and variability in the young borderline hypertensive and normotensive male. The effects of prolonged β -adrenergic blockade were also studied in a placebo-controlled trial of atenolol in 30 borderline hypertensives in whom echocardiographic and electrocardiographic parameters were examined for possible evidence of early hypertensive cardiac hypertrophy.

Borderline hypertension was defined on the basis of blood pressure variation about the arbitrary limits of 140 mmHg systolic and/or 90 mmHg diastolic during at least three separate office readings with random zero sphygmomanometry during a three month baseline period. The 15 normotensives in the study at no time exceeded these limits during a similar time period.

Office and home blood pressure levels were significantly greater for borderline hypertensives compared to controls. Home blood pressure, however, was not significantly different from that recorded in the "stressful" hospital environment and this is contrary to the findings of previous studies.

The significant difference in blood pressure between normotensives and hypertensives was apparent for the majority of 24 hours when continuous ambulatory, intra-arterial records were analysed. Both blood pressure categories demonstrated profound night-time falls

in blood pressure, with an early morning rise. Day-time continuous arterial pressure corresponded closely to indirect office and home readings.

β -adrenergic blockade effectively lowered blood pressure in borderline individuals and although a non-significant fall in pressure was seen in office recordings in placebo-treated subjects this was not demonstrated in 24 hour recordings. The use of atenolol was accompanied by minimal side effects and was well tolerated.

Baroreflex sensitivity was found to be reduced in borderline hypertensives, but after chronic β -adrenergic blockade there was a return of sensitivity towards the normotensive range. There was no correlation between the degree of blood pressure reduction and increase in sensitivity, so it seems unlikely that β -blockers exert their antihypertensive action by a direct effect on the carotid baroreceptor mechanism.

Despite reduced baroreflex sensitivity there was no evidence of increased blood pressure variability, measured by the standard deviations of the hourly means, from analysis of continuous ambulatory blood pressure records of borderline hypertensives.

In a study of epidemiological data 27% of 913 young males aged between 16 and 35 years were found to have a blood pressure abnormality and 18% of these fell into the borderline category. Thirty per cent of young men of the remaining 9% with mild hypertension satisfied criteria for electrocardiographic left ventricular hypertrophy.

Despite this observation there was no significant difference in electrocardiographic maximum precordial voltage between normotensives and borderline hypertensives in the main area of this study. However, after identifying seven borderline hypertensives who fulfilled electrocardiographic left ventricular hypertrophy criteria it was found that their 24 hour intra-arterial blood pressure was significantly elevated throughout most of the day-time period when compared to non-hypertrophy individuals. These findings indicate a possible relationship between prolonged elevation of left ventricular afterload and electrocardiographic appearances of ventricular hypertrophy.

Blood pressure reduction had no effect on precordial voltage of the electrocardiogram, but at the end of six months there had been a significant increase in this measurement in the electrocardiograms of placebo-treated individuals.

Echocardiographic measurement of posterior left ventricular wall thickness was found to be anatomically accurate, but no correlation was found between electrocardiographic maximum precordial voltage and septal and posterior wall thickness. At the same time no difference between the echo measurements was seen when normotensive and borderline hypertensive values were compared, but blood pressure lowering prevented the increase in septal and left ventricular wall thickness which was found at the end of six months in the placebo-treated group.

The finding of a significant inverse relationship between baroreflex sensitivity and posterior wall and septal thickness suggested that early structural changes involving the vasculature and myocardium might already be operative and this observation is supported by the electrocardiographic and echocardiographic findings in this study of borderline hypertension.

CHAPTER ONE - INTRODUCTION AND GENERAL REVIEW

The benefits of blood pressure lowering in severe or moderate degrees of hypertension are now well-established. Following the pioneer work of Smirk (1953), which showed an improved prognosis in patients with malignant hypertension in congestive cardiac failure, treated with the ganglion-blocking agent hexamethonium, reports quickly followed on the improved prognosis seen in patients in malignant phase treated with blood pressure reduction (Morrison, 1953; Rosenheim, 1954; Schroeder, 1955; and McMichael and Murphy, 1955). Hodge, McQueen and Smirk (1961) reported an improvement in overall mortality in treated, non-malignant, hypertension while Hamilton, Thompson and Wisniewski (1964) described a significant reduction in stroke occurrence in a small series of treated hypertensive males.

The Veterans Administration Cooperative Study (1967) examined the effects of antihypertensive treatment on morbidity and mortality in patients with diastolic blood pressures between 115 mmHg and 129 mmHg. Despite recognised limitations the study demonstrated quite conclusively that there was a significant reduction in morbidity and mortality when antihypertensive therapy was instituted in a male population with diastolic blood pressure in excess of 115 mmHg. Little or no data was available, however, on the effects of moderately elevated blood pressure until the second Veterans Administration Cooperative Study (1970) which examined the effects of treatment on morbidity in males with diastolic blood pressure in the range 90 mmHg to 114 mmHg. Three hundred and eighty men entered the placebo-controlled antihypertensive study and during a five-year treatment period the

risk of developing a morbid event was reduced from 55% to 18%.

Despite the obvious benefits of therapy the results tended to support the view that the degree of benefit was related to the pre-treatment blood pressure. However, subsequent studies have concluded that the achieved, and not the baseline, blood pressure is the more important predictor of subsequent morbidity (Beevers, Johnston and Devine et al, 1978 and Trafford, Horn and O'Neal et al, 1981). The majority of previous pronouncements on the risks of elevated blood pressure were based upon only the diastolic blood pressure. Reports from the Framingham Study, however, suggested that systolic, and not diastolic, blood pressure was a better predictor of heart disease in subjects aged 45 years and over (Kannel, Gordon and Schwartz, 1971; Kannel, Dawber and McGee, 1980) and this was subsequently confirmed by Beevers, Davies, Johnston and Larkin (1982).

There was thus general acceptance that moderate and severe degrees of hypertension resulted in increased morbidity and mortality, but doubt and disagreement persisted about the effects of milder blood pressure elevation. Although the second Veterans' trial (1970) had studied patients with diastolic pressures between 90 and 114 mmHg, it was only in the group with pressure in excess of 105 mmHg that a clear difference in outcome was detected between treated and non-treated subjects. In those with pressures below 165 mmHg systolic and 105 mmHg diastolic the difference in the incidence of morbid events was less well defined. It was felt that organic manifestations might have progressed more slowly in milder forms of the disease and might therefore not have revealed

themselves during the relatively short-term period of the study. Although no substantial benefit was demonstrated by blood pressure lowering in this milder group of hypertensives it has long been recognised that each increment of systolic or diastolic pressure, even within the "normal" range, is associated with steadily increasing risks, but there is no absolute cut-off at which mortality suddenly increases (Society of Actuaries, 1959; Kannel, Schwartz and McNamara, 1969 and Kannel, Wolf, Verter and McNamara, 1970).

The second Veterans' Study had been criticised on a number of points, chief amongst these being that it was a males only study, blood pressure classification was based on hospital in-patient recordings, there was already a high prevalence of cardiovascular complications in the population studied and a substantial number of blacks had been included. These study limitations prompted the establishment of a number of further studies in mild hypertension.

The United States Health Service Hospitals Cooperative Study Group (McFate Smith, 1977) studied 398 subjects, aged 21-55, with mild hypertension for a period of 7-10 years, but with a very high drop out rate. Active treatment did not confer any benefit in the prevention of myocardial infarction and stroke, although it should be emphasised that only 17 such events occurred. However, so-called lesser events occurred more frequently in the placebo group and these included the development of electrocardiographic left ventricular hypertrophy. A further point of importance was that 12.2% of the placebo group had an increase in arterial

pressure during the period of the study, rendering them no longer in the mild hypertensive category.

The Australian National Blood Pressure Study was begun in 1973. This was a controlled therapeutic trial of antihypertensive drug treatment in 3,427 men and women with diastolic blood pressures between 95 and 110 mmHg with a systolic blood pressure of less than 200 mmHg. (The Australian Therapeutic Trial in mild hypertension, 1980). The study employed rigid exclusion criteria and all subjects, of whom almost 50% were less than 50 years, were free of prior cardiovascular or cerebrovascular symptoms with a low prevalence of smokers. During an average follow up period of 4 years there was a significant reduction in mortality in the actively treated group, mainly due to a reduction in cardiovascular-related deaths - myocardial infarction, stroke and myocardial ischaemia. The number of deaths due to myocardial infarction was small - 2 and 8 - in the active and placebo groups respectively while the incidence of non-fatal myocardial infarctions was almost identical. The number of ischaemic, non-infarction, end-points was, however, less in the actively treated group. The Australian results were comparable with those seen in the Hypertension Detection and Follow-Up Program Study (HDFP) (1979) - a study of so-called stepped care and referred care for hypertension in the United States. Although the American study was somewhat unique in that both stepped care and many referred care subjects received antihypertensive therapy results in this large group of mild hypertensives closely paralleled the Antipodean experience.

Despite the fact that hypertension is a well-established risk factor for the development of coronary artery disease (Tibblin,

Wilhelmsen and Werko, 1975 and Gordon and Kannel, 1972) only one study (Berglund, Sannerstedt and Anderson, et al, 1978) had shown any benefit in reducing coronary incidents by blood pressure lowering prior to the Australian and American HDFP reports.

The latter findings were, however, not corroborated in Norway by Helgeland, (1980). The Oslo Study - a 5-year controlled drug trial in 785 mild hypertensive males, aged between 40 and 49 - found no preventive effect on coronary artery disease, although there was a significant reduction in the development of electrocardiographic left ventricular hypertrophy. There was, as expected, a reduction in stroke frequency in the actively treated group. It may not be surprising that considering the small size of this study and the relatively short follow-up period that no significant difference emerged in cardiovascular morbidity and mortality between the treated and non-treated groups.

During the course of the studies 12% of placebo subjects in Australia and 17% of Norwegians exceeded mild hypertensive limits and were assigned to active therapy. These figures tended to further lessen the overall differences between active and placebo groups with mild hypertension.

It is estimated that there are three million middle-aged Britons with diastolic pressures of 90 to 99 mmHg (Editorial, 1980). The benefits of treating this large number by drug therapy are still not clearly defined and for this reason the British Medical Research Council trial has been set up with the somewhat daunting task of determining the potential for reducing morbidity and mortality from the complications of mild hypertension by

antihypertensive therapy (1977). A further question will be: Are the benefits of treatment likely to be offset by an increase in anxiety, distress and side effects as well as the cost of drug-taking? Doubtless, with these points in mind, a number of workers have suggested that simple, non-pharmacological factors may be effective in lowering blood pressure in mild hypertensives, employing sodium restriction (Morgan, 1978 and MacGregor, Markandu and Best, et al, 1982) and weight reduction (Reisin, Messerli and Dreslinski, et al, 1982), but no long-term studies have been conducted in what may be an exciting area of future hypertension research.

So far, the results of morbidity and mortality in mild hypertension have all applied to middle-aged subjects, of whom many already had pre-existent end organ damage. It is well recognised that hypertension is a slowly, but steadily, progressive disease and many authors acknowledge that by the time blood pressure lowering is instituted irreversible changes may already be established. The study of blood pressure levels, patterns, control mechanisms and possible effects on the heart in subjects with mild or borderline hypertension, offers the possibility of identifying factors that may initiate blood pressure elevation from those that sustain it.

A uniformly accepted definition of borderline hypertension is not available, but it could best be described as a condition of elevated blood pressure with readings not sufficiently high to warrant early treatment (Julius and Esler, 1975). Despite this somewhat loose definition it is a condition that has attracted wide investigative interest as it appears to be an early predictor

of future established hypertension (Levy, Hillman and Stroud, et al, 1944 and Julius and Schork, 1971). There is also evidence that the condition carries an excess of overall mortality (Levy et al, 1944; MacKenzie and Shepherd, 1937; Mathisen, Loken, Brox et al, 1965 and Lew, 1967) and an increased frequency of future cardiovascular complications (Thomson, 1950; Stamler, Lindberg, Berkson, et al, 1958; Mathewson, Brereton, Keltie, et al, 1965 and Kannel, Schwartz and McNamara, 1969).

The condition has been bedeviled by poly-terminology - mild, borderline, labile and pre-hypertension being among the terms used. Pre-hypertension has now been largely dropped as a descriptive term as it is now known that many subjects with mild, or borderline, hypertension do not go on to develop later, established forms of the disease (Julius and Schork, 1971; Doyle, 1982). The term labile would, at first glance, appear eminently suitable to describe the patient who is at one time within the hypertensive range while at another time appearing to be normotensive. Julius, Ellis, Pascual, et al, (1974) assessed blood pressure lability in young borderline and normotensive students by using the standard deviation from the mean of cuff readings recorded at home and in an office setting. Borderlines had an increased lability of systolic, but not diastolic, arterial pressure. However, Pessina, Normino Semplicini, et al, (1979) did not confirm this observation, but it should be added that their studies were confined to hospital in-patients.

There is thus cause for debate about the suitability of the term "labile" and for the remainder of this dissertation the terms mild and borderline hypertension will be used and assumed to be synonymous.

As arterial hypertension develops, many secondary cardiovascular changes occur and in the middle-aged patient there may also be the problem of coexistent atherosclerosis. Therefore observations of the pathophysiology of hypertension in the older subject become more complex in attempting to determine initiating factors of the process from those that are secondary consequences of raised arterial pressure, even in the mild or borderline range. The study of blood pressure in the young, apparently healthy individual would therefore appear to be an attractive area for future research into mechanisms which might initiate blood pressure elevation and those that sustain, and indeed might result from it. According to the hypothesis of Brown, Lever, Robertson and Schalekamp (1976) it is proposed that essential hypertension results from a small rise in arterial pressure during a period of autonomic overactivity, producing renal alterations which maintain the arterial pressure rise and become the basis for future pressure increments. The hypothesis supposes a borderline phase in young life with sequential incremental rises in systemic arterial pressure as time passes with resulting renal transformation maintaining the blood pressure at an elevated level.

Although many abnormalities have been reported in borderline hypertensives which could be explained by such a neurogenic mechanism, attempted correlation with catecholamine levels has proved somewhat inconsistent with Nestel and Doyle (1968) and Kuschke (1961) describing elevated levels while Esler and Nestel (1973) failed to confirm these findings. It is probably true, however, that a few patients in the borderline phase have raised peripheral catecholamines (De Quattro and Chan, 1972). There are several objections, however, to the application of plasma

noradrenaline levels as an index of overall sympathetic nervous activity in studies of human physiology - not least being that the concentration in the plasma is determined in part by the rate at which the catecholamine is removed. The measurement of noradrenaline spillover rate may provide a better index of overall autonomic activity (Esler, 1982).

As further supportive evidence of increased autonomic activity, β -adrenergic activity has been found to be increased in mild, borderline hypertension (Frolich, Dustan and Page, 1966), although this finding was not subsequently confirmed, by the same group, when borderline subjects with normal resting heart rate were examined (Frolich, Kozul and Tarazi, et al, 1970)

Major interest in the autonomic nervous system in this early stage of hypertension has largely been directed at the sympathetic arc but in studies using combinations of propranolol and atropine Julius, Pascual and London, (1971) and Julius, Esler and Randall, (1975) also found evidence of changes in parasympathetic function and postulated a central control abnormality.

One such area of central control of systemic arterial blood pressure is the baroreceptor control mechanism. Gribbin, Pickering and Sleight, et al, (1971) found reduced baroreflex sensitivity in some borderline hypertensives, as did Takeshita, Tanaka, Kuroiwa, et al, (1975), but this was not confirmed by Julius, et al, (1975). Using the neck suction method to stretch carotid baroreceptors Eckberg (1979) found that baroreceptor sensitivity was unchanged in young men with a "milder" form of borderline hypertension, but was decreased in subjects of the same age with a resting

average systolic arterial pressure of greater than 140 mmHg. Eckberg postulated that baroreflex responsiveness might predict the subsequent development of hypertensive cardiovascular disease. The description of excessive blood pressure variability in this borderline phase (Birkenhager, Van Es and Houwing, et al, 1968) raises the intriguing possibility that these blood pressure fluctuations result from relative baroreflex insensitivity which may be the starting point of Brown et al's hypothesis and thus the prime mover in the hypertensive process.

In the early, or borderline, phase of hypertension the cardiac output has been found to be elevated with an inappropriately low or normal total peripheral resistance (Widimsky, Fejfarova and Fejfar, 1957; and Eich, Peters and Cuddy, et al, 1962). It should be stressed, however, that this is a heterogenous group, with a raised cardiac output being found in only 40-50% of individuals. The finding - albeit not universally present - prompts the question; do all hypertensive patients start here? This forms the basis of the autoregulation theory put forward by Guyton and Coleman (1969) who postulate that the primary increase in cardiac output later triggers an autoregulatory increase in total peripheral resistance which acts to lower cardiac output, so that an equilibrium is obtained of normal cardiac output and raised total peripheral resistance - the situation existing in established hypertension.

A concept of "structural autoregulation" has, however, been advanced by Folkow (1975) and others. This theory, based upon vascular hypertrophy secondary to raised arterial pressure, is not new as Johnson (1868) described generalised arteriolar

thickening in "Bright's Disease". It assumes that adaptive hypertrophic changes occur in the left heart, conduit arteries and precapillary resistance vessels in response to increased pressor influences. This then assumes that increased vascular resistance can be maintained in the absence of increased humoral or vascular smooth muscle activity. It seems likely that this structural adaptation occurs early and may be important for not only the maintenance but also the initiation of hypertension. Recently Yamori, Mori and Nishio, et al, (1979) have reported the finding of cardiac hypertrophy in spontaneously hypertensive rats while the animals were still in the pre-hypertensive stage. Suggesting that the early detection of left ventricular hypertrophy might be a useful indicator of the incipient stage of vascular hypertrophy the same workers conducted a survey of Japanese schoolchildren aged 6 to 15 years (Saito, Mori and Nishio, et al, 1978 and Nishio, Mori and Saito, et al, 1978). Twenty-two subjects were identified as having borderline hypertension and 25% of these showed increased echocardiographic left ventricular mass. Recently Safar, Lehner and Vincent, et al, (1979) have described a finding of increased ventricular septal thickness in a group of young borderline hypertensives.

The detection of left ventricular hypertrophy has traditionally relied upon the electrocardiogram, using a variety of empirical criteria to facilitate the diagnosis. Most criteria employ arbitrary precordial voltage values and ST-T wave appearances which have been based on a comparison between electrocardiographic appearances and the weight of the heart at autopsy (McPhie, 1958 and Romhilt and Estes, 1968) or on clinical findings which might

have been expected to result in myocardial hypertrophy (Sokolow and Lyon, 1949).

Despite recognised limitations of sensitivity (Scott, Seiwert and Simon, et al, 1952) and both sensitivity and specificity (Allenstein and Mori, 1969; and Dolgin, Fisher and Shah, et al, 1977) the development of electrocardiographic evidence of left ventricular hypertrophy remains an important finding in hypertension and its appearance in the established hypertensive is an ominous harbinger of future cardiovascular complications (Kannel, 1974; and George, Breckenridge and Dollery, 1972). Certainly blood pressure lowering can result in regression of electrocardiographic left ventricular hypertrophy (George, et al, 1972; and Poblete, Kyle and Pipberger, et al, 1973), but this is by no means invariable.

Despite its obvious limitations the electrocardiogram can still be, with proper use and interpretation, a simple and widely used tool for the detection and follow up of left ventricular hypertrophy. There is no data, however, on its value or otherwise in the management of the young mild hypertensive, where there is preliminary evidence that anatomical left ventricular hypertrophy may already be present, even at this presumed early stage of the disease. Carter and Estes (1964) found an extremely close relationship between electrocardiographic precordial QRS amplitude and heart weight, but this only applied when the hearts were above the accepted limits of normal weight, suggesting that muscle mass is not the only factor to which amplitude is primarily related. This finding was corroborated by Sjorgen (1971) who found no significant correlation between left ventricular wall thickness measured by echocardiography and electrocardiographic voltage criteria. The

findings of Brown, Desser and Bechimol (1977) suggested that both left ventricular and septal thickness contributed to the appearance of increased QRS voltage on the electrocardiogram.

It should be stressed, however, that none of the studies involving left ventricular wall thickness and electrocardiographic appearances contained young subjects with borderline hypertension, thereby leaving the question of the possible value of electrocardiography in this particular area largely unanswered.

The use of ultrasound in examination of the left ventricle has already been mentioned. It should perhaps be remembered that although the technique was originally developed for the detection and hunting of submarines at the end of World War One its adaptation and introduction into clinical cardiology is comparatively recent.

Using commercially available flaw detecting equipment Edler and Hertz (1954) obtained information from the living heart by applying the crystal of the equipment sound head to the chest wall and recording echoes on a single time base. The first cardiological diagnosis using the new technique was pericardial effusion by Edler (1955) who described the separation of echoes between the anterior wall of the heart and the pericardium. Equipment at this stage was rudimentary and recognition of cardiac structures uncertain, but Wild, Crawford and Reid (1957) described findings on the excised human heart, thereby supplying additional information on the ultrasonic appearance of the organ.

During the fifties Edler and his colleagues continued their studies with the new technique and described the ultrasound features of mitral stenosis, left atrial tumours, aortic stenosis and pericardial effusion (Edler, Gustafson, Karlefors, et al, 1961). The technique for pericardial effusion detection provided the stimulus for subsequent detailed examination of the left ventricle and Feigenbaum, Popp and Chip, et al, (1968) described measurements of posterior left ventricular wall thickness, using echocardiography, as the technique had now been termed by the American Institute of Ultrasound in Medicine.

The accuracy of the technique was tested by Feigenbaum, et al, (1968) by comparing the echocardiographic measurement of posterior wall thickness with direct measurement at necropsy and at open heart surgery. Despite a good statistical correlation between the echo and direct measurement dimensions, methodological limitations must cast some doubt on the study's conclusions. The measurement at open heart surgery was, to say the least, crude with a needle being inserted into the apex of the left ventricle with the heart still beating. It is difficult to reconcile an apical measurement being representative of the wall thickness at the postero-basal surface where the echo measurement is taken, and this was indeed recognised by the authors. The absence of diastolic/systolic separation while performing measurement in a beating heart also renders the results somewhat suspect. A closer correlation was reported between the necropsy measurement - where direct measurement was actually performed at the postero-basal surface - and the echocardiographic end-diastolic dimension. This latter finding was also reported by Schroeder, Popp and Stinson, et al, (1969), but was not confirmed by Maron, Henry and Roberts, et al,

(1977) who found no necropsy correlation with the echocardiographic end-diastolic dimension, but rather a close comparison with the end-systolic dimension. Despite these reported inconsistencies there has been a plethora of echocardiographic studies of left ventricular function and mass etc. in a variety of cardiovascular states.

The ability to detect left ventricular hypertrophy by echocardiography in hypertensives before the appearance of electrocardiographic changes has been described by Dunn, Chandraratna and de Carvalho, et al, (1977). In the absence of coronary artery disease these workers also reported a decrease in left ventricular performance with increasing arterial pressure and left ventricular hypertrophy - a finding previously reported by Mehmehl, Mazzoni and Krayenbuehl, (1975). A later study involving echocardiographic assessment of left ventricular function and anatomy in 234 asymptomatic hypertensives detected a significant number of cardiac abnormalities which were not apparent on the electrocardiogram or chest x-ray (Savage, Drayer and Henry, et al, 1979). The ability of the technique therefore to detect increases in left ventricular wall thickness before the appearance of electrocardiographic changes makes echocardiography an appealing investigative tool in the study of mild hypertension. Few studies have been performed, but Safar, et al, (1979) have reported increased septal thickness in young borderline hypertensives, while the Japanese have detected echocardiographic abnormalities in hypertensive children (Nishio, et al, 1978).

Bearing in mind the importance of early hypertrophy recognition against the background of its possible role in the initiative

process of hypertension and the subsequent unfavourable prognosis that its development carries, it would appear to be extremely important that echocardiographic data be compared with accurate and prolonged periods of blood pressure measurement.

CHAPTER TWO - AIMS OF THE STUDY

From the work cited in the introduction it is likely that mild, borderline hypertension may be the earliest stage of the hypertensive process with all of its attendant complications.

The aims of this study were the examination of intra-arterial continuous blood pressure patterns in young unrestricted men in order to assess absolute levels of systolic and diastolic pressure and to determine the extent of their pressure variability. The so-called "lability" of blood pressure has been linked to a possible abnormality of the baroreflex mechanism and it was felt that this arc should be studied in normotensives and in mild hypertensives before and after chronic β -blockade. As increased β -adrenergic receptor activity has been postulated as a possible contributory mechanism in borderline hypertensives the observation of effects of β -blockade on baroreflex sensitivity was of added interest.

No previous study has reported on the long-term useage of β -blockers in young, otherwise healthy, mild hypertensives. Do they lower blood pressure? Do they have an unacceptable level of side effects? These were thought to be important questions to answer as evidence accumulates that the treatment of mild hypertension in the older age groups confers benefit.

Surprisingly little or no information is available regarding electrocardiographic appearances in this area of hypertension research. The examination of the electrocardiogram was undertaken alone and in conjunction with echocardiography in an attempt to

examine the effects of mild blood pressure elevation on left ventricular wall thickness. This was coupled with accurate and detailed blood pressure profiles, employing office and home measurements with, for the first time, 24 hour, continuous, ambulatory intra-arterial blood pressure recording.

CHAPTER THREE - SUBJECTS AND METHODS

Young, apparently healthy, males aged between 18 and 35 were recruited for the purposes of the project. Volunteers were obtained primarily from two sources - the Australian Public Service and an institute of tertiary education - but also included medical staff. No fee or other inducement was offered to volunteers.

During a three month lead-in period subjects underwent a number of preliminary investigations, including a full physical examination, chest radiology and routine biochemical screening.

An initial attempt was made to quantify salt intake, but this was eventually abandoned owing to a number of factors. As a result of widespread television and press coverage dietary salt had been conclusively implicated in the genesis of hypertension in the minds of most young Australians. Food manufacturers either were unaware of salt content of their products or were loathe to supply information. When pre-weighed salt shakers were given to individuals in an effort to assess the amount of added salt used, few used them because of already referred to indoctrination.

Blood pressure was recorded on at least three separate occasions under rigidly standardised conditions according to recommendations of the Australian National Blood Pressure Study (Abernethy, 1974). Subjects remained sitting quietly for five minutes before blood pressure was measured by a Hawksley Random Zero Sphygmomanometer taking phase V Korotkoff as diastolic. After a further three minutes the procedure was repeated. The mean of both values was recorded as the representative figure.

Individuals were deemed to be normotensive if their systemic arterial blood pressure at no time exceeded 140 mmHg systolic or 90 mmHg diastolic. Those subjects who displayed a "constant" blood pressure abnormality - ie a sustained elevation of systolic arterial blood pressure > 140 mmHg and/or 90 mmHg diastolic were classified as established hypertensives and were further investigated and kept under review at a Renal Hypertension Clinic. Those individuals who displayed a variation in blood pressure whereby at least one reading exceeded the arbitrary limits and at least one below were classified as mild or borderline hypertensives.

On the basis of the above criteria and in the absence of underlying pathology, 30 young men were classified as mild hypertensives while 15 were found to be normotensive. There was a certain bias in favour of hypertensive volunteers as young men who had previously been found to have a blood pressure abnormality came forward more readily for investigation.

TABLE 1PHYSICAL CHARACTERISTICS OF STUDY SUBJECTS

	<u>Normotensives</u>	<u>Mild Hypertensives</u>	
	(n=15)	(n=30)	
Age (years)	26.3 \pm 5.10	27.2 \pm 4.96	N S
Height (cm)	181.3 \pm 5.2	179.7 \pm 6.57	N S
Weight (Kg)	76.1 \pm 7.6	79.78 \pm 12.73	P < 0.01

RESULTS : mean \pm S D.

Hypertensives were therefore slightly, but significantly, heavier than their normotensive counterparts. The level of activity and physical fitness was generally high, but did not differ between groups. There were no trained athletes in either group.

These individuals participated in the studies to be described except in the study of precordial variation in the normal electrocardiogram, (chapter 10) where, for logistical purposes, 16 young, normotensive hospital workers formed the study population, and in the determination of the anatomical accuracy of M - mode echocardiography (chapter 12) where study subjects were hospital patients undergoing cardiac investigation and surgery.

The methodological procedures employed in the study will be described in relevant chapters.

CHAPTER FOUR - THE METHODS FOR MEASUREMENT OF
SYSTEMIC ARTERIAL BLOOD PRESSURE

The arterial pressure in man may be measured in two basic ways; directly, by inserting a catheter into an artery, or indirectly, by applying a pneumatic cuff to the upper arm which initially occludes the brachial artery when inflated and, on slow deflation, the pulse wave first passes through representing systolic pressure and diastolic pressure is represented by its maximum amplitude.

Direct Method

The final arbiter of the accuracy of systemic arterial pressure measured by indirect methods is the pressure measured directly in the arterial lumen. This latter technique requires expertise and is not without hazard. It demands that relatively wide-bore cannulae be inserted into arteries of reasonable size, that the connecting tubing be short and that the pressure transducer and recording system have high frequency characteristics to ensure absolute accuracy. The system should be insensitive to temperature changes and easily calibrated. Air bubbles in any area will result in damping and inaccuracy and the system should therefore be designed in order to ensure that these are easily seen and readily removed.

The direct, intra-arterial, measurement of systemic arterial pressure is the final standard of comparison for all measurement methods and should be used when comparing blood pressure with other physiological parameters and in clinical situations where

continuous access to blood pressure levels is required. The recent advent of automatic, portable direct methods of measuring blood pressure has exciting implications, but must, at present, remain largely a research tool and this is detailed in full later.

Indirect Method

In 1905 in the Medical Bulletin of the Imperial Military Academy of St Petersburg, Dr M S Korotkoff described a method for the indirect measurement of blood pressure. He described sounds heard over the brachial artery immediately distal to the cuff. The Korotkoff sounds are:

- Phase I Sudden appearance of a clear, but often faint, tapping sound growing louder.
- Phase II The sounds are prolonged into a murmur.
- Phase III The sounds become clearer and increase in intensity.
- Phase IV The sounds quickly decrease in intensity.
- Phase V Disappearance.

Korotkoff's description was an advance on the standard method of Riva-Rocci (1896), and modified by Von Recklinghausen (1901, 1906, 1930), who recommended a 13 cm wide and 30 cm long cuff connected to a mercury manometer.

The mercury instrument has through the years become the mainstay of blood pressure measurement and life assurance statistics and all large epidemiological studies of blood pressure have relied on this device. The accuracy of the method when compared to

direct measurement has been attested to by early workers (Hamilton, Woodbury and Harper, 1936 and Steele, 1942) and more recently by Hunyor, Flynn and Cochineas, 1978 who found that the indirect method underestimated systolic pressure by 10 mmHg and overestimated diastolic pressure (phase V Korotkoff) by 8 mmHg.

Phase V Korotkoff is now generally regarded as representing true diastolic pressure and will be used throughout this study. However, there are situations of high flow such as pregnancy, fever and thyrotoxicosis, where Korotkoff sounds may persist to zero and here phase IV is used to represent diastolic blood pressure.

Great care has to be taken, particularly in severe hypertensives, to recognise the possible existence of an auscultatory (silent) gap (Ragan and Bordley, 1941).

A further possible source of error in blood pressure measurement by the indirect method is the use of an incorrect size of arm cuff. It has been found that the standard 12 cm wide cuff gives falsely high values for pressure when applied to fat arms (Pickering, Roberts and Soury, 1954 and King, 1967). Kirkendall, Burton, Epstein and Freis, 1967, recommended that the length of the cuff bladder should be such that it half encircled the arm while a cuff width of 12 to 14 cm was adequate for the 30 cm adult arm circumference. Geddes and Whistler (1978). in an elegant study have reaffirmed that a cuff that is too narrow overestimates and a cuff that is too wide underestimates systemic arterial pressure.

Digit preference and observer bias are further areas of error, particularly in epidemiological studies and in hypertension research. Largely as a result of this, the London School of Hygiene sphygmomanometer (Rose, Holland and Crawley, 1964) and the Random Zero Machine have been devised to minimise these tendencies. In this study all office blood pressure measurements were performed by the Hawksley Random Zero Sphygmomanometer (Garrow, 1963 and Wright and Dore, 1970). The instrument consists of a conventional 0-300 mmHg sphygmomanometer, but fitted with a zero shifting device so that true zero cannot be determined until after the blood pressure has been taken.

CHAPTER FIVE - RESULTS OF HOME BLOOD PRESSURE READINGS
IN NORMOTENSIVE AND BORDERLINE INDIVIDUALS

"One of the most tantalizing aspects of the study of arterial pressure is that the methods used for measurement affect the value we seek to measure" (Pickering, 1968).

Perhaps the simplest, safest and cheapest way of assessing blood pressure levels away from the anxiety-producing hospital or surgery environment is by instructing the subject in the measurement of his own home blood pressure.

This method of home blood pressure assessment has been used by a number of investigators (Wilkinson and Raftery, 1978 and Raftery, 1974). Julius et al, (1974) employed the technique in a large study of borderline hypertensives and found that although blood pressure was generally lower at home approximately 30% of the borderline subjects maintained "hypertensive" levels at home.

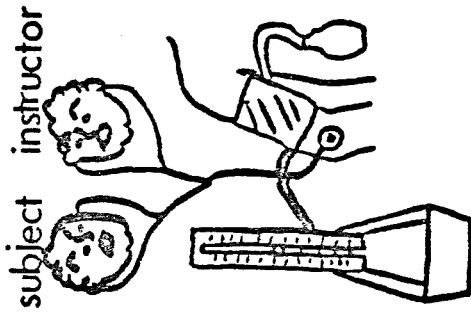
The technique may therefore be useful in identifying subjects who may show substantial deviations from office readings and also in compiling a blood pressure "profile", rather than isolated readings at a point in time.

Method

Subjects were instructed in the use of an aneroid instrument - the Bosch Home Blood Pressure Sphygmomanometer. This unit is comprised of a pneumatic cuff with a built-in stethoscope diaphragm which is positioned over the brachial artery of the

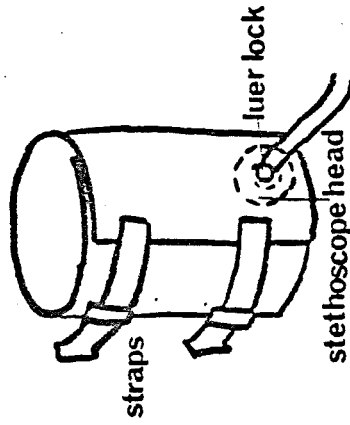
TRAINING WITH INTERCONNECTED STETHOSCOPES

46



(a)

SELF APPLICATION CUFF



(b)

non-dominant arm. The cuff is then tightened by means of adjustable straps; the device is represented diagrammatically in figure 1b. Each subject was instructed in quite intensive fashion, to recognise Korotkoff sounds I, IV and V until he was in agreement, to within 2 mmHg, with the instructor using an interconnected stethoscope (fig 1a).

Each individual was provided with a record sheet and instructed to record his blood pressure in the morning at least 30 minutes after rising and again in the evening before retiring to bed. The mean of the 14 readings recorded over seven days was taken as the representative home blood pressure.

TABLE 2

RESULTS

Comparison (mean \pm SD) of Normotensive and Borderline Hypertensive Blood Pressure Levels and Heart Rate

	<u>Normotensive</u>	<u>Borderline Hypertensive</u>	<u>Significance</u>
<u>Office Readings (mmHg)</u>			
Systolic	119.9 \pm 6.30	136.8 \pm 9.11	P < 0.001
Diastolic	70.8 \pm 6.44	86.6 \pm 6.41	P < 0.001
Heart Rate (beats/min)	66.5 \pm 8.51	76.2 \pm 8.50	N S
<u>Home Readings (mmHg)</u>			
Systolic	122.2 \pm 8.14	134.6 \pm 8.88	P < 0.001
Diastolic	76.2 \pm 6.03	85.4 \pm 8.92	P < 0.001

The results in table 2 demonstrate that the significant difference in both systolic and diastolic blood pressure seen in office readings between normotensives and mild hypertensive individuals was maintained in the home environment. Conversely, there was no significant difference between office and home blood pressure values, although the rise in home diastolic blood pressure in normotensives just failed to reach statistical significance at the 5% level.

Discussion

These results, and indeed the absolute values, are in close accord with those obtained by Julius et al (1974) in a study of large numbers of young males with borderline (labile) hypertension. Certainly there are objections to home blood pressure; the subject must perform isometric exercise to inflate the cuff, with the resultant theoretical objection that this will raise his blood pressure. Simultaneous measurement of intra-arterial pressure during this manoeuvre shows that this objection is unfounded (personal observation). Certainly there is no foolproof safeguard against observer bias and digit preference, but when dealing with highly motivated and intelligent individuals this artefact is hopefully lessened.

Despite these possible limitations, the method is of considerable value in corroborating careful, repeated office readings.

The absence of any difference in heart rate between both groups should be stressed, as the commonly held belief that an office tachycardia with raised blood pressure being due to anxiety is not supported by these findings.

CHAPTER SIX - THE EQUIPMENT AND TECHNIQUE OF CONTINUOUS
AMBULATORY 24 HOUR INTRA-ARTERIAL BLOOD
PRESSURE MONITORING

The first description of automatic recording of directly measured arterial blood pressure was by Bevan, Honour and Stott (1966). The equipment incorporated a perfusion pump and transducer with connection to a galvanometer which recorded optically on to slow moving paper. The analysis of the blood pressure record was tedious and time-consuming as the paper trace had to be enlarged five to six times and then viewed through a calibration grid. Resolution of individual arterial waveforms was extremely poor because of the very slow paper speed.

With the advent of micro-electronics miniaturisation was incorporated into a system based upon the pioneer device. This resulted in increased reliability and greatly improved recording characteristics (Littler, Honour, Sleight and Stott, 1972). The present instrument basically consists of three units, a perfusion pump, transducer and miniature analogue tape recorder - the Oxford-Medilog system (Bevan, Honour and Stott, 1969 and Goldberg, Raftery and Green, 1976).

Perfusion/Transducer System

The transducer is an Akers 831B* series, designed for use where small dimensions are required. A silicon beam with a planar resistor diffused on each side is the basic element of the

* Akers Electronics 1191 Horton, Norway.

FIGURE 2

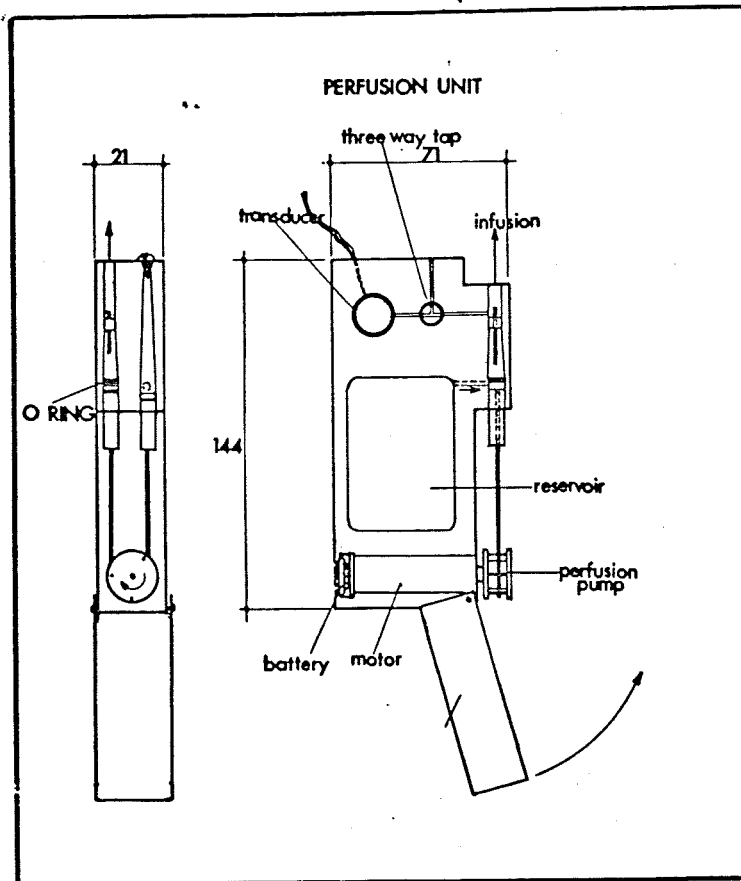
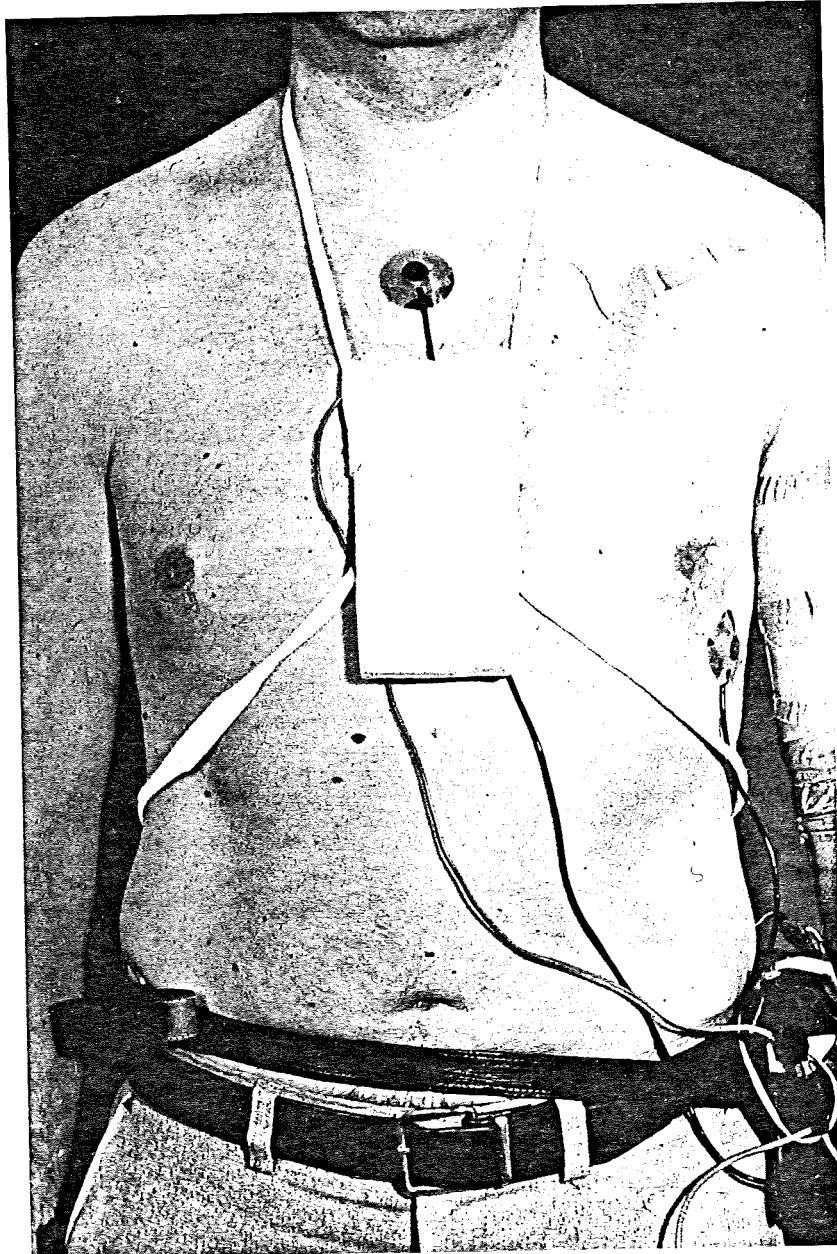


FIGURE 3



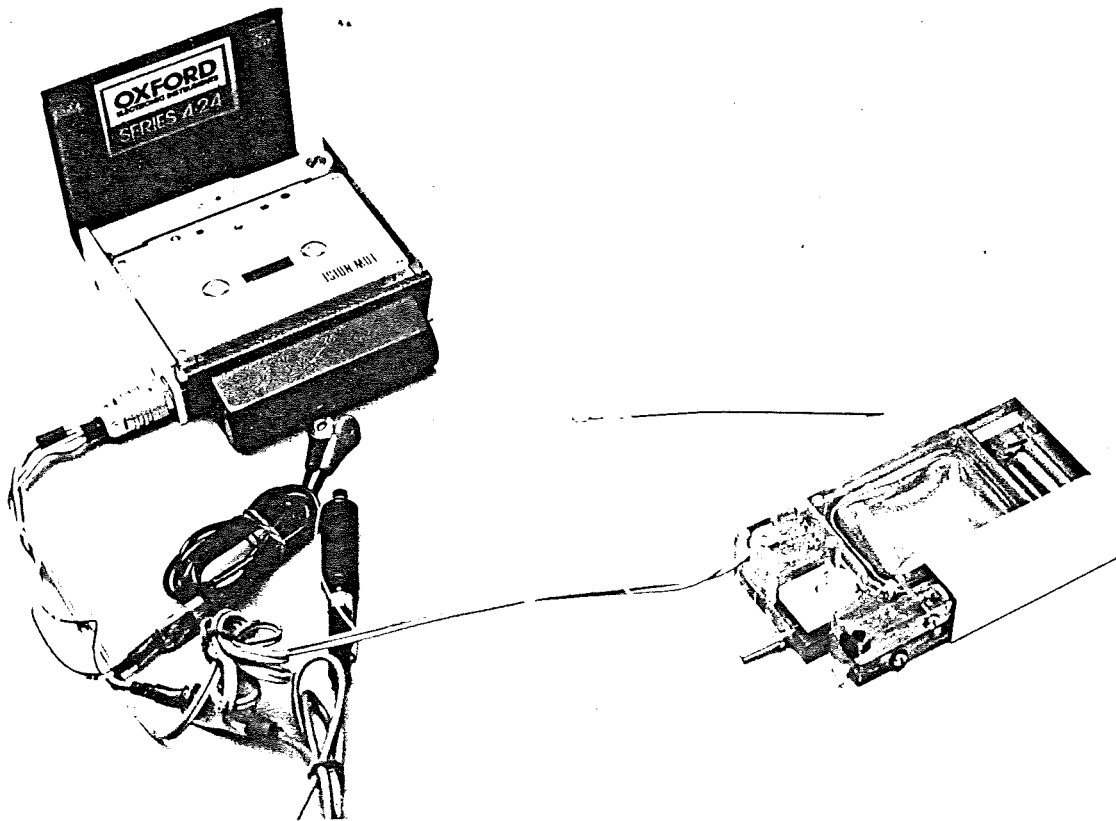
of the transducer. The pressure sensitive membrane converts the applied pressure into a proportional deflection of the beam. This deflection gives a linear change in the two diffused resistors. By the application of a DC voltage the gauge pressure is converted into electrical signals.

The perfusion system was developed at Northwick Park, Middlesex (Millar-Craig, Hawes and Whittington, 1978) where a major innovation was the replacement of the former butane gas perfusion pressure drive by a perfusion pump driven by a constant speed motor, which, in turn, is powered by a commercially available camera battery. The flushing fluid is contained in a 35 ml reservoir within the reinforced perspex unit. The flushing fluid was normal saline with 3,000 iu of heparin in 500 mls with a flow rate of 1.5 - 2 ml/hour and at this rate of flow replenishment was required every 15 hours. The unit's dimensions are shown in figure 2. In operational use the perfusion/transducer unit was held in a pouch which was suspended from the neck by a harness with the transducer being held at the level of the right atrium (fig 3).

Recorder

The signal from the transducer was recorded on one channel of a miniature four-channel analogue tape recorder (Medilog, Oxford Medical Systems) which had been modified for voltage stabilisation (Kenny, Hunyor and Renwick, 1980) (fig 4). The second channel was utilised by the electrocardiogram from electrodes in the V_1 and V_5 position. On the third channel signals from the "event marker" were recorded. The miniature tape recorder was contained

FIGURE 4



in a leather pouch and this was worn on a belt. The slow speed of the tape recorder allowed a commercially available cassette to run for 24 hours without changing sides.

Arterial Cannulation

Brachial artery cannulation was performed in the non-dominant arm under sterile conditions. A point of maximum pulsation was identified on the medial aspect of the upper arm, well clear of the ante-cubital fossa. Under local anaesthesia a 3F Grandjean teflon cannula was inserted into the artery using a Seldinger technique with a flexible guide wire (Ronald Howell Ltd).

After scrupulous inspection of the connection system to eliminate possible bubbles the cannula was connected to the perfusion/transducer unit by means of a clear, narrow bore tubing. This was taped to the inner aspect of the arm and chest wall incorporating safety loops, to ensure safety and comfort. (Fig 5).

Prior to use the perfusion system was wet-sterilised using Cidex on an overnight basis. Before filling with heparinised saline the entire system was thoroughly flushed free of the sterilising agent.

Before arterial pressure recording was commenced the transducer was calibrated by connecting directly to a mercury manometer and recording 50 mmHg increments from 0-300 mmHg, holding each value for two minutes. By the use of a centre zero galvanometer and a monitoring plug in point on the case of the recorder it was possible to check the integrity of input signals to the magnetic tape. (Fig 6).

FIGURE 5

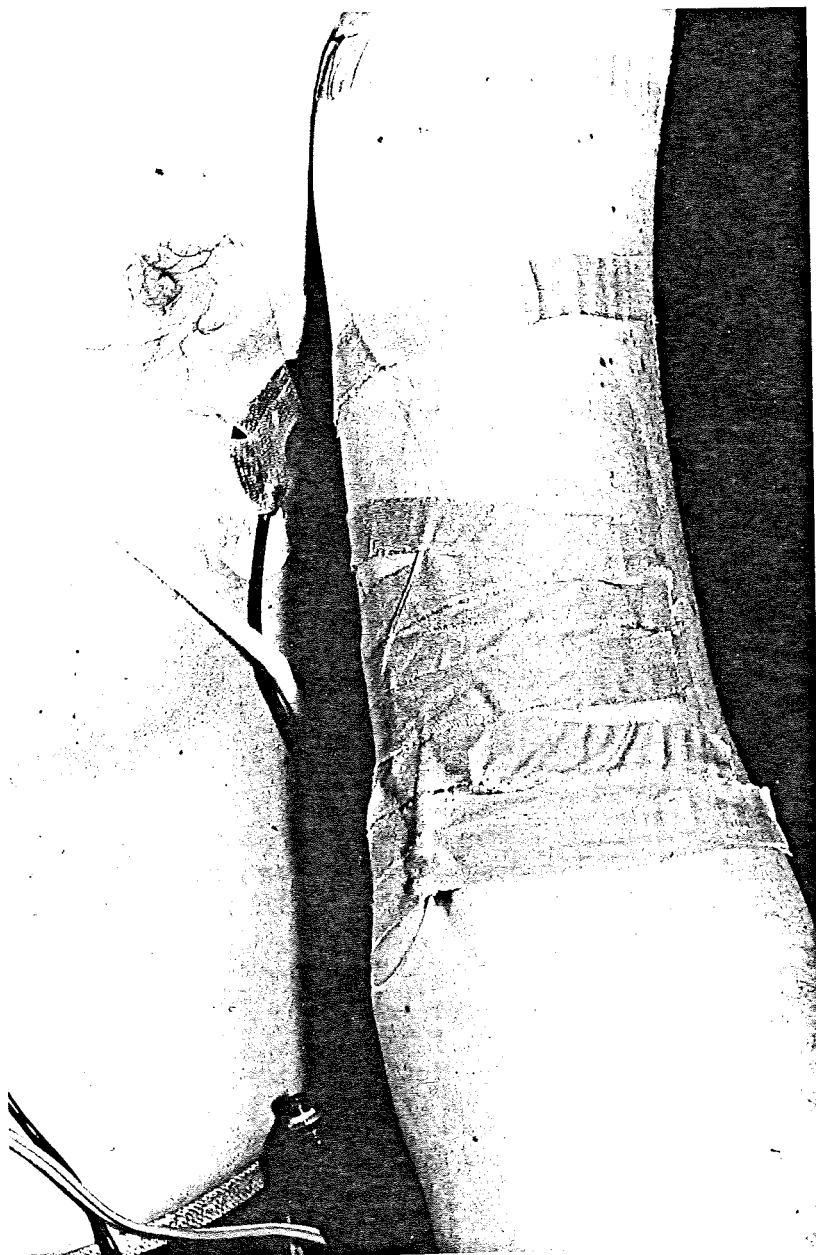
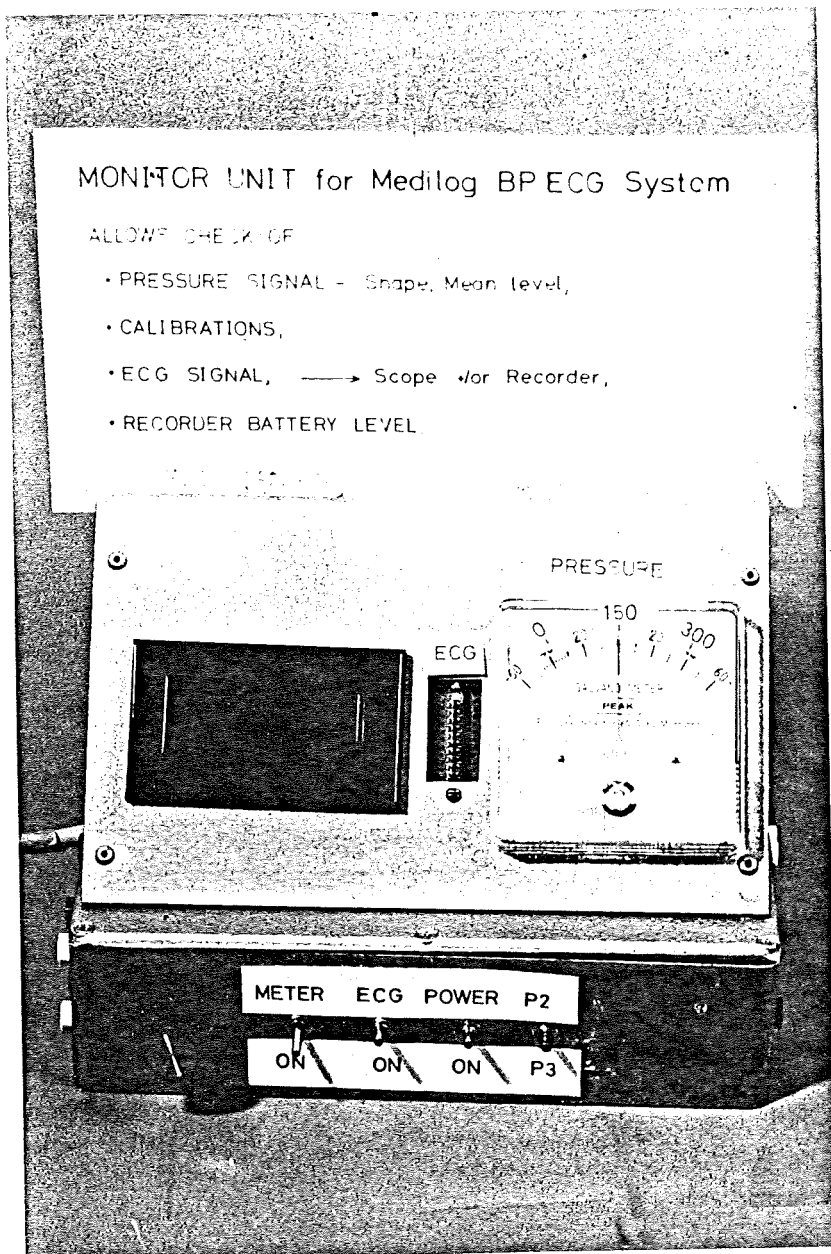


FIGURE 6



Arterial pressure was directed to the transducer by means of a three-way safety-lock connector on the superior aspect of the perfusion device (fig 2). Subjects were instructed in the use of the "event-marker" and supplied with a laminated card which contained details of the equipment and emergency telephone numbers. All subjects in the study were fully ambulant individuals who went about their daily business after the system had been calibrated and connected. All studies commenced between 0900 and 1000 and subjects returned between 6 and 7 hours later for topping up of the perfusion chamber and further calibration.

CHAPTER SEVEN - CONTINUOUS AMBULATORY BLOOD PRESSURE AND
HEART RATE IN UNTREATED BORDERLINE
HYPERTENSIVE AND NORMOTENSIVE YOUNG MEN

Blood pressure is a continuous physiological variable. During a 24 hour period the heart beats approximately 115,000 times with the corresponding generation of systolic and diastolic arterial pressure pulses; no two beats generate exactly the same pressures and beat-to-beat pressure variation appears to be a random process influenced by an almost infinite number of variables (Goldberg, 1977). It is therefore inconceivable that any random measurement of blood pressure should be representative of any individual patient's "blood pressure". It is, of course, random measurements of blood pressure which have formed the basis of blood pressure risk studies (Actuarial Society, 1941; Metropolitan Life Insurance Co, 1961; Kannel and Dawber, 1974), but the large numbers of subjects involved in these studies has gone a long way to make their results reliable.

In a detailed study of the pathophysiology of blood pressure isolated cuff measurements would seem to be less than ideal. Largely for this reason, 24 hour intra-arterial ambulatory monitoring was performed in this study group of young normotensives and mild hypertensives. No previous study has examined the 24 hour blood pressure patterns of young normotensives, although Millar-Craig, Bishop and Raftery (1978) did report on the blood pressure circadian rhythm of five young men who although reported as normotensive, had originally been referred because of hypertension.

Subjects and Methods

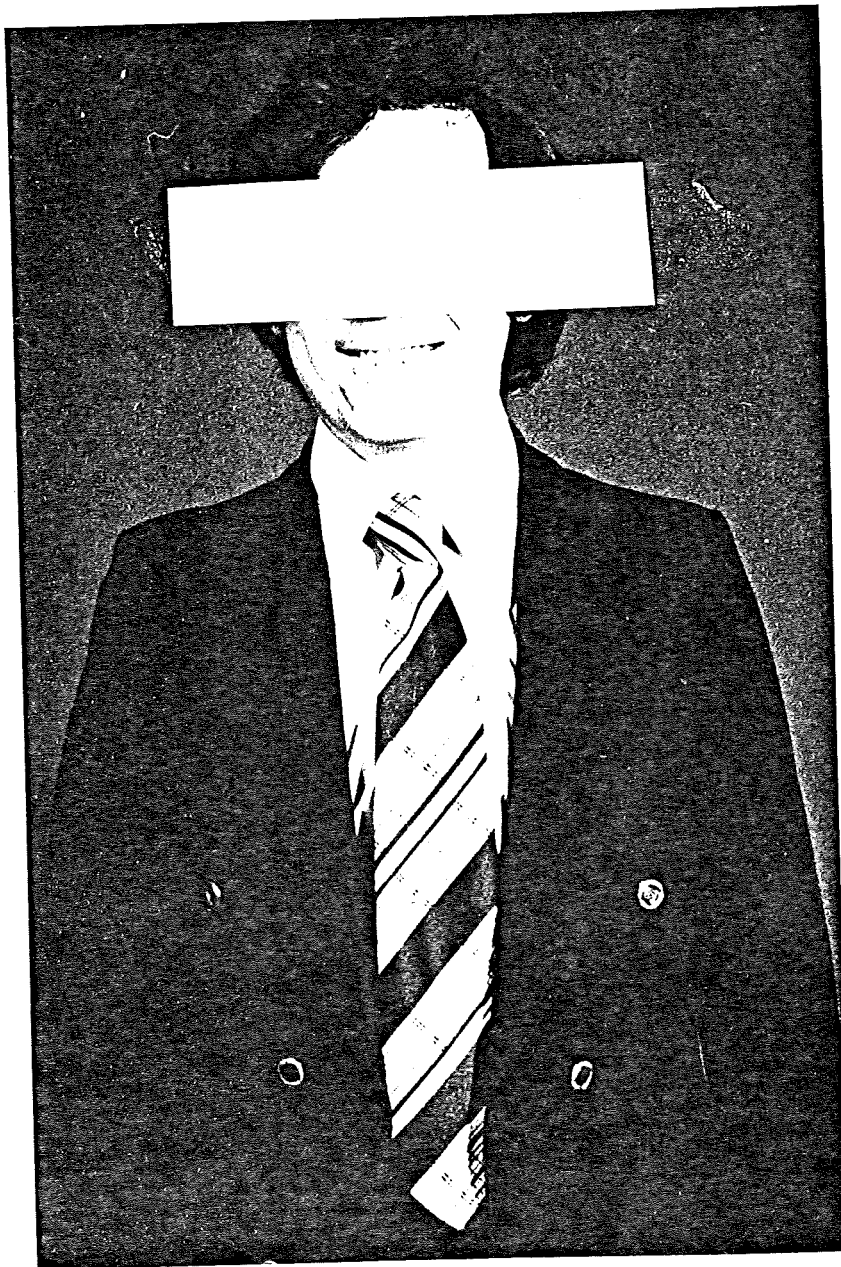
Ambulatory blood pressure was recorded in 30 mild hypertensives and 15 normotensive young men, the details of whom have already been described.

All studies were begun at between 0900 - 1000 with insertion of the intra-arterial cannula and transducer calibration. The young men were all outpatients and returned to their everyday activities after being fitted with the equipment which was quite unobtrusive (fig 7). They were encouraged to engage in normal pursuits and this included one individual continuing to ride his motorbike! The only limitation imposed by the equipment was the inability to shower or take a bath during the 24 hour period. They returned to hospital between 1600 and 1800 for calibration and topping-up of the fluid reservoir, finally returning the following morning for a third and final calibration and removal of the device after completion of a 24 hour period.

Scrupulous attention was paid to the attainment of satisfactory haemostasis following removal of the intra-arterial cannula. Firm pressure was applied for exactly 20 minutes over the arterial puncture site and a tight elastic bandage was then fitted, which was worn for 24 hours. All subjects were requested to report back immediately should problems arise, but apart from mild local superficial bruising no complications were encountered.

It should be stressed, however, that the procedure is not without potential risk. Littler (1976) reported four cases of median nerve palsy after cannula removal from the brachial artery. These

FIGURE 7



complications followed approximately 200 problem-free studies.

In one patient the catheter had actually come out of its own accord with subsequent haematoma formation, while in the remainder symptoms followed some hours after study completion.

The exact cause of the neurological symptoms is unclear, but Macon and Futrell (1973) have reported an association between haemorrhage and median nerve lesions after cardiac catheterisation.

It is felt likely that bleeding in the constricted area of the ante-cubital fossa results in nerve compression. Certainly in Littler's studies arterial puncture was made low towards the elbow crease and this may have been a large contributory factor.

The lack of micro-embolic phenomena reports suggests that the heparin/saline perfusion system is efficient in prevention of clot formation on the cannula tip.

No problems were encountered with infection, but on theoretical grounds no individuals were studied with a congenital or acquired valvular lesion.

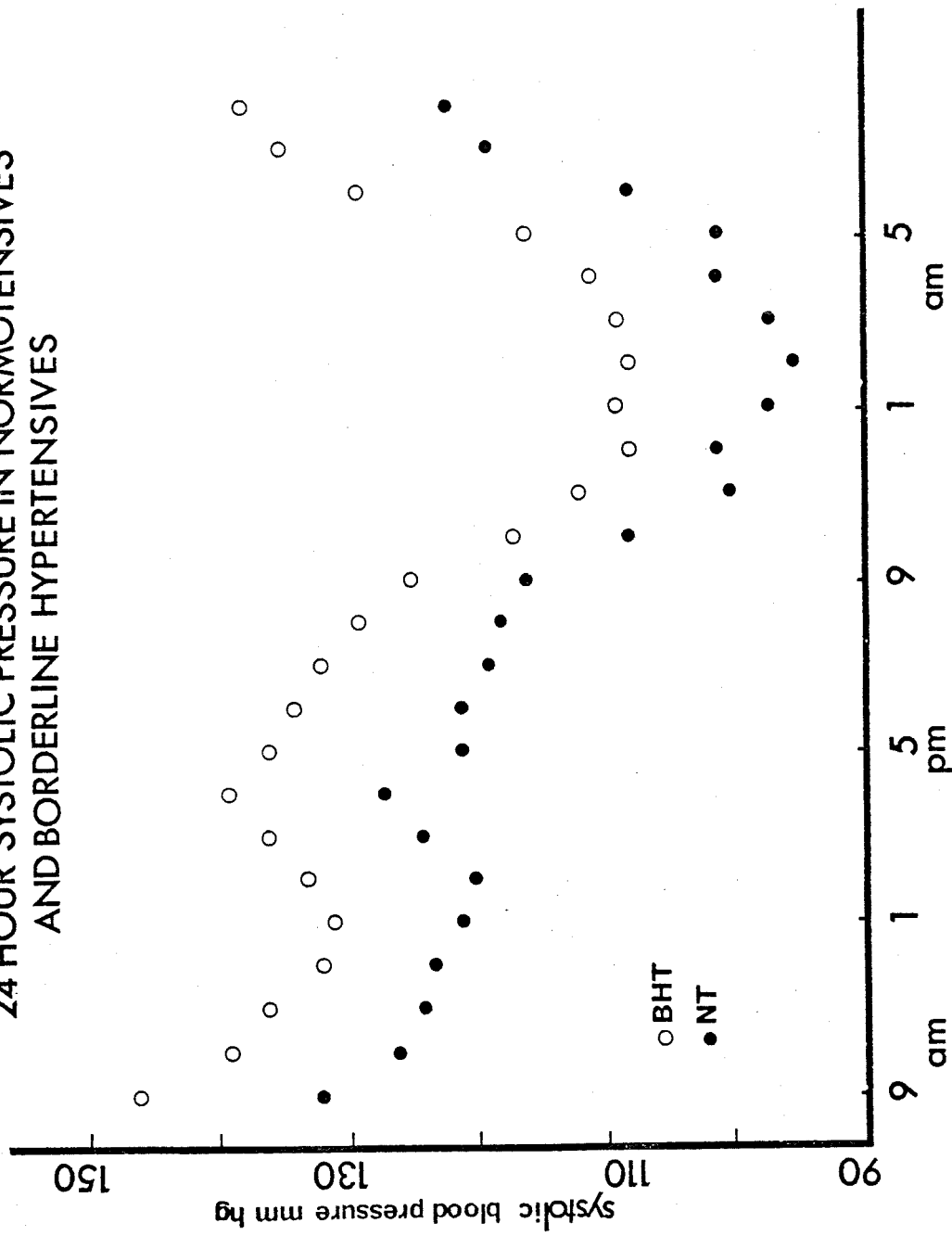
CHAPTER EIGHT - RESULTS OF 24 HOUR BLOOD PRESSURE
AND HEART RATE ANALYSIS IN YOUNG
BORDERLINE HYPERTENSIVES AND NORMOTENSIVES

A least squares regression line was computed from the three pressure calibration sets and from this an overall calibration factor was derived. The taped blood pressure signal was replayed at 50 times normal speed on a commercially available Oxford Instruments replay unit (fig 8) and this was then fed to a pre-processor (Hunyor, Larkin and Kenny, 1980) whose accuracy was checked with a series of known simulated pressure signals. The average blood pressure (systolic, diastolic and mean) and heart rate over one minute was taken as the unit of measurement and from this 10 minute and 60 minute averages were derived together with a "global" 24 hour mean. Beat to beat analysis was only undertaken on periods of particular interest. The digitised values for pressure and heart rate were stored on disc (computer PDP-11/03) and these values and patterns during 24 hours periods were plotted using an XY plotter. Variability of mean systolic and diastolic arterial pressure and heart rate was measured as the standard deviation (Watson et al, 1979; and Ogawa, Arai and Takata et al, 1981).

Periods of pressure damping and artefact were excluded by visual scrutiny. Any record having a total period in excess of two hours during the 24 hour period of damping or artefact was excluded from analysis.

Satisfactory records were available on 15 normotensives and 30 borderline hypertensives and these results will be described

24 HOUR SYSTOLIC PRESSURE IN NORMOTENSIVES AND BORDERLINE HYPERTENSIVES



Standard deviation and significance values are contained in Appendix I, pp 166-168 inclusive.

in this chapter.

Results

All values are expressed as mean \pm SD and data were analysed by Student's t-test for paired and non-paired data.

TABLE 3

Mean 24 hour systolic and diastolic arterial pressure (mmHg) and heart rate (beats/minute) of normotensives and mild hypertensives

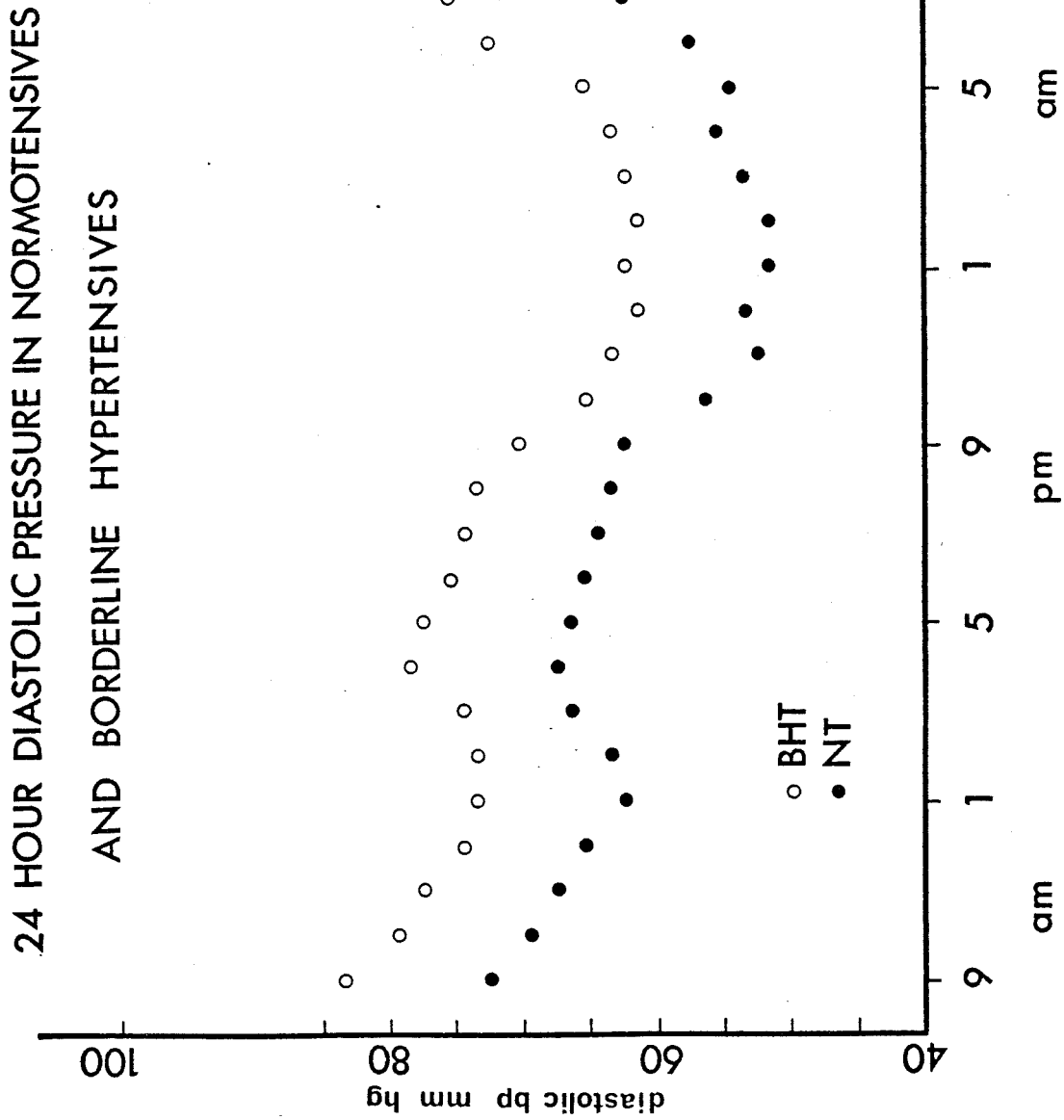
	Mild Hypertensives (n=30)	Normotensives (n=15)	Significance
Systolic	127.3 \pm 15.33	113.0 \pm 8.99	P < 0.01
Diastolic	71.4 \pm 12.05	60.3 \pm 10.55	P < 0.01
Mean*	93.3 \pm 12.83	78.6 \pm 11.31	P < 0.002
Heart rate	83.1 \pm 11.56	80.6 \pm 9.83	NS

* Mean \pm 1 SD. NS - not significant.

Results from Table 3 demonstrate the significant difference in global 24 hour blood pressure between normotensive and borderline subjects. Heart rate, however, was the same for both groups.

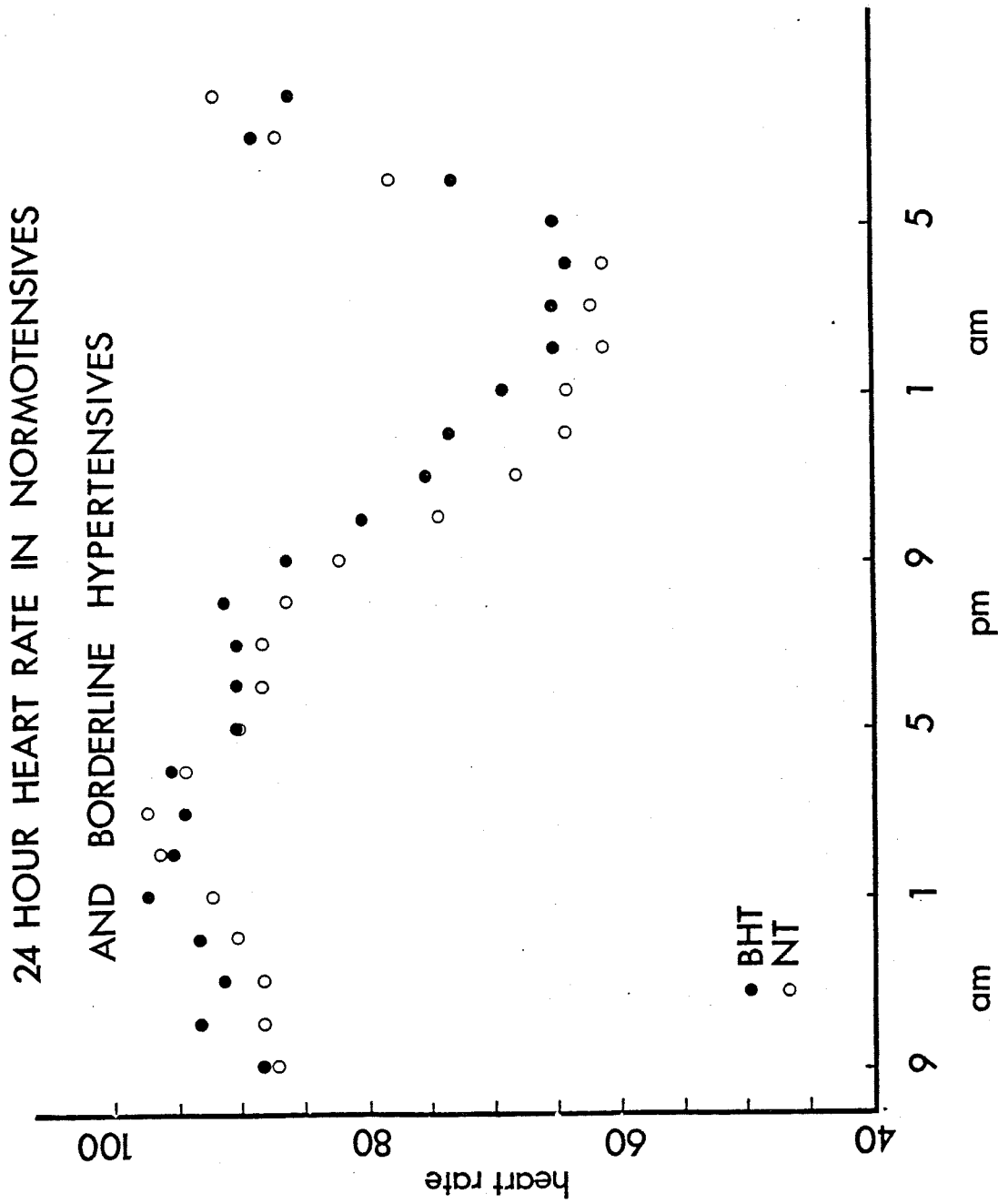
It has been recognised for some time that blood pressure shows a bimodal pattern over 24 hours with a marked fall during sleep (Millar-Craig et al, 1978) and this is convincingly demonstrated in figures 8 and 9.

FIGURE 9



Standard deviation and significance values are contained in Appendix I, pp 166-168 inclusive.

FIGURE 10



Standard deviation and significance values are contained in Appendix I, pp 166-168 inclusive.

The fall in night-time pressure was highly significant for both normotensives and hypertensives and interestingly the degree of fall was virtually identical in both groups. The other striking feature was the close correspondence between daytime ambulatory blood pressure and office and home readings. This was particularly the case for systolic pressure. The higher readings for diastolic pressure in both office and home readings may be explained, at least in part, by cuff overestimation when compared to intra-arterial measurement (Hunyor et al, 1978). (Table 4).

24 Hour Blood Pressure and Heart Rate Pattern

The graphical representation of systolic and diastolic arterial pressure and heart rate during a 24 hour period is illustrated in figures 8,9 and 10 respectively. At first glance, the most striking feature is the quite marked fall in all three parameters during night-time hours with a return to daytime levels in the early morning.

Despite the significant difference in values systolic and diastolic arterial pressure patterns for both normotensives and borderlines show a remarkable constancy with "tracking" throughout the 24 hour period. The same is not true for the heart rate, however, where there is no sustained difference between the two groups.

Blood pressure was generally higher in early morning with a fall in mid-morning and afternoon and a pronounced peak at about 1700 hours. This corresponded to the subject returning to hospital for re-filling of the perfusion unit and calibration of the transducer - the effect of the doctor on the patient's blood pressure!

TABLE 4

Mean 24 hour systolic and diastolic arterial pressure analysed according to day and night time values and compared to office and home recordings in normotensives and borderline hypertensives

<u>ARTERIAL PRESSURE (mmHg)</u>						
		<u>24 HOUR</u>	<u>DAY</u>	<u>NIGHT</u>	<u>OFFICE</u>	<u>HOME</u>
			(0900-2400)	(0001-0500)		
NORMOTENSIVES:	S	113.0 ± 8.99	120.0 ± 7.74	100.0 ± 4.28	119.9 ± 6.30	122.2 ± 8.14
	D	60.3 ± 10.55	63.9 ± 4.89	52.8 ± 1.60	70.8 ± 6.44	76.2 ± 6.03

BORDERLINE	S	127.3 ± 11.99	131.8 ± 8.58	110.2 ± 3.06	136.8 ± 9.11	134.6 ± 8.88
	D	71.4 ± 12.05	73.8 ± 5.08	62.3 ± 1.51	86.6 ± 6.41	85.4 ± 8.92

68

*** P < 0.001

S: Systolic

D: Diastolic

There was a progressive fall in pressure throughout the evening with a more pronounced drop during sleep and beginning to rise again around 0500.

Systolic and diastolic arterial pressures were significantly different between both groups throughout most of the 24 hourly intervals ($P < 0.05 - 0.001$) and in the others differences did not quite achieve statistical significance at the 5% level. For reasons of clarity and completeness standard deviation bars and significance values have been omitted from the figures, but are contained in Appendix I.

Heart rate displayed exactly the same diurnal pattern as blood pressure (fig 10), but whereas there had been a significant difference in arterial pressure this was not the case with heart rate between both groups. This confirmed observations made during office blood pressure measurements (table 2), but is at odds with reports that borderline hypertensives maintain a higher resting heart rate than normotensive counterparts (Sannerstedt, Julius and Conway, 1970; and Julius et al, 1974).

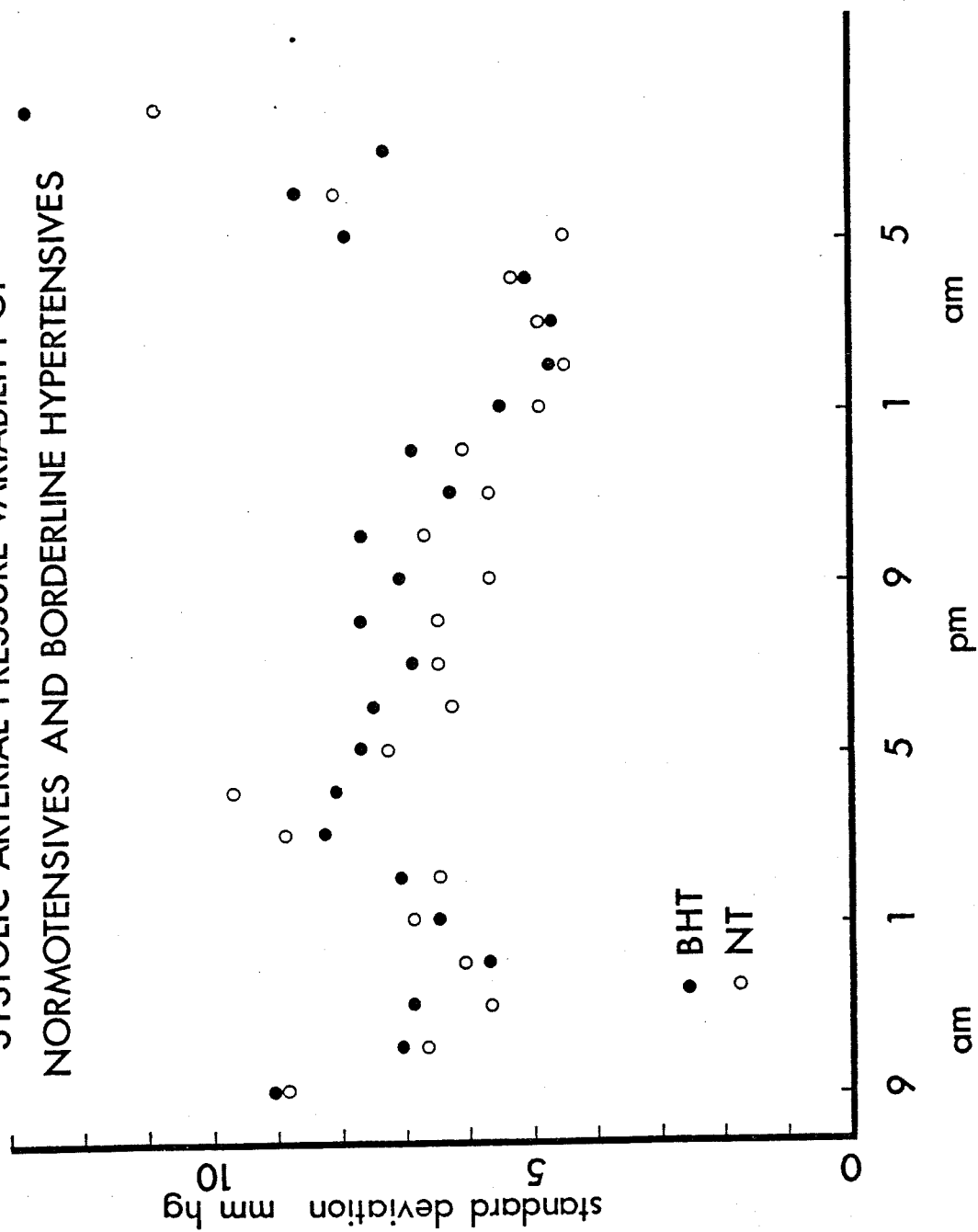
Blood Pressure Variability

Variability of systolic and diastolic arterial pressure was measured as the standard deviation of the hourly means.

Systolic arterial pressure variability is demonstrated in fig 11 and it is clear that there was no difference between groups. For the most part diastolic pressure variability obeyed the same rules, but there were points in the 24 hours when borderline variability

FIGURE 11

SYSTOLIC ARTERIAL PRESSURE VARIABILITY OF NORMOTENSIVES AND BORDERLINE HYPERTENSIVES



Standard deviation and significance values are contained in Appendix I, page 169.

significantly exceeded the normotensive range (fig 12).

DIASTOLIC ARTERIAL PRESSURE VARIABILITY OF NORMOTENSIVES AND BORDERLINE HYPERTENSIVES

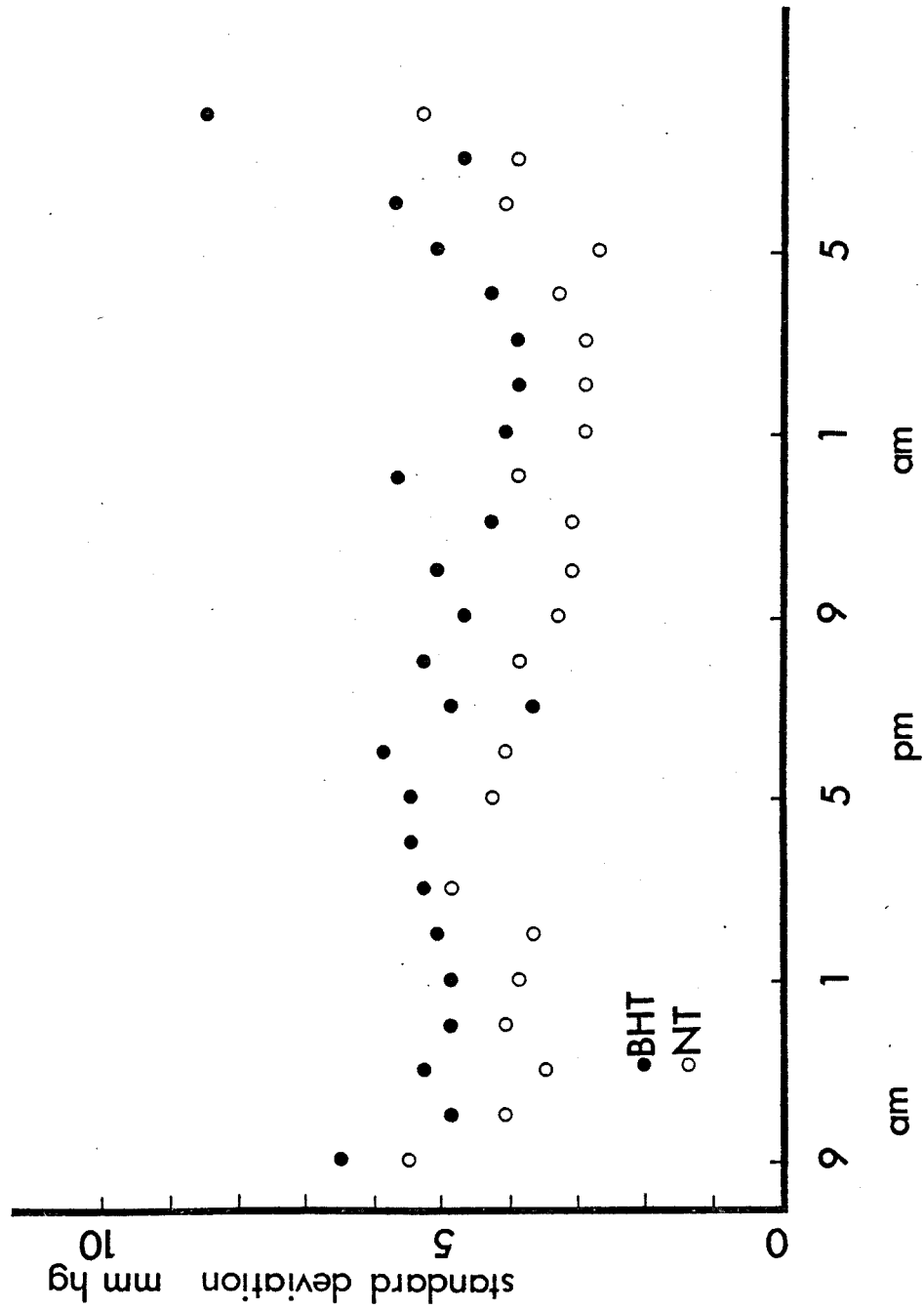


FIGURE 12

Standard deviation and significance values are contained in Appendix I, page 169.

CHAPTER NINE - THE EFFECTS OF LONG-TERM β -ADRENOCEPTOR
BLOCKADE ON BLOOD PRESSURE AND BAROREFLEX
SENSITIVITY IN YOUNG BORDERLINE HYPERTENSIVES

Despite the relative "mildness" of blood pressure elevation in borderline hypertension it should still be emphasised that levels do consistently exceed those found in normotensive individuals, as amply demonstrated in the previous chapter. This elevation may be consistent with the initial rise in the blood pressure renal cascade as postulated by Brown et al (1976) and it might therefore be suggested that blood pressure lowering at this presumed early, possible autonomic stage of the condition might prevent the onset of established hypertension.

With the prospect of possible life-long therapy any possible consequences of long-term drug administration assume great importance, particularly in the young, otherwise healthy, individual. It has been shown that β -adrenoreceptor blocking agents are effective in once daily dosage. Gordon (1976) demonstrated effective blood pressure lowering in a group of men aged 20 - 33 years with essential hypertension. No previous study has described long-term therapy with β -adrenergic blockade in the young borderline hypertensive, however.

It was decided to use the β -adrenoreceptor blocker atenolol (ICI 66.082, Tenormin), 4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide. The important properties of this compound are (a) cardioselectivity; (b) lack of intrinsic sympathomimetic properties; (c) lack of membrane-stabilising effect; (d) inability to cross the blood-brain barrier (Barrett, Carter and Fitzgerald, et al, 1973). It has been shown that the

drug is an effective antihypertensive in small doses, within a narrow range (Hansson, Karlberg and Aberg et al, 1976; and Jensen, Rasmussen and Mosbaek, 1976) and the once-daily administration with 24 hour control (Floras, Fox and Hassan, et al, 1979) offered obvious advantages.

It has been suggested that β -adrenoreceptor antagonists lower blood pressure by altering baroreflex activity (Prichard and Gillam, 1969). However, subsequent reports have been inconsistent and controversial.

It is generally accepted that baroreflex control of the heart is impaired in established essential hypertension (Gribbin, et al, 1971; and Korner, West and Shaw, et al, 1974), but some doubt exists in the borderline group where Julius, Esler and Randall (1975) found no abnormality, while Takeshita, et al, (1975) reported a significant reduction in baroreflex sensitivity.

It was felt that the reflex control of the heart in response to acute elevations of blood pressure should therefore be examined in borderline hypertensives and compared with results from normotensive subjects. It was also decided to repeat the manoeuvre after six months of placebo-controlled atenolol therapy.

It was hoped that these techniques might also allow comment on the question of possible β -adrenoceptor hyperactivity in borderline hypertension.

The subsequent description will be divided into two sub-sections - Chapters 9A and 9B, the former containing details of the blood pressure lowering effects and the efficacy while 9B will concentrate

on baroreflex sensitivity before and after β -blockade.

CHAPTER NINE A - RESULTS OF A SIX MONTH PLACEBO -
CONTROLLED TRIAL OF THE B-ADRENORECEPTOR
BLOCKER ATENOLOL IN BORDERLINE HYPERTENSION

Thirty young men who fulfilled previously described criteria for mild hypertension participated. The design was that of a randomised, double-blind, placebo-controlled trial, recognising the problems of bradycardia detection in any B-blocker-placebo study.

Sixteen subjects (Group A) were randomly allocated to the active compound, while the remainder (Group B) received placebo. Both compounds were identical in appearance and were contained in "Calendar-Packs". Both groups were matched for age, height and weight.

TABLE 5

PHYSICAL CHARACTERISTICS OF SUBJECTS
 ACCORDING TO BOTH TREATMENT REGIMENS

	<u>Age (years)</u>	<u>Height (cm)</u>	<u>Weight (Kg)</u>
Tablet A	26.8	178.9	77.07
Tablet B	28.1	180.6	82.01
Significance level of difference	Not sig.	Not sig.	Not sig.
Standard error of difference	1.83	2.43	4.54

Mean baseline systolic and diastolic arterial blood pressure and heart rate was not significantly different for both groups and is illustrated in table 6.

TABLE 6

Values for baseline blood pressure and heart rate.

	Systolic <u>(mmHg)</u>	Diastolic <u>(mmHg)</u>	Heart Rate <u>(B/min)</u>
Tablet A	137.6	87.2	72.4
Tablet B	135.9	86.0	65.7
Significance level of difference	Not sig.	Not sig.	Not sig.
Standard error of difference	3.38	2.38	3.29

Subjects in both groups were prescribed half a tablet (50 mg atenolol) for the first week of the study, at the end of which time the dosage was increased to one full tablet (100 mg atenolol) as there were no reports of side effects or profound bradycardia. It was decided that one tablet daily would be the maximum dose during the period of the study and subjects were asked to take their medication at 0800.

Blood pressure was measured at monthly visits by random zero sphygmomanometer and compliance checked by tablet count. The period of treatment was six months and at the end of this time a side effects questionnaire was administered.

Prior to randomisation each subject underwent 24 hour continuous, ambulatory, intra-arterial monitoring and measurement of baroreflex sensitivity. These procedures were repeated upon completion of the six month therapy period and details and results are described in relevant chapters. During a similar time course each volunteer measured his home blood pressure using a Bosch

home blood pressure sphygmomanometer.

TABLE 7

Baseline home blood pressure levels

	Systolic <u>(mmHg)</u>	Diastolic <u>(mmHg)</u>
Tablet A	136.7	86.9
Tablet B	132.1	83.0
Significance level of difference	Not sig.	Not sig.
Standard error of difference	3.30	3.43

Home blood pressure was recorded for one week, at the same time morning and evening, prior to commencing the study and during the final week.

Statistics

Data on blood pressure and heart rate were analysed by one way and two factor analysis of variance.

Results

Table 8 shows the mean decrease of systolic and diastolic blood pressures and heart rate from the baseline period in subjects taking tablets A and B using office recordings.

FIGURE 13

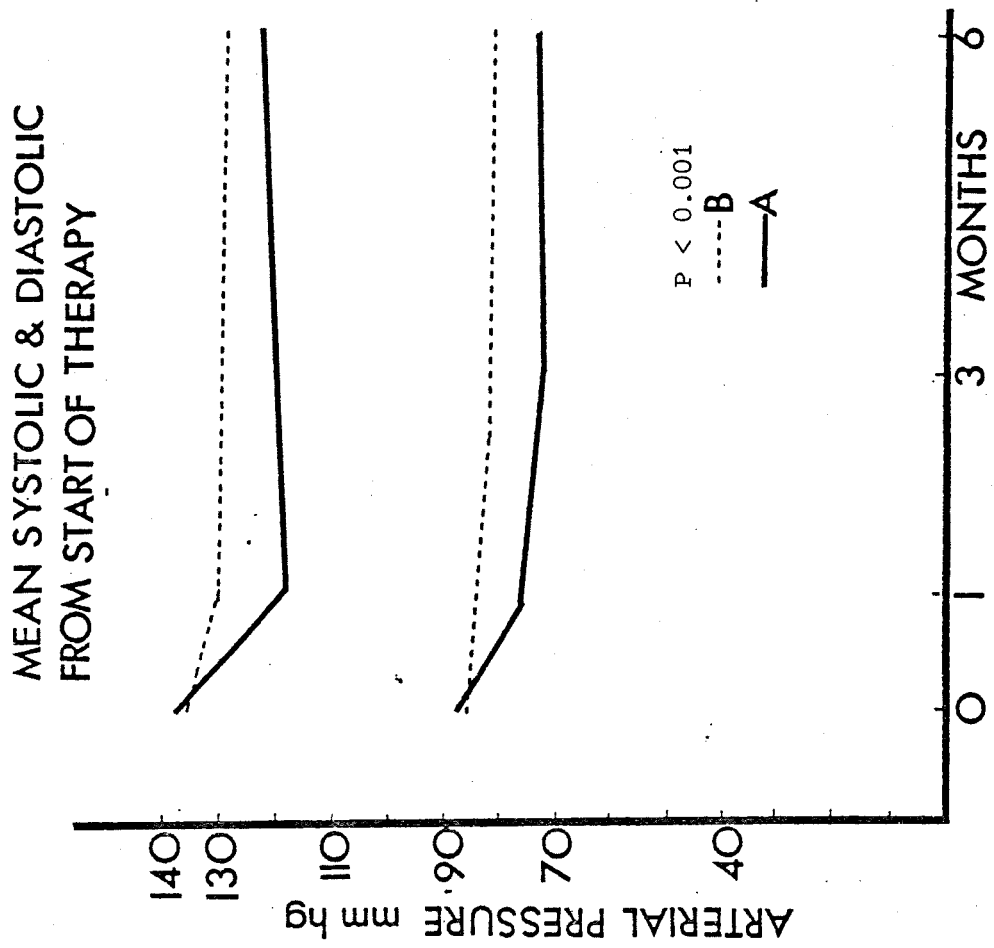


TABLE 8

Mean decrease of office measured systolic and diastolic arterial pressure and heart rate during the six month trial period

<u>Treatment</u>	<u>Systolic BP</u>	<u>Diastolic BP</u>	<u>Heart Rate</u>
Tablet A	16.4	13.4	12.7
Tablet B	6.0	3.8	-5.7
Significance of difference	P < 0.001	P < 0.001	P < 0.001
Standard error of difference	2.45	2.33	2.85

At the end of six months treatment there was a highly significant fall in all parameters in the actively treated group.

Table 9 lists the decrease in systolic and diastolic blood pressure recorded at home. The format used was as follows:

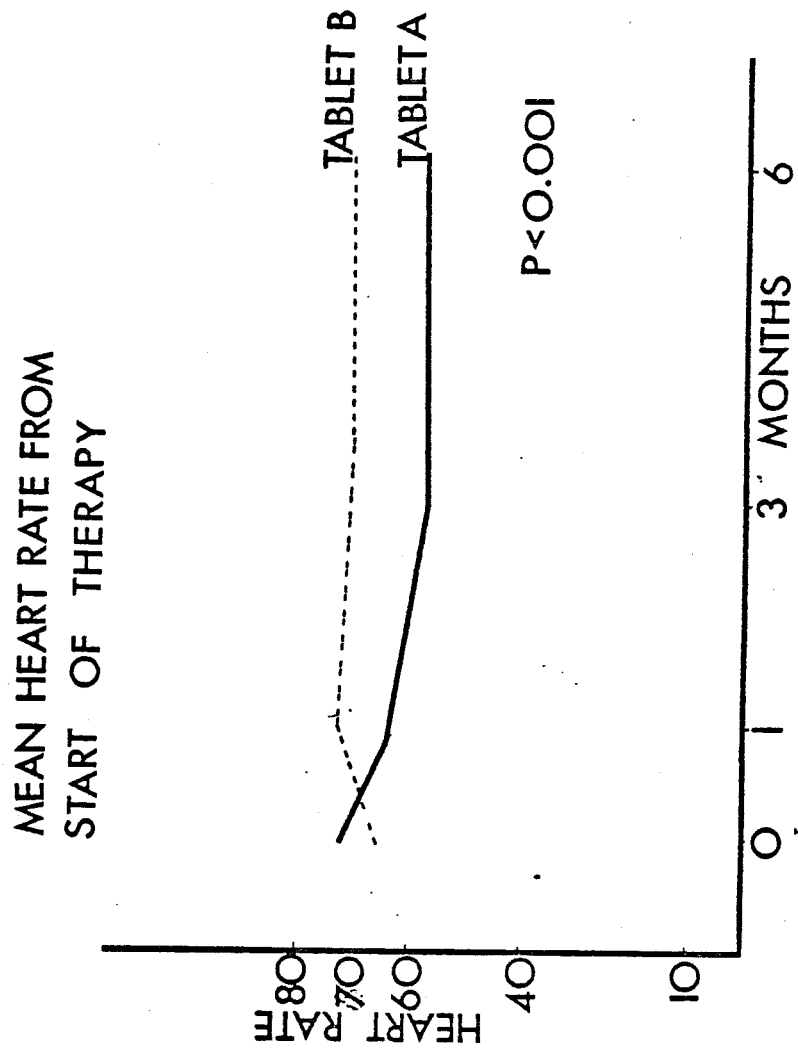
TABLE 9

Mean decrease of home measured systolic and diastolic arterial pressure during the six month trial period

<u>Treatment</u>	<u>Systolic BP</u>	<u>Diastolic BP</u>
Tablet A	10.3	8.1
Tablet B	+1.3	+5.5
Significance of difference	P < 0.001	P < 0.001
Standard error of difference	3.75	3.7

Fig 13 demonstrates the trend for diastolic and systolic blood pressure during the six month treatment period, while fig 14 illustrates the heart rate pattern during the same period.

FIGURE 14



Side Effects

A side effects questionnaire based upon that used in the Australian National Blood Pressure Study (Bauer, Baker, Hunyor and Marshall, 1978) was administered to each subject upon his completion of the six month treatment period.

Each questionnaire consisted of 22 questions as detailed in Appendix II. Due to an oversight, the questionnaire was not administered to two subjects, both of whom had taken placebo.

Physical Activity

Subjects were asked about limb weakness and symptoms of shortness of breath. Only two subjects listed symptoms under this heading - "Shortness of breath on exertion". Both were taking the active compound and both had suffered from childhood asthma. Pulmonary function testing was performed before and after oral atenolol, but only one subject showed a slight reduction in FEV_1 . This was not sufficient to cause symptoms and both young men completed the trial.

Sexual Activity

There were no reports of altered sexual habits or performance, although one young man was too embarrassed to answer the relevant questions!

Skin Rashes

Skin problems were reported by two subjects - one on placebo. The placebo subject had been receiving treatment for an eczema-like eruption for some time prior to entering the study. A pruritic rash in the actively treated subject was situated at the anal cleft and was related to obvious haemorrhoids.

Sleep

Although nightmares are reportedly a common accompaniment of β -blocker therapy only one subject volunteered this side-effect and he was taking the active compound.

Others

The only other side-effects complained of were dry mouth and running nose and these were divided equally between placebo and actively treated subjects.

The Assessment of the Blood Pressure Lowering Effect of Atenolol During 24 Hours Using Intra-arterial, Continuous Blood Pressure Monitoring

The details of the intra-arterial, continuous blood pressure monitoring technique have already been described in regard to the comparison between normotensive and borderline hypertensive 24 hour blood pressure patterns.

It was felt that the technique would also provide interesting data on the assessment of antihypertensive therapy in the borderline hypertensive, particularly as the hypotensive agent used, atenolol, is claimed to lower blood pressure throughout 24 hours with a single daily dose.

A total of 30 young men participated in the placebo-controlled trial of atenolol. Ambulatory monitoring of blood pressure was performed in all prior to randomisation and a second intra-arterial study was performed in 23 - 12 on active compound and 11 on placebo - at the end of the six month trial period. Instructions were given to take tablets between 0700 and 0800 on the morning of the second study, but to omit medication the following morning.

Results

The average global 24 hour blood pressure and heart rate data for groups A and B before and during antihypertensive therapy is illustrated in Table 10.

TABLE 10

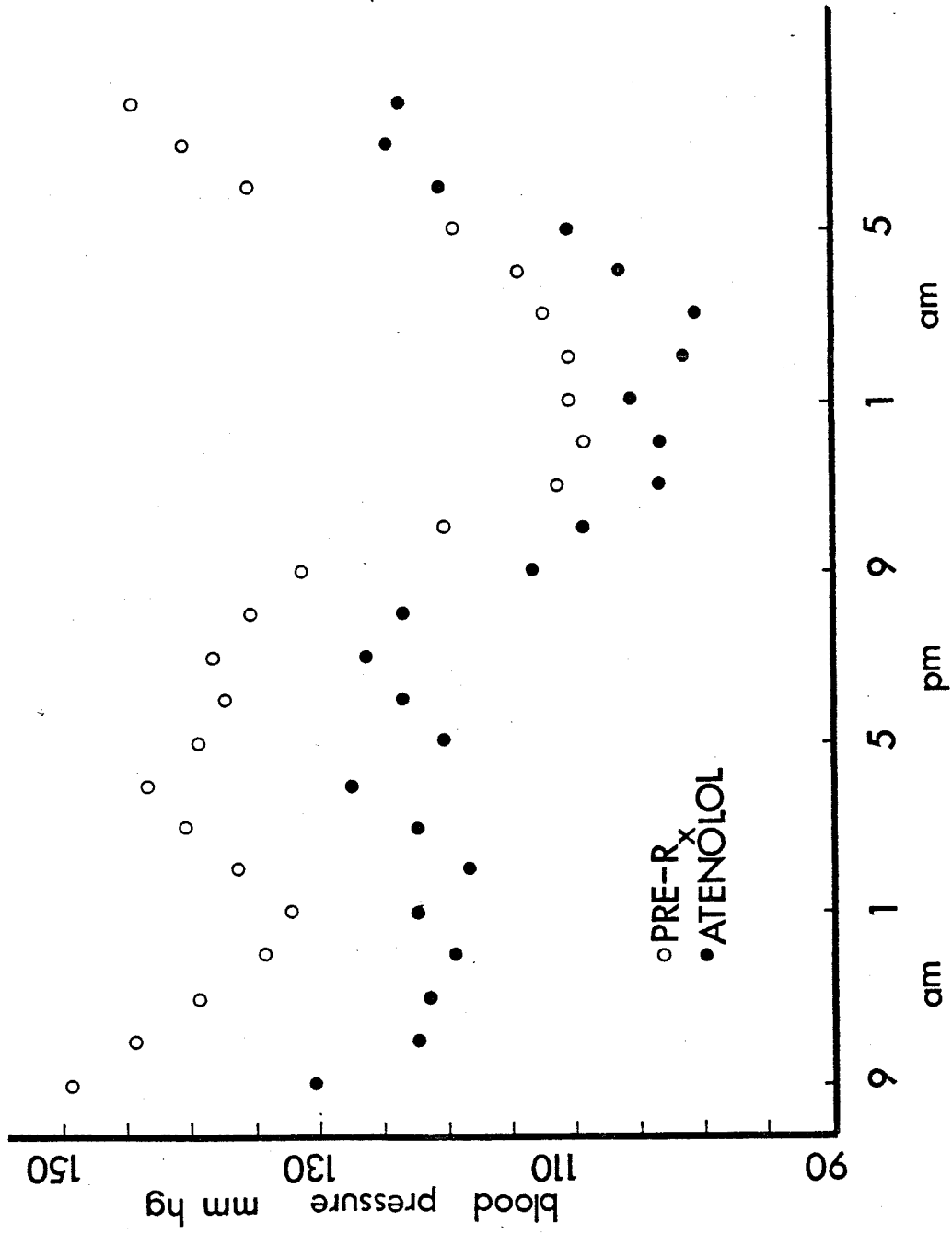
24 hour systolic and diastolic arterial pressure and heart rate before and during placebo-controlled atenolol

	Group A (n=12)		Significance	Group B (n=11)		Significance
	<u>Pre-Rx</u>	<u>On Rx</u>		<u>Pre-Rx</u>	<u>On Rx</u>	
Systolic (mmHg)	130.3 ± 13.03	116.25 ± 9.28	P < 0.001	123.7 ± 10.20	125.9 ± 10.42	NS
Diastolic (mmHg)	72.3 ± 7.29	61.8 ± 5.62	P < 0.001	69.5 ± 5.18	72.04 ± 5.20	NS
Heart Rate (beats/min)	84.6 ± ±4.05	67.08 ± 8.3	P < 0.001	77.6 ± 12.41	78.4 ± 12.52	NS

± 1 SD

FIGURE 15

SYSTOLIC PRESSURE RESPONSE TO ATENOLOL



Standard deviation and significance values are contained in Appendix I, pp 170-172 inclusive.

Atenolol substantially reduced systolic and diastolic arterial pressure and heart rate, while placebo had no effect on any of these parameters. However, the presentation of global data masks the 24 hour effectiveness of atenolol in lowering systemic arterial pressure and this is conclusively demonstrated in figures 15 and 16 .

The fall in blood pressure was significant ($P < 0.05 - 0.001$) for all hourly periods except during the hours 2300-0600 when the reduction in pressure did not quite reach the level of significance, but at a time when untreated blood pressure was already at its lowest level. The 24 hour antihypertensive effect of atenolol is demonstrated, however, by the highly significant blunting of the early morning rise in both diastolic and systolic pressure.

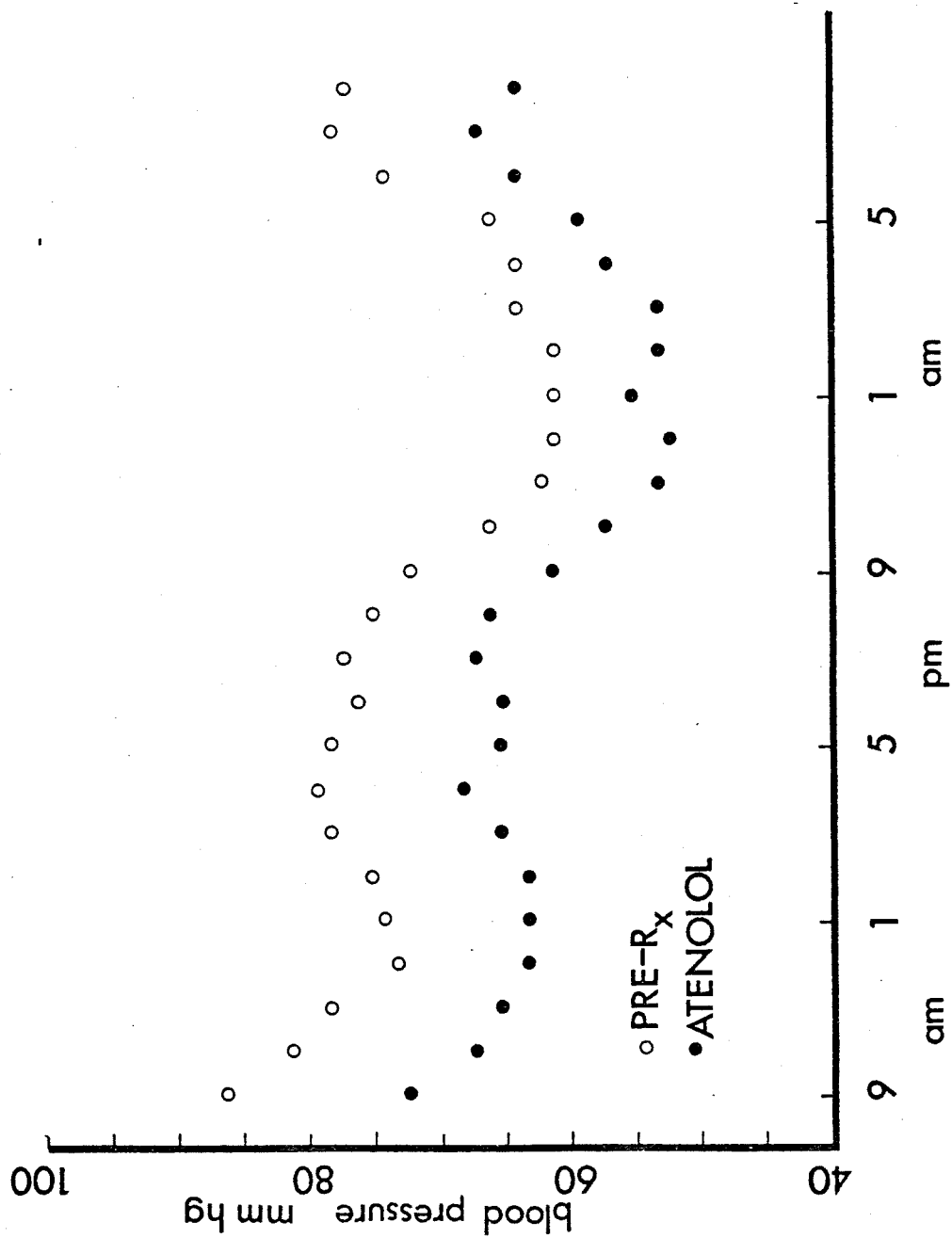
The fall in heart rate followed approximately the same pattern as blood pressure (fig 17) although the reduction in the morning rise in heart rate did not achieve statistical significance - suggesting that the 24 hour effect of atenolol on heart rate reduction is not complete.

The non-significant fall in systolic and diastolic arterial pressure seen in placebo-subjects with office cuff blood pressure readings was not apparent in continuous ambulatory blood pressure data (figs 18 and 19), where the similarity between studies 1 and 2 was quite remarkable. Indeed, a slight, but significant, rise in pressure was evident and this was analagous to the results obtained on home blood pressure recording (table 4).

Comparison of standard deviations of systolic and diastolic arterial pressure and heart rate before and during atenolol failed to demonstrate any significant difference (appendix I, pages 173-174).

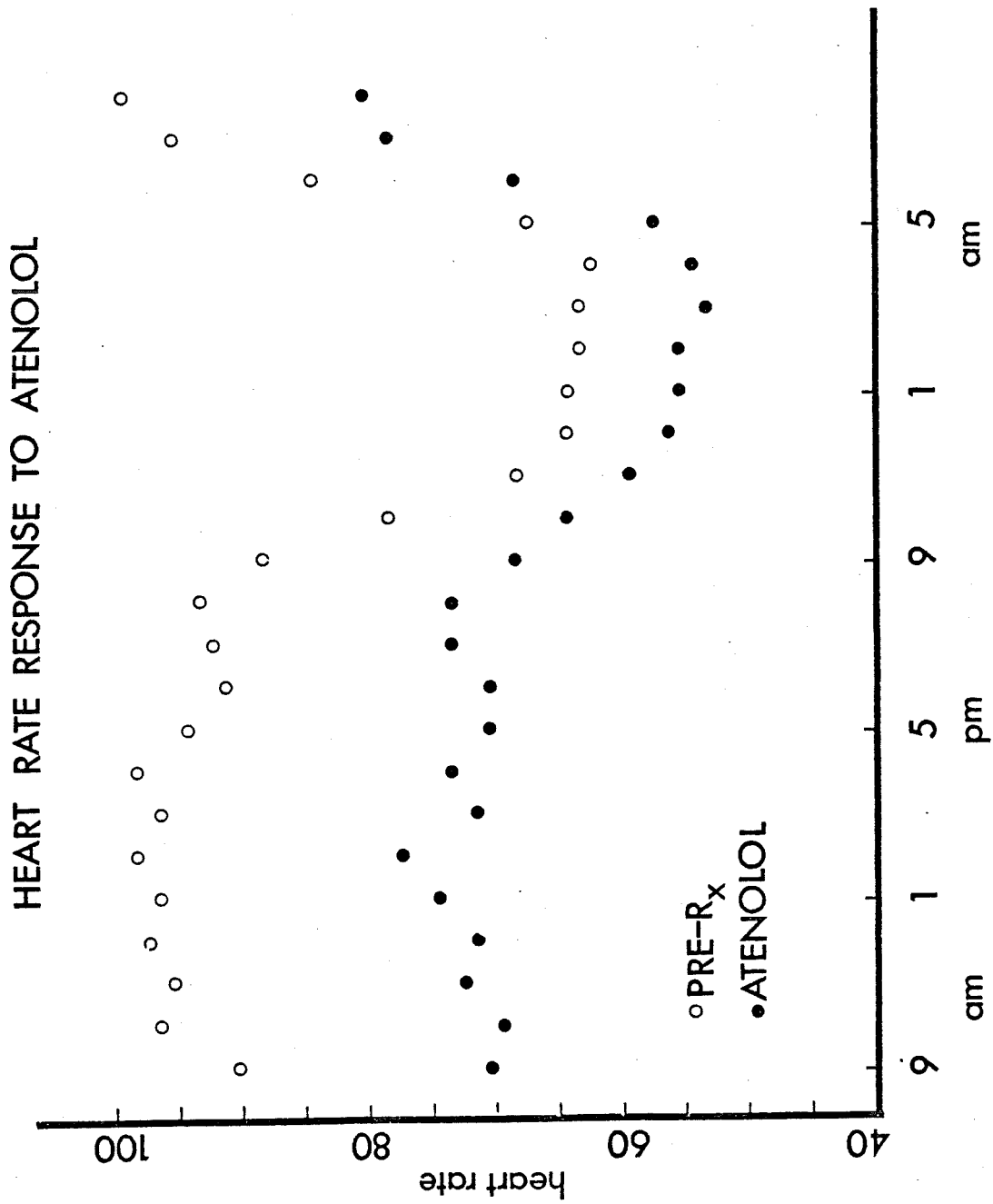
FIGURE 16

DIASTOLIC PRESSURE RESPONSE TO ATENOLOL



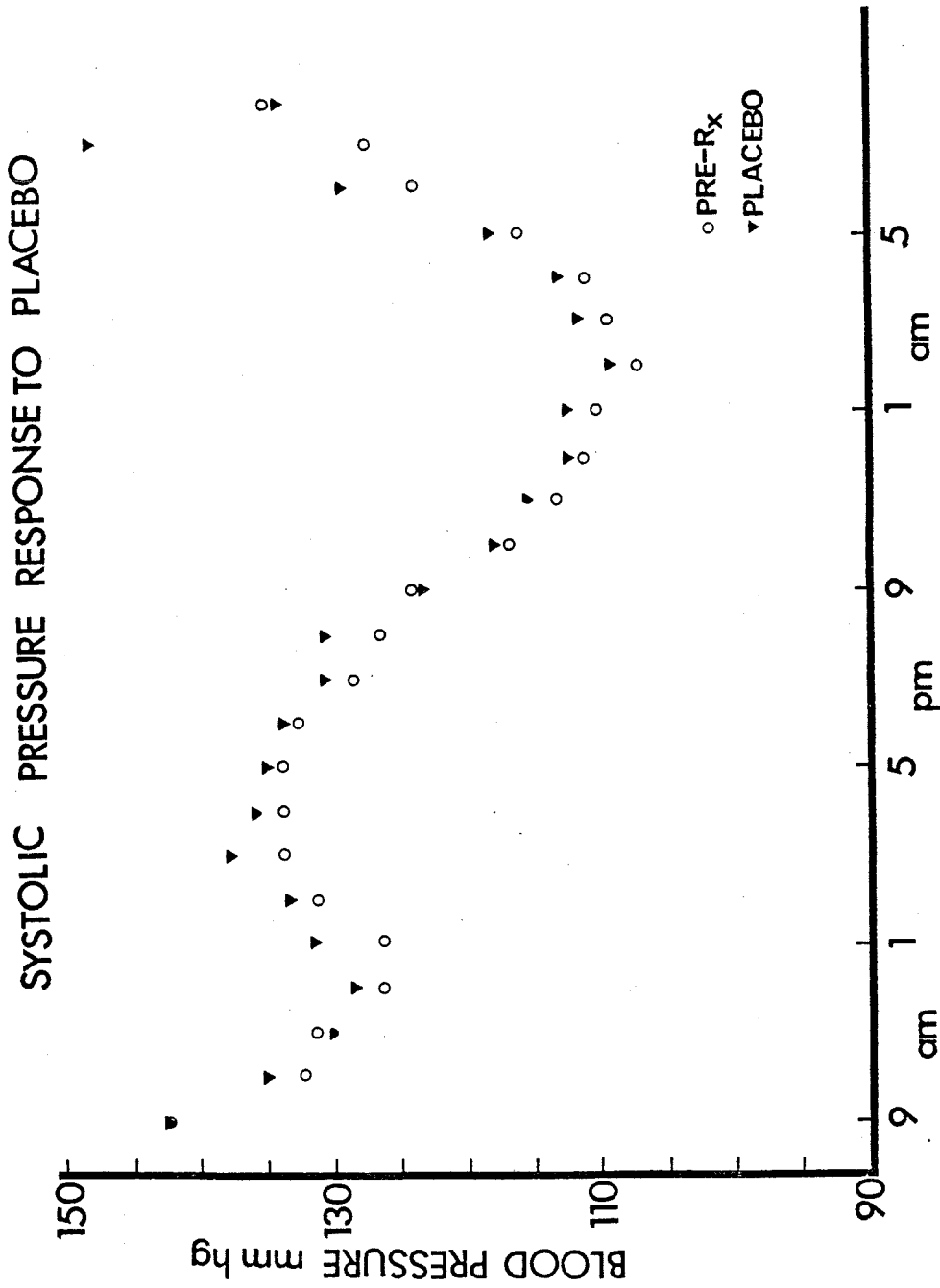
Standard deviation and significance values are contained in Appendix I, pp 170-172 inclusive.

FIGURE 17



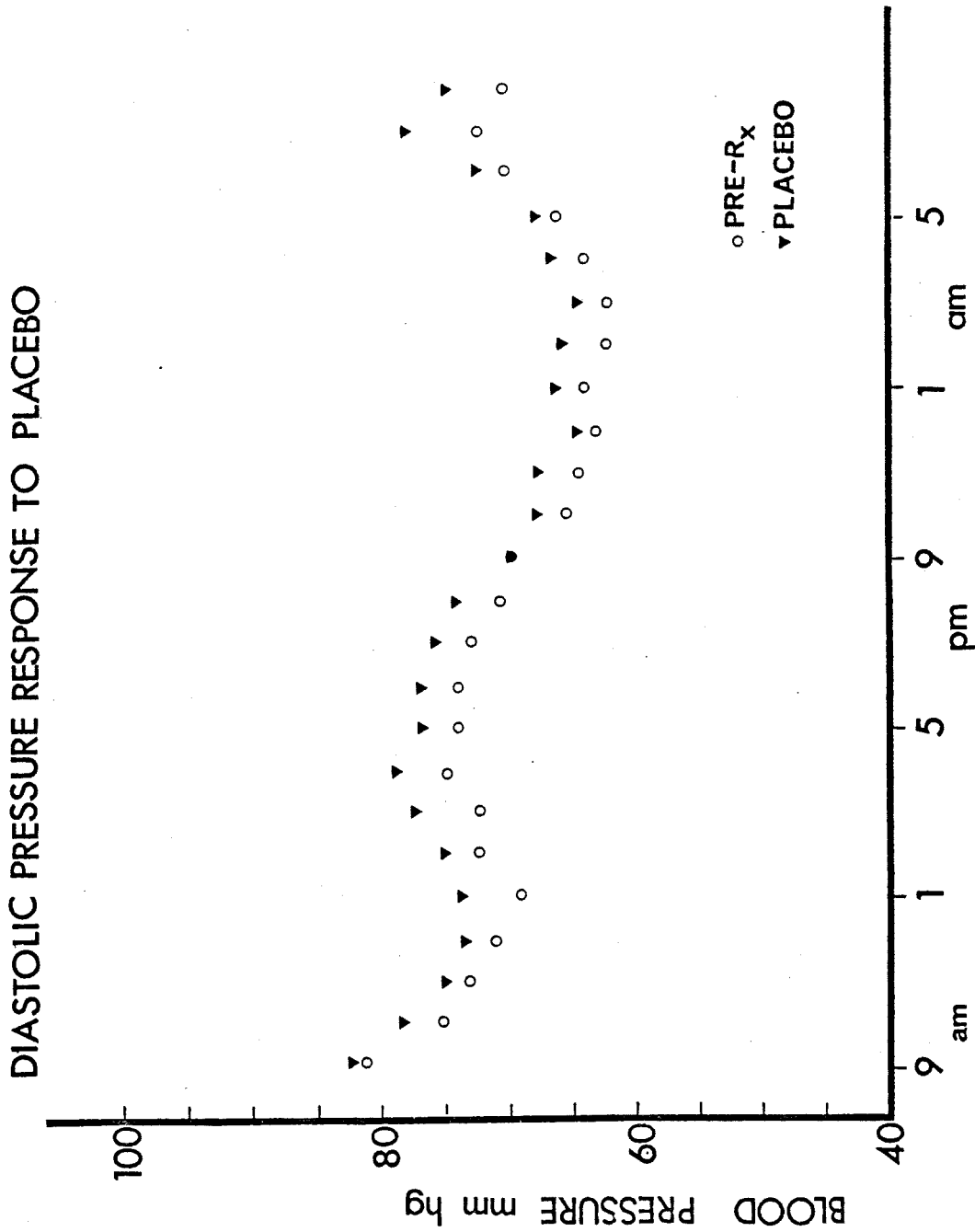
Standard deviation and significance values are contained in Appendix I, pp 170-172 inclusive.

FIGURE 18



Standard deviation and significance values are contained in Appendix I, pp 175-177 inclusive.

FIGURE 19



Standard deviation and significance values are contained in Appendix I, pp 175-177 inclusive.

CHAPTER NINE B - ASSESSMENT OF THE BLOOD PRESSURE/HEART
RATE RESPONSE IN NORMOTENSIVES AND IN
MILD HYPERTENSIVES BEFORE AND AFTER
B-BLOCKADE

It is now generally agreed that baroreflex control of the heart is impaired in established arterial hypertension (Gribbin, et al, 1971 and Korner, West and Shaw, et al, 1974). However, the evidence for baroreflex impairment in young, mild hypertensives is not so well defined (Takeshita, et al, 1975). The finding of a baroreceptor abnormality at this presumed early stage of the hypertensive process might be interpreted as indirect evidence that this control malfunction may have a role in the initiation of the hypertensive process.

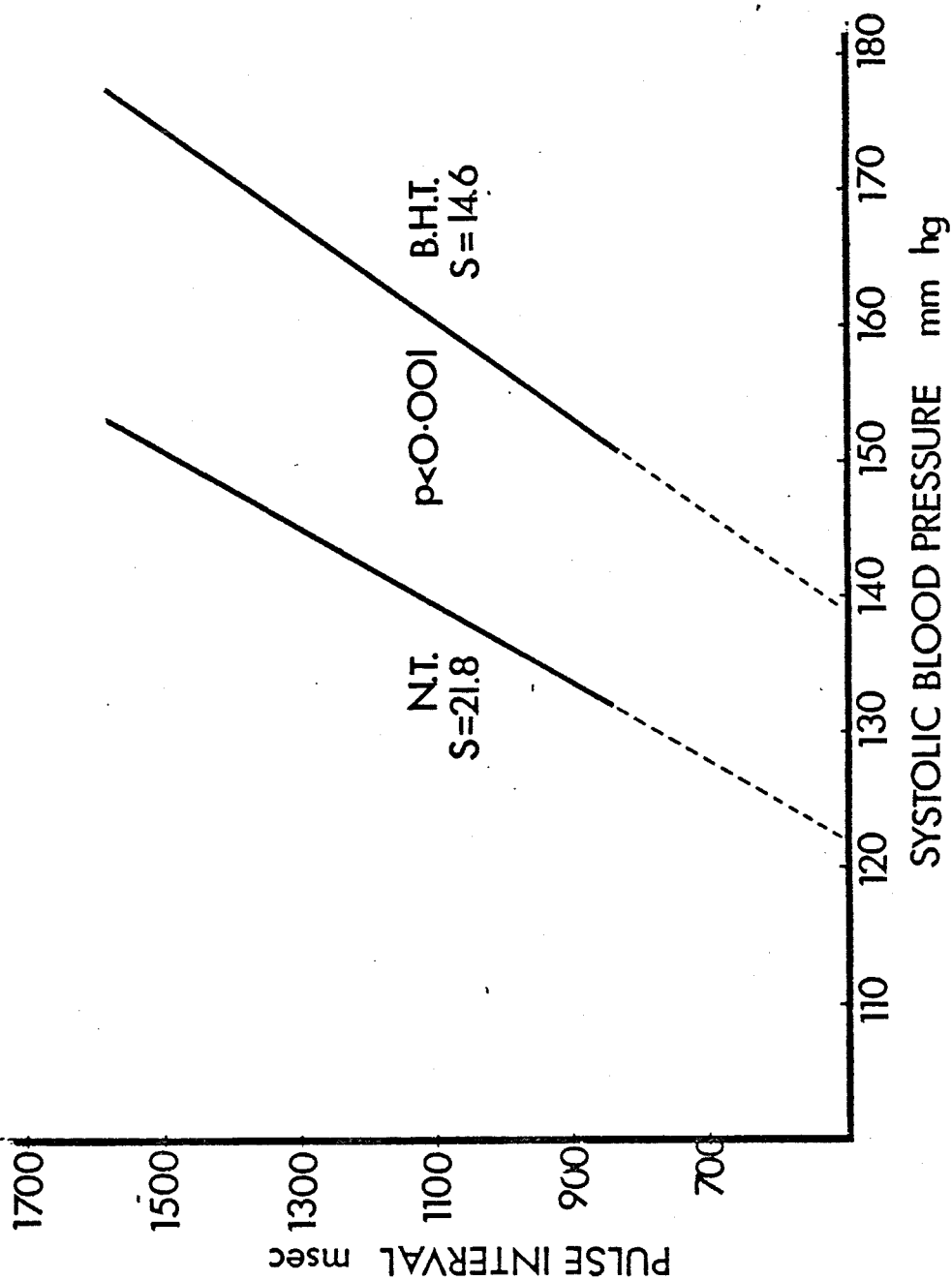
It was therefore decided to compare baroreceptor sensitivity of young, mild hypertensive males with their normotensive counterparts.

Subjects and Methods

There were 18 hypertensive and 8 normotensive males in this part of the study. Criteria for blood pressure classification have already been described. The mean age of the subjects was 27.2 ± 4.1 years. Studies were performed with subjects lying quietly supine in a temperature-controlled room. Intra-arterial blood pressure - via the brachial artery - and continuous electrocardiograms were recorded on a *Mingograf multi-channel recorder at a paper speed of 50 mm/sec. Intravenous bolus injections of angiotensin II (Hypertensin CIBA), in increments of 0.5 μg to a maximum of 2.5 μg , were administered via a

BAROREFLEX GAIN OF NORMOTENSIVES
AND BORDERLINE HYPERTENSIVES

FIGURE 20



peripheral venous cannula.

Baroreflex sensitivity was calculated using the method of Smyth, Sleight and Pickering (1969). This involved plotting systolic arterial pressure against the succeeding pulse interval during the angiotensin-induced rise in systemic arterial pressure to obtain a linear plot. Following the return of pressure and heart rate to baseline levels the procedure was repeated with incremental angiotensin dosage until a rise of 30-50 mmHg systolic arterial pressure was achieved.

Reflex sensitivity was expressed as the slope of the regression line (m sec increase in RR interval per mmHg rise in systolic arterial pressure).

Results

The resting intra-arterial systolic blood pressure of hypertensives was greater than the normotensive controls (138.9 ± 17.8 vs 122 ± 9.5 mmHg ; $P < 0.001$). The average resting heart rate, however, was not significantly different (69 ± 9.8 vs 68 ± 9.2 beats/min; NS). Baroreflex sensitivity was significantly reduced in the hypertensive group when the slopes of both groups were compared. (14.6 ± 5.5 m sec/mmHg vs 21.8 ± 7.8 m sec/mmHg ; $P < 0.001$). (Fig 20).

Effects of B-Blockade

Resetting of the baroreceptor mechanism has been postulated as a possible contributory mechanism to the hypotensive action of

B-blockers (Prichard and Gillam, 1966 and Prichard and Gillam, 1969).

Hansson (1973) detected an increase in baroreflex sensitivity with propranolol, but this was not confirmed by Simon, Kiowski and Julius (1977) in a study with another β -blocker, timolol.

The mild hypertensives participated in a placebo-controlled study of atenolol (chapter 9A) and it was therefore decided to re-examine their baroreflex sensitivity at the end of a six month treatment period.

Nine hypertensives received atenolol while the remainder received placebo. Repeat sensitivity at six months was determined in identical manner to that already described.

Pre-treatment baroreflex sensitivity in the atenolol group increased from 16.4 to 25.9 m sec/mmHg ($P < 0.001$), (fig 21) while remaining unchanged in the placebo group (13.9 to 13.4 m sec/mmHg; N S) (fig 22) at the end of six months.

There was a significant reduction of systolic arterial pressure in the atenolol group (138.0 mmHg vs 118.0 mmHg; $P < 0.001$), while the systolic arterial pressure reduction in the placebo group was not statistically significant (133.7 mmHg vs 126.3 mmHg).

The effect of acute administration of atenolol on baroreflex sensitivity was also determined in four mild hypertensives receiving no antihypertensive therapy. Mean age was 22.3 years with systolic arterial pressure of 141.3 ± 17.2 mmHg. The method for assessing baroreflex sensitivity has already been described. A baseline value was obtained after which oral atenolol 100 mg was administered. Each subject then remained quietly supine and the

FIGURE 21

BAROREFLEX GAIN ON LONG-TERM ATENOLOL

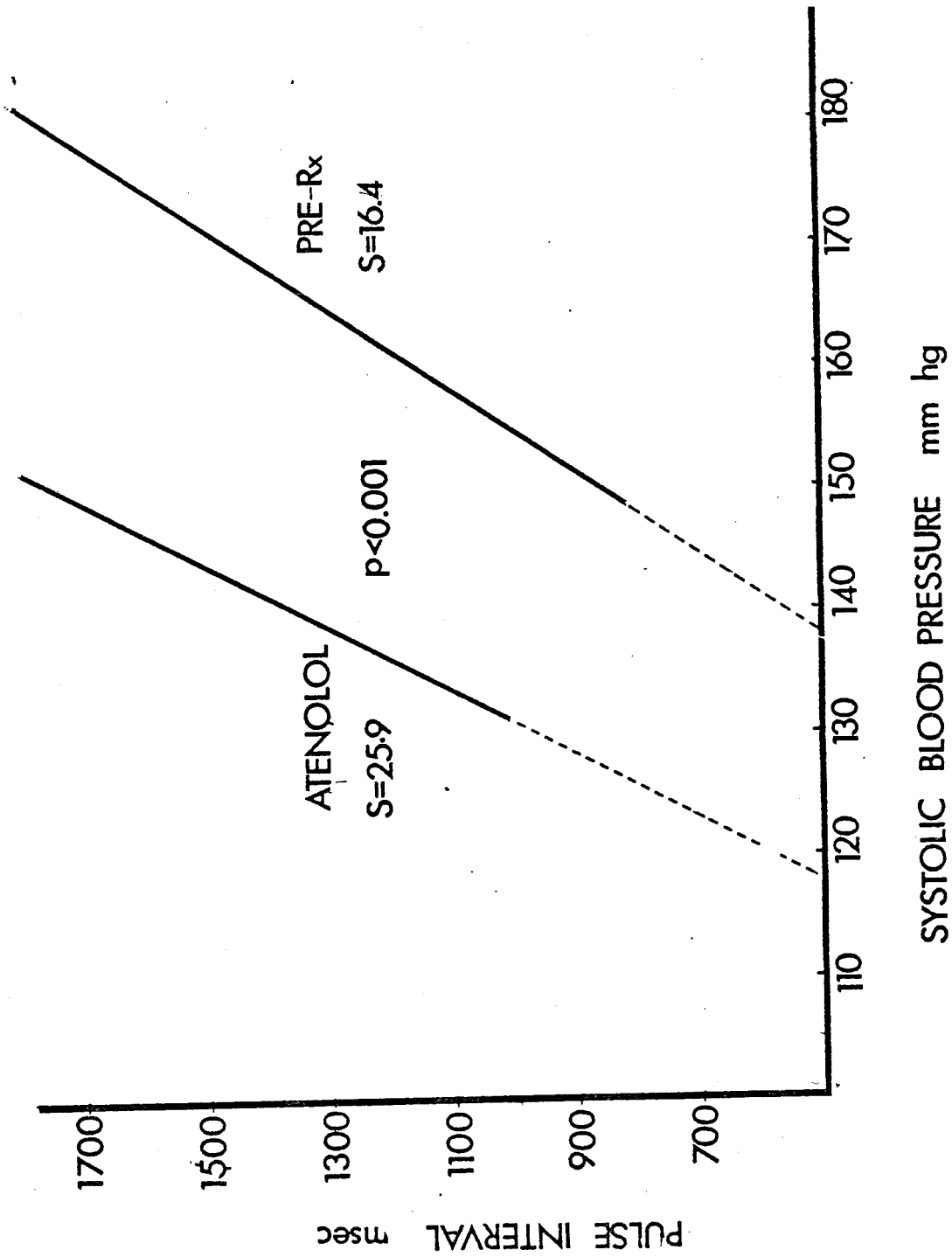
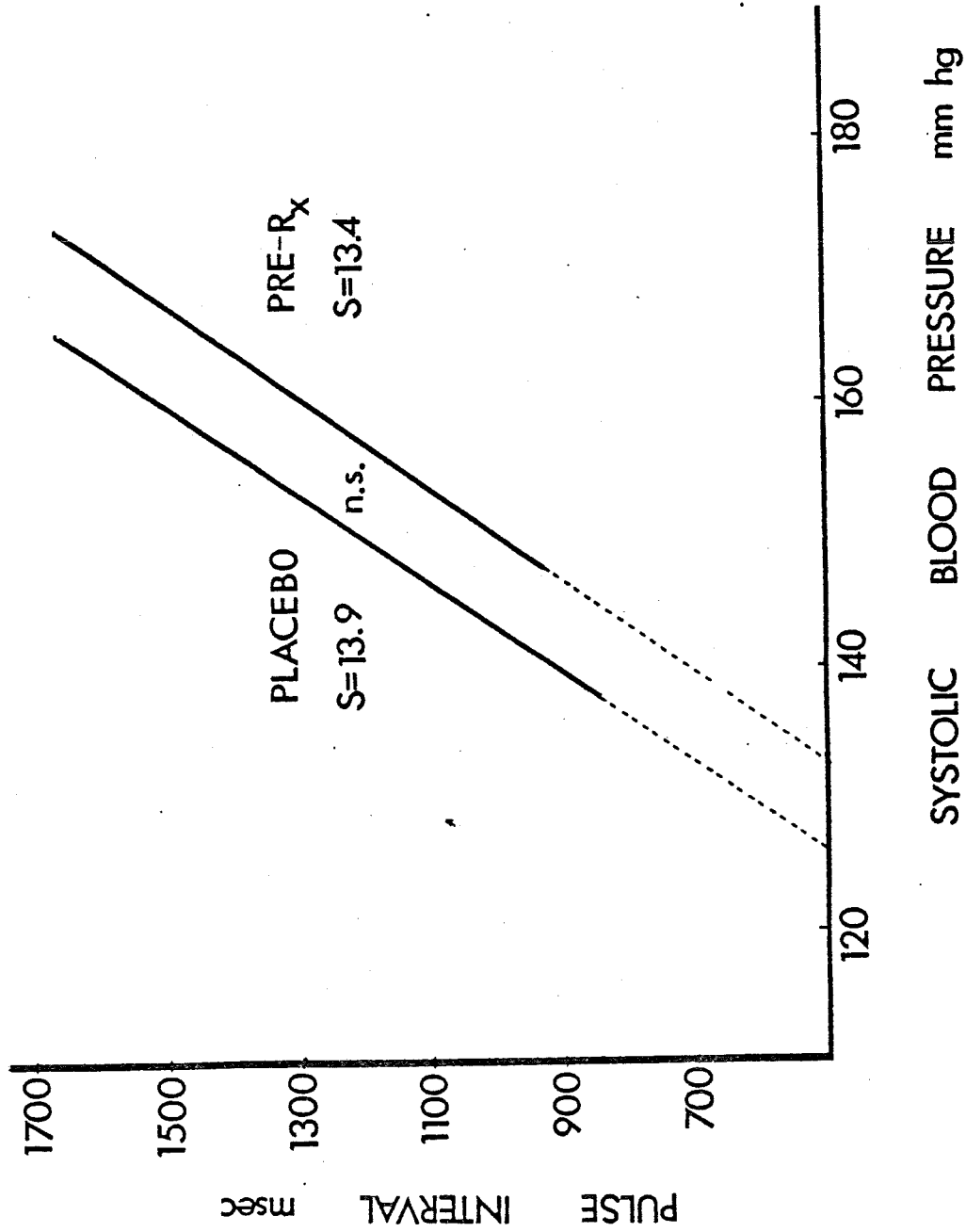


FIGURE 22

BAROREFLEX GAIN ON PLACEBO



procedure was repeated at the end of one hour.

There was no significant change from baseline blood pressure after acute atenolol (141.3 ± 17.2 vs 138.0 ± 11.7 mmHg; N S).

There was, however, a significant reduction in heart rate (72.5 ± 8.9 vs 64.5 ± 6.3 beats/min; $P < 0.001$).

The baseline slope was 15.3 ± 10.2 m sec/mmHg and although this increased to 19.1 ± 12.2 m sec/mmHg after atenolol this change did not reach statistical significance.

There was no statistical relationship between baseline systolic blood pressure and baroreflex slope in any group, nor was the increase in baroreflex sensitivity after chronic atenolol therapy related to the degree of fall in blood pressure.

A Comparison of Baroreflex Sensitivity and Variability of Blood Pressure in Borderline Hypertensives

Following baroreceptor denervation Cowley, Liard and Guyton (1973) observed that there was considerable arterial pressure variation in dogs. This observation added confirmation to the view that the baroreflex system is of importance in buffering blood pressure variation. Watson, et al, (1979); and Ogawa, et al, (1981) reported an inverse relationship between variability of intra-arterial pressure measured by standard deviation and baroreflex sensitivity in established hypertensives.

Borderline hypertensives in this study showed no significant difference in systolic blood pressure variability compared to normotensive controls. There was, however, an inconstant difference in diastolic pressure, but this was never striking.

Methods

Baroreflex sensitivity was compared to 24 hour systolic and diastolic arterial pressure standard deviation, which was used as the index of pressure variability. Data were analysed by linear regression analysis.

Results

There was no correlation between systolic and diastolic arterial blood pressure variability and baroreflex sensitivity in borderline hypertensives ($r=0.3$ and 0.1 respectively; NS).

Discussion

These results confirm the view that baroreflex sensitivity is decreased in borderline hypertension, while also demonstrating that long-term β -adrenoreceptor blockade exerts a "normalising" effect on the baroreceptor mechanism. Acute atenolol administration appeared to have no significant effect on sensitivity and this is in agreement with other workers (Watson, Stallard and Littler, 1979). The same workers also noted that the fall in arterial blood pressure after long-term β -blockade was unrelated to the increase in baroreflex sensitivity.

There was no relationship between blood pressure variability and baroreflex sensitivity. This is, perhaps, not surprising as hypertensives did not demonstrate increased variability when compared to normotensive controls.

CHAPTER TEN - PRECORDIAL VOLTAGE VARIATION IN THE
NORMAL ELECTROCARDIOGRAM

In assessing any therapeutic effect on the electrocardiogram it would be valuable to determine the extent of co-existent spontaneous variability. Variation of electrocardiographic precordial voltage between individuals is well-known, but little information is available regarding intra-individual variation in serial electrocardiography. Although significant repeat variation has previously been described (Simonson, Brozek and Keys, 1949; and Michaels and Cadoret, 1967) results may have been largely influenced by electrical errors arising from skin-electrode resistance variability. Recognition of this problem resulted in the recommendation that high impedance input circuits might reduce the effect of skin-electrode resistance on amplitude variation (Frank, 1956 and Spach, Barr, Havstad and Long, 1966). Subsequently, the effective elimination of this source of error was demonstrated by the incorporation of buffer amplifiers into modern electrocardiograph recorders (Berson and Pipberger, 1968).

It was decided to study precordial voltage variation in the 12 lead electrocardiogram of normal male subjects and attempt to quantify this in a context which might be useful in determining the presence or absence of left ventricular hypertrophy.

Materials and Methods

Sixteen normotensive, healthy, male volunteers, aged 18 to 35 years (mean 24 years) took part in the study. They were randomly allocated to one of two groups: A (n=9), B (n=7).

Group A: Two 12 lead electrocardiograms were recorded 10 minutes apart, following a five minute introductory period, at the same time on each of four consecutive days. Chest electrodes were removed between same-day recordings. Care was taken to obtain sequential electrode position accuracy throughout the study.

Group B: The procedure here differed from group A only insofar as precordial electrodes were not removed in between same-day recordings, which were performed at the same time on each of three consecutive days.

Studies were performed at the same temperature-controlled location in a relaxed atmosphere with subjects remaining supine throughout. All were in a post-absorptive state.

The same Nihon Kohden* 3 channel direct writing recorder, input impedance 5 Mohm, was used for each study which was preceded by careful calibration with a standard deflection of 1 mm = 0.1 mV.

Precordial electrode positioning was performed according to recommendations of the American Heart Association (1954).

Optimum skin electrode contact was ensured by shaving hirsute areas of the chest before silver chloride electrodes of the suction type (11 mm diameter and filled with low impedance coupling gel) were applied. In group B volunteers, where electrodes remained in position during the ten minutes between same-day recordings, prominent petechial rings developed after the first day, thereby greatly assisting sequential accuracy of

* Model ECG-4103. Nihon Kohden, Kogyo Co., Ltd., Tokyo, Japan.

TABLE 11

Precordial R + S Amplitude (in 0.1 mv) and
Heart Rate (Beats/Min) of Group A Subjects on
Four Consecutive Days

Subject	Heart Rate	ECG I	ECG II
C.N.	67	38.8	37.4
	67	33.3	34.2
	59	44	45.3
	57	31.9	40.9
P.W.	60	31.2	22.1
	55	38.8	34.5
	58	33.6	37.6
	64	27.4	38
J.R.	86	21.7	20.7
	77	18.6	14.4
	79	24	26.6
	75	24.6	18.7
K.H.	54	26	19.4
	58	21.7	19.5
	52	16.8	22.2
	52	16.3	22.3
H.H.	63	28.2	28.2
	68	25.6	21.5
	71	28.2	25.5
	77	27.3	24.9
F.A.	61	28.8	31.5
	59	35.2	30.1
	64	29.8	27.7
	58	29.1	29.7
T.S.	57	35.9	42.2
	55	39.3	36.4
	50	40.1	42.4
	52	32.6	35.6
M.P.	60	20.8	20.6
	60	26.7	25.7
	60	24	20.9
	59	27.9	22.5
M.C.P.	58	44.8	37.5
	60	45.6	43
	58	35	48.4
	58	44.5	39.9

TABLE 12

Precordial R + S Amplitude (in 0.1 mv) and
Heart Rate (Beats/Min) of Group B Subjects on
Three Consecutive Days

Subject	Heart Rate	ECG I	ECG II
D.B.	64	44.4	43.7
	64	39.3	44
	64	42.6	42.5
P.K.	56	37	36
	58	34.2	34.9
	57	33.9	32.5
J.K.	58	44.9	44
	65	42.8	41.6
	63	43	43
M.R.	53	27.2	27.6
	55	27.25	28.5
	55	32.4	32.3
R.S.	71	33.4	33.4
	70	33.3	33.6
	68	34.4	34.2
A.H.	70	47.7	46
	70	45.2	44.2
	67	44.7	41.7
E.B.	51	45.5	44.5
	48	44.4	44.5
	50	42.7	41.2

electrode placement. All 114 traces were of high technical quality and none fulfilled criteria for bundle branch block. Traces were coded by an assistant to ensure unbiased assessment. Measurement of R and S amplitude was made to the nearest 0.5 mm using hand calipers and taking the mean of ten consecutive complexes in the precordial leads displaying the largest R and the largest S waves. These leads remained consistent for individuals throughout the study.

As the aim of the study was the investigation of precordial voltage variation as it might be interpreted in the context of left ventricular hypertrophy detection, data were analysed using a model based upon McPhie's criteria, which are:

greatest	$R + S > 40 \text{ mm}$	
	or	in the precordial leads
greatest	$R + S > 45 \text{ mm}$	

Statistical Method

Both inter and intra-individual variation was assessed by performing an analysis of variance on the additive decomposition of the sum of R + S amplitudes (appendix III).

Results

R + S and heart rate data are contained in Tables 11 and 12.

Group A: The range of variation for same-day and day to day recordings was quite large. Intra-individual variation within each day was approximately equal to day to day variation, the difference being statistically non-significant (Table 13).

TABLE 13

Comparison of Intraindividual Variation of Greatest R + S Amplitude (in 0.1 mv) in Precordial Leads

	Group	Range	Mean	S.D.	Significance
Same Day	A	0 - 13.4	5.9	3.62	P < 0.01
	B	0 - 3	2.3	1.21	
Day to Day	A	0 - 12.7	5.2	3.03	P < 0.01
	B	0 - 4.7	1.5	1.11	

* No significant difference in variation between same day and day to day.

TABLE 14

95% Range of Intraindividual Greatest R + S

Precordial Voltage Amplitude Variation (in 0.1 mv)

Group	Same Day	Day to Day
A	6	7.2
B	2.4	2.2

Group B: Same day and day to day variation was considerably reduced when compared to Group A and this reduction was statistically significant ($P < 0.01$). As in Group A intra-individual variation within each day was approximately equal to day to day variation.

Inter-individual variation in both groups was 60-80% greater than intra-individual variation, as might be expected. Comparing coefficients of variation for each subject in both groups no extreme was seen despite the wide spectrum of R + S values.

Heart rate was calculated from the mean of the longest and shortest R-R intervals in the ten consecutive complexes used for amplitude measurement. Mean heart rates were 61.9 ± 8.37 and 60.8 ± 7.28 beats per minute) for Groups A and B respectively.

Summary

These results demonstrate the existence of significant precordial voltage variation in serial 12 lead electrocardiography, despite every effort to minimise known possible causes of variation through the application of standardised conditions. Sources of possible precordial voltage variation which have been previously described include electrode placement, beat to beat variation, tachycardia, the post-prandial state, changes in body habitus and fitness and drug therapy.

Benson, et al, 1978, demonstrated that repeat variation was large in the orthogonal system with intentional displacement of precordial electrodes. In this study of the 12 lead electrocardiogram repeat variation was reduced by approximately 60% when precordial electrodes were not removed between successive recordings. This manoeuvre effectively eliminated variation resulting solely from alteration in electrode positioning.

Respiration is the most important physiological variable causing beat to beat variation (Fischmann, Cosma and Pipberger, 1968; and Ishikawa, Batchlor and Pipberger, 1971) and this may be quite striking in a clinical setting. The use of 10 consecutive complexes for amplitude measurements ensured that respiratory variation was substantially lessened.

Changes in R wave amplitude are known to occur during exercise tachycardia (Bonoris, Greenberg, Christison, Castellanet and Ellestad, 1977). Brody (1956) suggested that this arose as a result of changes in cardiac intracavity blood mass. Overall, Group A subjects demonstrated slightly greater variation in heart rate when compared to Group B and this heart rate stability may have contributed to reduction in voltage variation, although it should be emphasised that no subject in either group was tachycardic.

The study of variation over a short time period eliminated effects which might have been encountered in the long term, such as changing body habitus or altered fitness status. Certainly a positive correlation has been reported between increased ponderal index and higher precordial Q R S voltages in normal men (Kilty and Lepeschkin, 1965). Increasing physical fitness correlates with increased precordial voltage (Van Ganse, Versee, Eylenbosch and Vuylsteek, 1970) and echocardiographic studies indicate that this may result from increased left ventricular wall thickness (Roeske, O'Rourke, Klein, Leopold and Karliner, 1976).

Although none of the subjects in this study was in a post-prandial state, changes in the electrocardiogram have been noted at this time.

Ostrander and Weinstein (1964) described changes in the ST segments and T-waves during glucose ingestion.

The choice of young healthy men in this study ensured that none was on drug therapy. Digoxin, for example, has been reported as causing a sharp rise in Q R S amplitude (Manoach, Grosman, Varon and Gitter, 1972), while such unlikely agents as vitamins and ferrous sulphate have been shown to have effects on the electrical activity of the heart.

Higher precordial voltages are not uncommon in young men (Manning and Smiley, 1964) and in this study four subjects intermittently fulfilled McPhie's criteria for left ventricular hypertrophy. This latter observation demonstrates that "normal" variation may thus interfere with interpretation of serial precordial voltage changes in the clinical setting.

The 95% range of variation in Group A is of importance in the assessment of precordial voltage changes in an individual. Failure to appreciate this degree of variation may result in the misclassification of an electrocardiogram as showing or failing to show, left ventricular hypertrophy. The range of variation found in this study may be a conservative estimate of that seen in the clinical situation, where many of the sources of possible precordial voltage variation, minimised in this study, may be operative.

Although the effects of these other factors might not necessarily be additive it does appear likely that their effects would serve to compound variation.

CHAPTER ELEVEN A - THE ELECTROCARDIOGRAM IN HYPERTENSION

"Electrocardiographic evidence of left ventricular hypertrophy is an important result of hypertension; its incidence is directly related to the height of the arterial pressure." Ibrahim, et al, 1977.

"In the under 35 year age groups there is no relationship between systolic pressure and precordial voltage criteria for left ventricular hypertrophy, and this suggests that high voltage R waves have a different significance in youth." Beaglehole, Tyroler, Cassel, Deubner, Bartel and Hames, 1975.

THE PREVALENCE OF ELECTROCARDIOGRAPHIC LEFT VENTRICULAR HYPERTROPHY
IN YOUNG MALES - A POPULATION STUDY

The relatively small numbers of normotensives and mild hypertensives in the study rendered it impossible to make any firm pronouncement on the prevalence, and therefore the significance, of electrocardiographic left ventricular hypertrophy in the young male population.

Sydney University School of Public Health and Tropical Medicine had initiated a study designed to explore occupational factors in hypertension and coronary heart disease among the public service population under the auspices of Professor D Ferguson (1973). By early 1980 4,000 individuals had entered the study and access was kindly allowed to computer files to analyse blood pressure and electrocardiographic data on males aged between 16 and 35 years.

Subjects and Methods

There were 913 individuals in the age range 16 - 35 years with a mean age of 25.3 ± 4.2 years. Twelve lead electrocardiograms were performed by trained personnel and classified according to Minnesota Code criteria (Blackburn, et al, 1960). Doubtful tracings were referred to an independent cardiologist for adjudication. Minnesota code 3,1 and or 3,3 was taken to signify electrocardiographical left ventricular hypertrophy.

Blood pressure was measured according to recommendations of the Australian National Blood Pressure Study (ANBPS) (Abernethy, 1974) on at least two occasions six weeks apart. On the basis of these blood pressure readings subjects were classified into three categories -

normal, mild hypertension and established hypertension. These categories were defined around an arbitrary division of 140 mmHg systolic and 90 mmHg diastolic. Those individuals who at no time exceeded these limits were classified as normotensive (n=670) while established hypertensives (n=83) consistently exceeded either 140 mmHg systolic and/or 90 mmHg diastolic. The mild or borderline hypertensive group (n=160) comprised those individuals with an intermittent variation of arterial pressure about 140 mmHg systolic or 90 mmHg diastolic.

At the initial screening visit each subject's height and weight was measured and the Quetelet Index - an indicator of body habitus - was derived from the formula $\frac{\text{weight (Kg)}}{\text{height}^2 \text{ (cm)}} \times 1,000.$

Statistical Analysis

Data were analysed using X² analysis and Students' t Test for non-paired data.

Results

The details of blood pressure (BP) and electrocardiographic (ECG) classification are contained in table 15.

TABLE 15Blood pressure and electrocardiographic classification

ECG evidence of left ventricular hypertrophy

<u>BP CATEGORY</u>	<u>PRESENT</u>	<u>ABSENT</u>	<u>TOTAL</u>
Established hypertension	25 (30.1)*	58	83 (9.1)
Mild hypertension	24 (15.0)	136	160 (17.5)
Normal	74 (11.04)	596	670 (73.4)

* Percentages in parenthesis.

TABLE 16

Levels of blood pressure and ECG classification

	NT		BHT		EHT	
	S	D	S	D	S	D
L V H	122.3 ± 9.4	72.5 ± 9.2	138.6 ± 9.2	77.8 ± 11.2	145.1 ± 12.3	88.5 ± 11.4
NON - L V H	121.0 ± 9.3	73.1 ± 9.1	136.1 ± 10.4	80.1 ± 10.9	143.8 ± 12.5	89.8 ± 11.2
TOTAL	121.2 ± 9.3	73.0 ± 9.1	136.2 ± 10.2	80.3 ± 11.0	144.2 ± 12.4	89.4 ± 11.3
SIGNIFICANCE (P)	NS	NS	NS	NS	NS	NS

NT - normotensive; BHT - borderline hypertensive; EHT - established hypertensive; S - systolic arterial pressure; D - diastolic arterial pressure; LVH - left ventricular hypertrophy; NS - not significant.

Values represented as mean ± SD.

Table 16 contains levels for the three blood pressure categories subdivided according to ECG status. The difference in blood pressure between left ventricular hypertrophy and non-hypertrophy subjects, within blood pressure categories, was not significant (NS).

Within the arbitrarily defined limits of 140 mmHg systolic and 90 mmHg diastolic arterial pressure 26.6% of individuals (n=913) had a blood pressure "abnormality" - 91% with established hypertension while 17.5% fell into the borderline category.

A total of 123 individuals (13.5%) fulfilled the Minnesota Code criteria for electrocardiographic left ventricular hypertrophy. Almost 1 in 3 of those with established hypertension had evidence of electrocardiographic left ventricular hypertrophy and this increased incidence was statistically significant when compared to borderline and normal individuals ($P < 0.01$). The prevalence rate of left ventricular hypertrophy in borderline hypertension and normotensive groups was not significantly different.

TABLE 17

Values for Quetelet Index by ECG and blood pressure status

	NT	BHT	EHT	SIGNIFICANCE
ENTIRE GROUP	23.0 \pm 2.9	24.7 \pm 3.2	24.9 \pm 3.4	$P < 0.01$
NON-L V H	23.1 \pm 3.0	24.9 \pm 3.3	25.3 \pm 3.3	$P < 0.01$
L V H	22.6 \pm 2.6	23.2 \pm 2.6	24.4 \pm 3.1	$P < 0.01$
SIGNIFICANCE (P)	NS	< 0.01	NS	

Quetelet index was greater in hypertensive individuals than in their normotensive counterparts ($P < 0.01$). There was no significant difference

in quetelet index between borderline and established hypertensive groups; however, the presence or absence of electrocardiographic left ventricular hypertrophy determined the relationship between normotensive and borderline individuals. Those borderline subjects without ECG evidence of LVH had a higher quetelet index ($P < 0.01$), but this was not evident in the ECG hypertrophy group (NS). There was no significant difference in quetelet index between ECG hypertrophy and non-hypertrophy individuals, except in the borderline hypertensive group.

CHAPTER ELEVEN B - ELECTROCARDIOGRAPHIC PRECORDIAL
VOLTAGE IN MILD HYPERTENSION

The previous chapter described a significant increase in the occurrence of left ventricular hypertrophy ECG criteria in those individuals with a mild blood pressure "abnormality".

It was therefore decided to compare electrocardiographic precordial voltages of mild hypertensive subjects (n=30) with those of their normotensive controls (n=15). It was also decided to examine the effects, if any, of blood pressure lowering by B-adrenoreceptor blockade on precordial voltage upon completion of the six month treatment period.

Methods

Twelve lead electrocardiograms were recorded on all individuals and repeated at the end of six months in hypertensives. The same equipment was used throughout - a Nihon Kohden, model ECG-4103, direct writing, heated stylus, three channel recorder with a pen system frequency response of 100Hz (-3db). Recordings were performed in a temperature, noise-controlled environment under relaxed conditions. Careful skin preparation was undertaken to ensure excellent electrode contact and this involved shaving of hirsute areas, light abrasion of the skin with fine sandpaper and finally cleansing with alcohol. Precordial electrodes were of silver chloride suction type (11 mm diameter and filled with low impedance coupling gel) and were positioned according to the recommendations of the American Heart

Association (1954). Absolute accuracy of precordial electrode positioning in sequential studies after a six month period was of course difficult, but this was overcome in some degree with all electrode positioning being performed by myself.

Measurement of the precordial R and S waves was performed in the leads showing maximum deflections. Measurements were made by hand calipers and the mean of 10 consecutive complexes taken in an effort to eliminate respiratory variation. The R + S values were summed and are presented in mm.

All electrocardiographic recordings were of high technical quality.

Data were analysed by Student's 't' Test for paired and non-paired data and analysis of variance.

Results

The mean value for the sum of the greatest R plus the greatest S in the precordial leads of the normotensives was 37.04 ± 11.25 mm and this was not significantly different from that found in hypertensives (38.99 ± 9.85 mm; NS). After six months of atenolol therapy there was a significant reduction in the precordial voltage of those individuals treated with the active compound (37.64 ± 10.57 vs 33.12 ± 8.33 mm; $P < 0.01$), while no change occurred in the placebo group (39.69 ± 9.39 vs 40.97 mm; NS). The difference in precordial voltage between the two groups at the end of six months was highly significant (33.12 ± 8.33 vs 40.97 ± 8.02 ; $P < 0.02$). Body habitus appeared to play some role in the appearance of left ventricular hypertrophy in

borderline hypertensive individuals as judged from the population study data previously cited. There was no apparent association, however, in the other groups. Only 7 hypertensive individuals fulfilled voltage criteria for left ventricular hypertrophy (McPhie, 1958) in this section of the study. There was no significant difference between quetelet index of the hypertrophy and non-hypertrophy groups (24.4 ± 3.6 vs 24.1 ± 2.7 ; NS).

In the population study previously described, there was no significant difference in office blood pressure levels between electrocardiographic hypertrophy and non-hypertrophy groups. This also applied in this area of the study where the blood pressure difference between hypertrophy and non-hypertrophy groups just failed to reach statistical significance (Table 18).

TABLE 18

Systolic and diastolic arterial pressure levels according to electrocardiographic left ventricular hypertrophy criteria

<u>Arterial Pressure (mmHg)</u>	<u>ECG-LVH</u>	<u>NON-LVH</u>	<u>SIGNIFICANCE</u>
Systolic	142.3 ± 7.87	135.6 ± 8.90	NS
Diastolic	88.4 ± 5.50	85.9 ± 6.59	NS

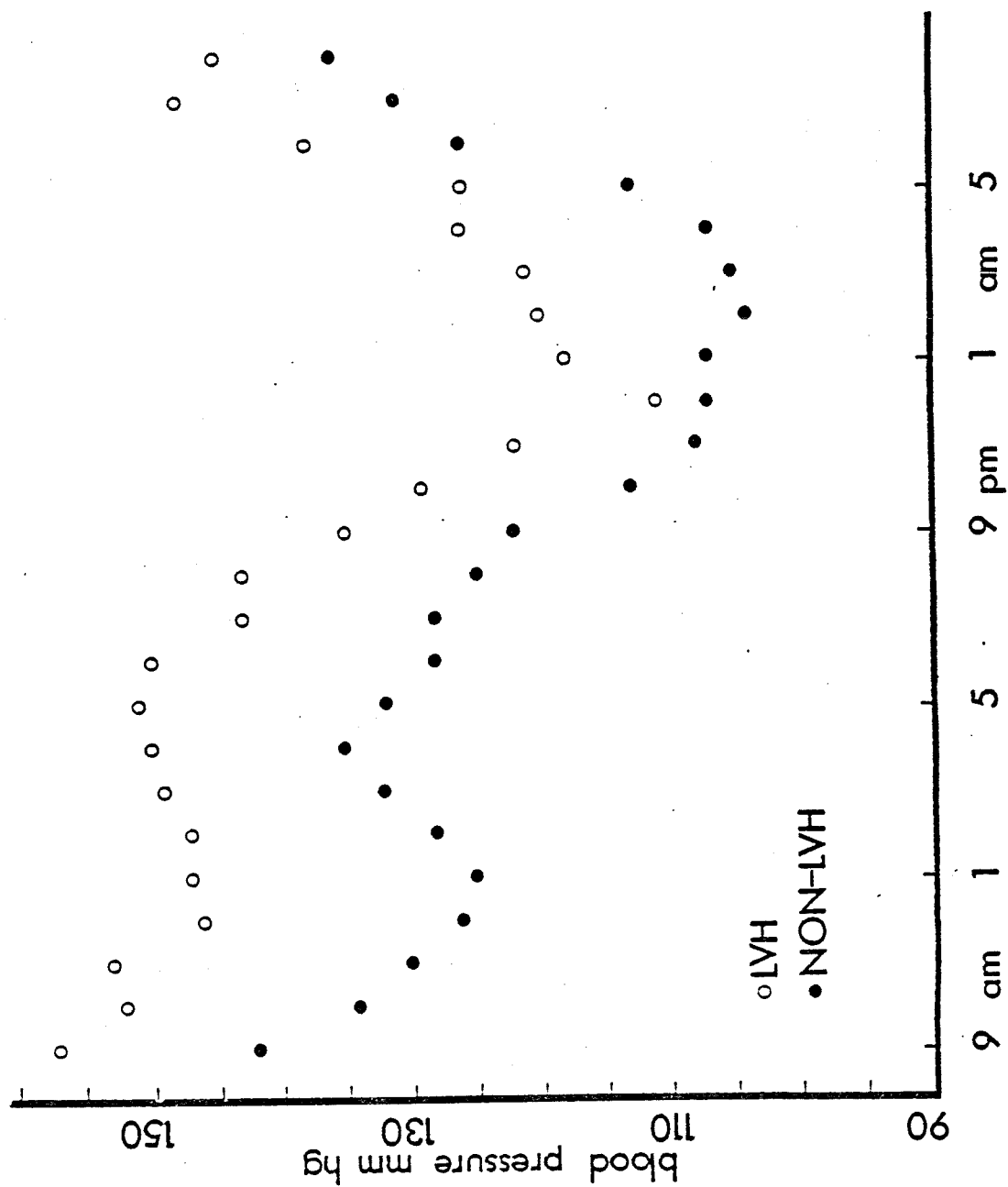
± 1 SD

The difference between groups, however, was quite striking, and highly significant, when the 24 hour intra-arterial blood pressure recordings were examined (Table 19).

FIGURE 23

COMPARISON OF SYSTOLIC PRESSURE OF ECG-LVH

AND NON-LVH BORDERLINE HYPERTENSIVES



Standard deviation and significance values are contained in Appendix I, pp 178-180 inclusive.

TABLE 19

24 hour ambulatory intra-arterial systolic and diastolic arterial pressure according to electrocardiographic left ventricular hypertrophy criteria

<u>Arterial Pressure (mmHg)</u>	<u>ECG-LVH</u>	<u>NON-LVH</u>	<u>SIGNIFICANCE</u>
Systolic	138.6 ± 13.4	122.7 ± 11.50	P < 0.01
Diastolic	79.8 ± 7.2	68.1 ± 6.24	P < 0.01

The significant difference in arterial pressure between the groups applied almost exclusively to the waking hours as demonstrated in figures 23 and 24 where levels of statistical significance ranged from P < 0.05 - 0.001.

There was no excessive variability of blood pressure, assessed by standard deviation, in either group (Appendix I, page 169).

ST-T Wave Abnormalities in Mild Hypertension

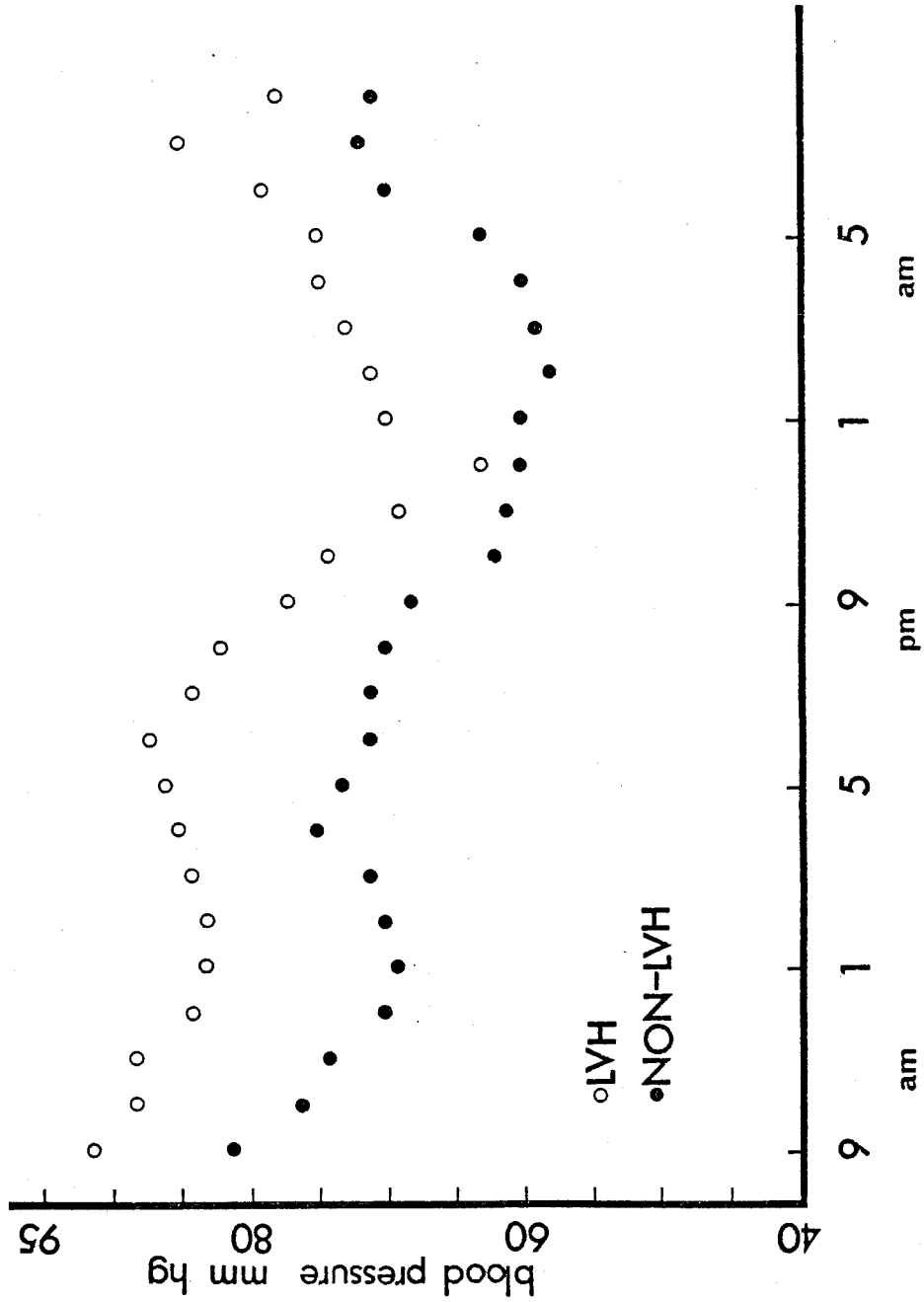
Little information is available on electrocardiographic changes, apart from precordial voltage, in young borderline hypertensive individuals. However, Guazzi, Fiorentini, Polese, Magrini and Olivari (1975) have reported T wave changes in their so-called "hyperkinetic heart syndrome" in which they postulate that the heart is under excess adrenergic drive. Frolich, Tarazi and Dustan (1969) postulated that this was a result of increased reactivity of β -receptors.

Methods

ST-T wave segments were carefully examined. Apart from some non-specific T wave flattening in lead AVL none of the normotensive individuals displayed any abnormality. However, 10 of the 30 borderline subjects

FIGURE 24

COMPARISON OF DIASTOLIC PRESSURE OF ECG-LVH AND NON-LVH BORDERLINE HYPERTENSIVES



Standard deviation and significance values are contained in Appendix I, pp 178-180 inclusive.

displayed t wave inversion in lead III, with one also having incomplete right bundle branch block and another t wave inversion in lead AVL. These changes were not altered by respiration and persisted despite long-term B-blockade.

Mean arterial pressure was significantly greater in the group with T wave abnormalities (107.1 ± 5.78 mmHg) when compared to the remainder (101.8 ± 5.71 mmHg; $P < 0.02$). There was no apparent association, however, with precordial voltage.

Orthogonal Electrocardiography in the Detection of Left Ventricular Hypertrophy in Borderline Hypertension

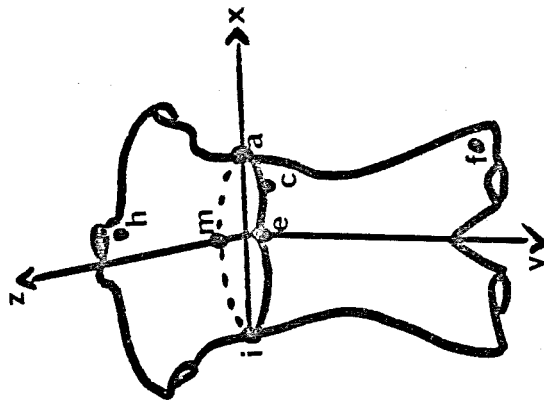
Of the various non-invasive techniques available to the clinician, the vectorcardiogram is among the least used. Since Frank (1956) described his practical, seven-lead system for the determination of orthogonal vectors the technique's accuracy in the diagnosis of left ventricular hypertrophy has been found to be greater (Mazzoleni, Wolff and Wolff, 1959 and McCaughan, Littman and Pipberger, 1973), the same (Dower and Horn, 1967 and Romhilt, Greenfield and Estes, 1968) and less than the 12-lead electrocardiogram (Borun, Chapman and Massey, 1966).

Bahler, et al, (1977) in a study of apparently normal young subjects found a close correlation with septal thickness and the absolute value of the Frank lead QRS vector (V_f), a scalar function represented by $\sqrt{X^2 + Y^2 + Z^2}$.

It was therefore decided to perform vectorcardiography in the study in order to determine its usefulness or otherwise in the detection

FIGURE 25

ELECTRODE POSITIONS & VECTORS
OF ORTHOGONAL LEAD SYSTEM



of possible left ventricular hypertrophy and to compare these findings with 12-lead electrocardiographic and echocardiographic data.

Subjects and Methods

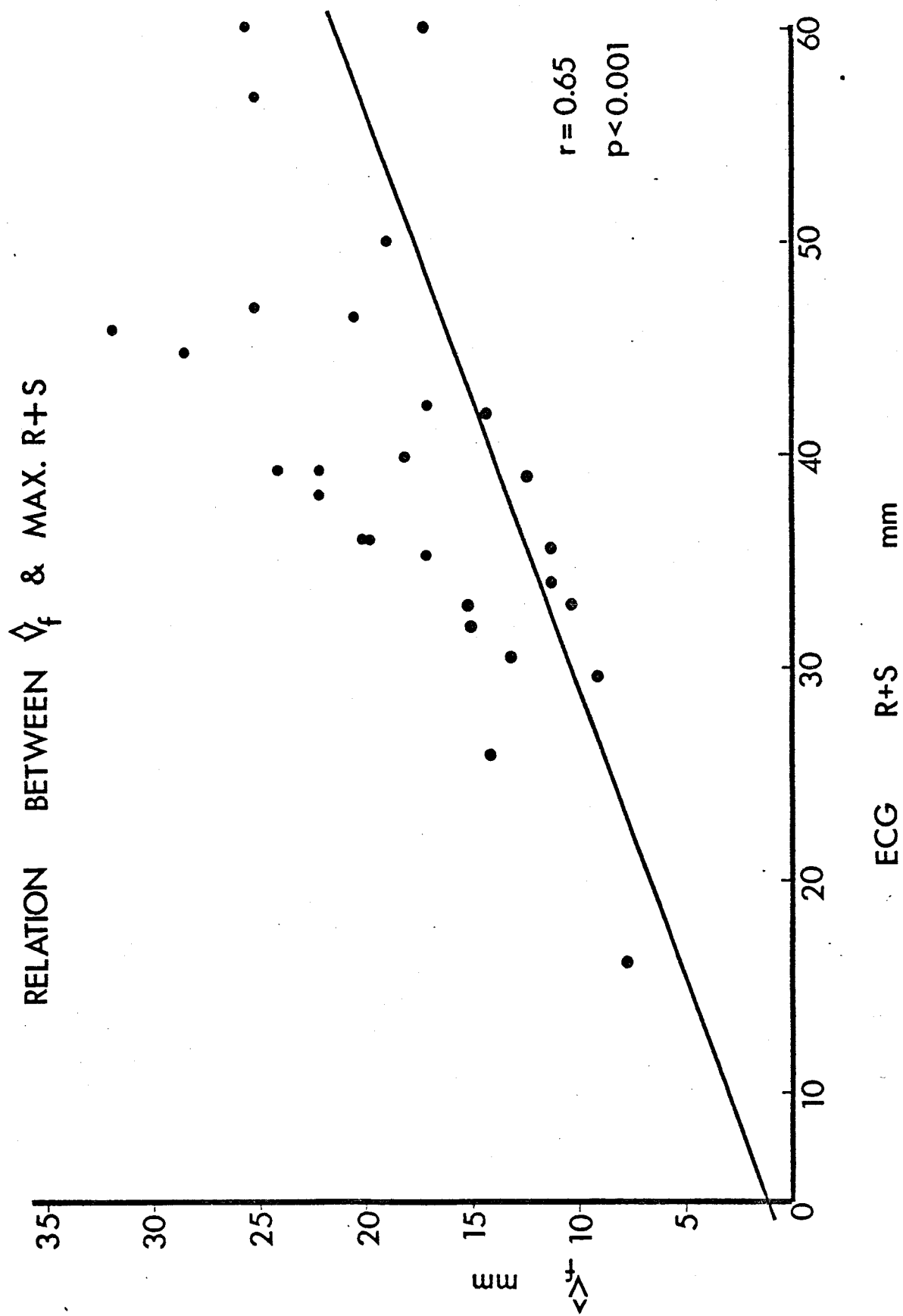
Frank lead electrocardiograms were performed on all individuals immediately after the recording of the 12-lead electrocardiogram by applying the monitoring electrodes in the positions shown (fig 25). The instantaneous values of the X, Y and Z components of the Frank lead vector system were generated by the appropriate channel on the same Nihon-Kohden, ECG-4103 used throughout the study.

The maximum Frank lead QRS vector (Vf) was calculated and data were analysed by t-test for paired and non-paired data and linear regression analysis.

Results

The value for Vf in the mild hypertensive group was significantly greater than the value for normotensives (1.3 ± 0.4 mv vs 0.18 ± 0.02 mv; $P < 0.02$). There was a highly significant correlation between Vf and the maximum R + S in the precordial leads of the conventional electrocardiogram but this relationship was only found in the hypertensive group (fig 26).

FIGURE 26



CHAPTER TWELVE A - ANATOMICAL ACCURACY OF ECHOCARDIOGRAPHICALLY
DETERMINED LEFT VENTRICULAR WALL THICKNESS

Although a good statistical relationship has been reported between posterior left ventricular wall thickness measured by M-mode echocardiography and direct measurement on the heart during surgery, methodological limitations of the study have cast doubt on its conclusions (Feigenbaum, et al, 1968). Correlative studies between echocardiography and direct measurement at necropsy have been contradictory in their findings.

Earlier studies reported a close correlation between direct measurement and the measurement of posterior wall thickness in end-diastole on echocardiography (Feigenbaum, et al, 1968 and Schroeder, et al, 1969). However, Maron, et al, 1977 found that the systolic measurement of wall thickness on echocardiography related closely to that measured at autopsy.

In view of these discrepancies it was decided to re-examine the relationship between posterior left ventricular wall thickness as determined by M-mode echocardiography, in both diastole and systole, and direct measurement of wall thickness performed at open heart surgery and autopsy.

Materials and Methods

High quality echocardiograms were available on 21 patients undergoing open heart surgery for a variety of cardiac conditions (table 20). Patients were randomly selected from the operating list of one surgeon. Prior to the echocardiographic study the purpose and nature of the study was explained to patients who gave their informed consent.

TABLE 20

Comparison of Echocardiographic Left Ventricular Wall Thickness with Direct Surgical Measurement

SUBJECT	SEX	AGE (YEARS)	OPERATION	PLVWT DIMENSION (mm)	
				ECHOD	SURGICAL
1	F	56	CABG	7.1	7.5
2	M	61	CABG	10.4	11.5
3	M	74	AVR	12.2	13.5
4	F	36	CABG	7.7	7.8
6	M	49	CABG	11	11
7	M	52	CABG	13	12.5
8	M	52	CABG	11.8	7
10	M	47	CABG	11.5	14.5
11	M	41	AVR	10	11
12	M	57	CABG	7.9	7
13	M	67	CABG	9	9
14	M	48	CABG	10	10
15	M	62	CABG	9	11
16	M	54	CABG	9.2	8.6
17	M	47	AVR	10.8	10
18	M	51	CABG	6.4	7
19	M	51	CABG	7.5	7.5
20	M	50	CABG	8.2	9
21	M	41	AVR/MVR	13.9	13
*5	F		REPAIR ASD		
*9	M		REPAIR ASD		

MEAN \pm 52.4 \pm 9.8 \pm 9.9
S.D. \pm 9.16 \pm 2.09 \pm 2.37

* Not included in statistical analysis

Abbreviations: CABG = CORONARY ARTERY BYPASS GRAFT; AVR = AORTIC VALVE REPLACEMENT;
ASD = ATRIAL SEPTAL DEFECT; MVR = MITRAL VALVE REPLACEMENT.

TABLE 21

Comparison of Echocardiographic Left Ventricular Wall Thickness (LVWT) with Direct Post Mortem Measurement

AGE (YEARS)	DIAGNOSIS	PLVWT (mm)		AUTOPSY
		ECHOd	ECHOS	
46	AS (POST AVR)	21	26	26
48	POST CABG	9	16.6	17
55	MI	10	17	18
67	MVD	8.8	13.8	14.5
71	IHD	8.2	13	13.5

57.4
± 11.2

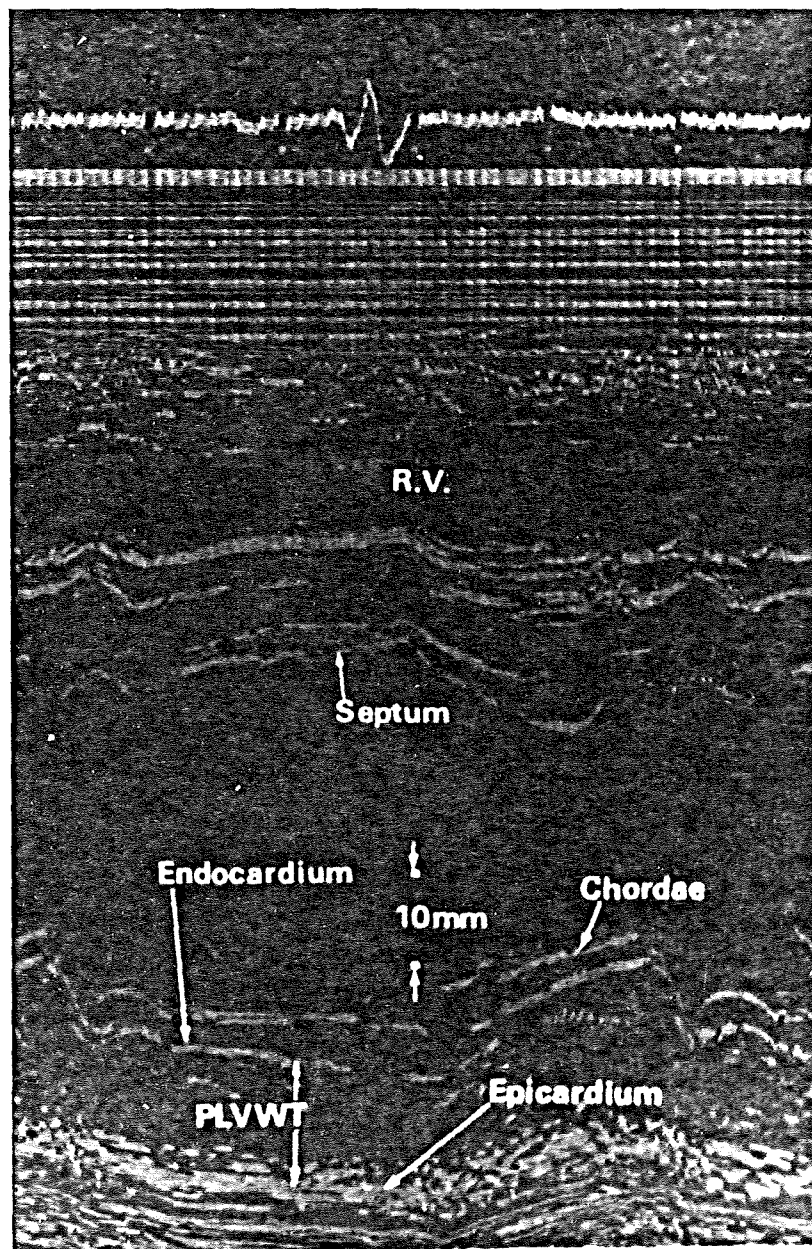
11.4
± 5.41

17.3
± 5.17

17.8
± 4.93

Abbreviations: AS = AORTIC STENOSIS; AVR = AORTIC VALVE REPLACEMENT;
CABG = CORONARY ARTERY BYPASS GRAFT; MI = MYOCARDIAL INFARCTION;
MVD = MITRAL VALVE DISEASE; IHD = ISCHAEMIC HEART DISEASE.

FIGURE 27

LEFT VENTRICULAR ECHOGRAM

The autopsy group comprised five other cardiac patients (table 21) who had undergone echocardiography within one month of their death.

Echocardiography

Echocardiography was performed using an Ekoline 20 echocardiograph*, and a Unirad 2.25 MHz transducer interfaced with an Ekoline strip chart recorder operating at 100 mm/sec. Echograms of the left ventricle were obtained in a standard manner with the patient semi-recumbent in the left lateral position, by positioning the transducer at the left sternal edge in the third or fourth intercostal space and directing it in an inferior and slightly lateral direction so that the ultrasound pathway transversed the left ventricular cavity at a level corresponding to the tips of the mitral valve leaflets (Feigenbaum, 1976). The diastolic measurement of posterior wall thickness, using leading edge methodology, (Sahn, De Maria and Kisslo, et al, 1978) was made at the point immediately prior to the atrial contribution to ventricular filling - calculating the mean value over four consecutive cardiac cycles. The systolic dimension was measured at the peak of posterior wall motion using the same criteria. Measurements were only performed on high quality echograms which permitted unambiguous assessment of wall thickness. (Figure 27).

Echocardiography was performed one to two days before surgery, while studies had been carried out within one month of death in the autopsy group.

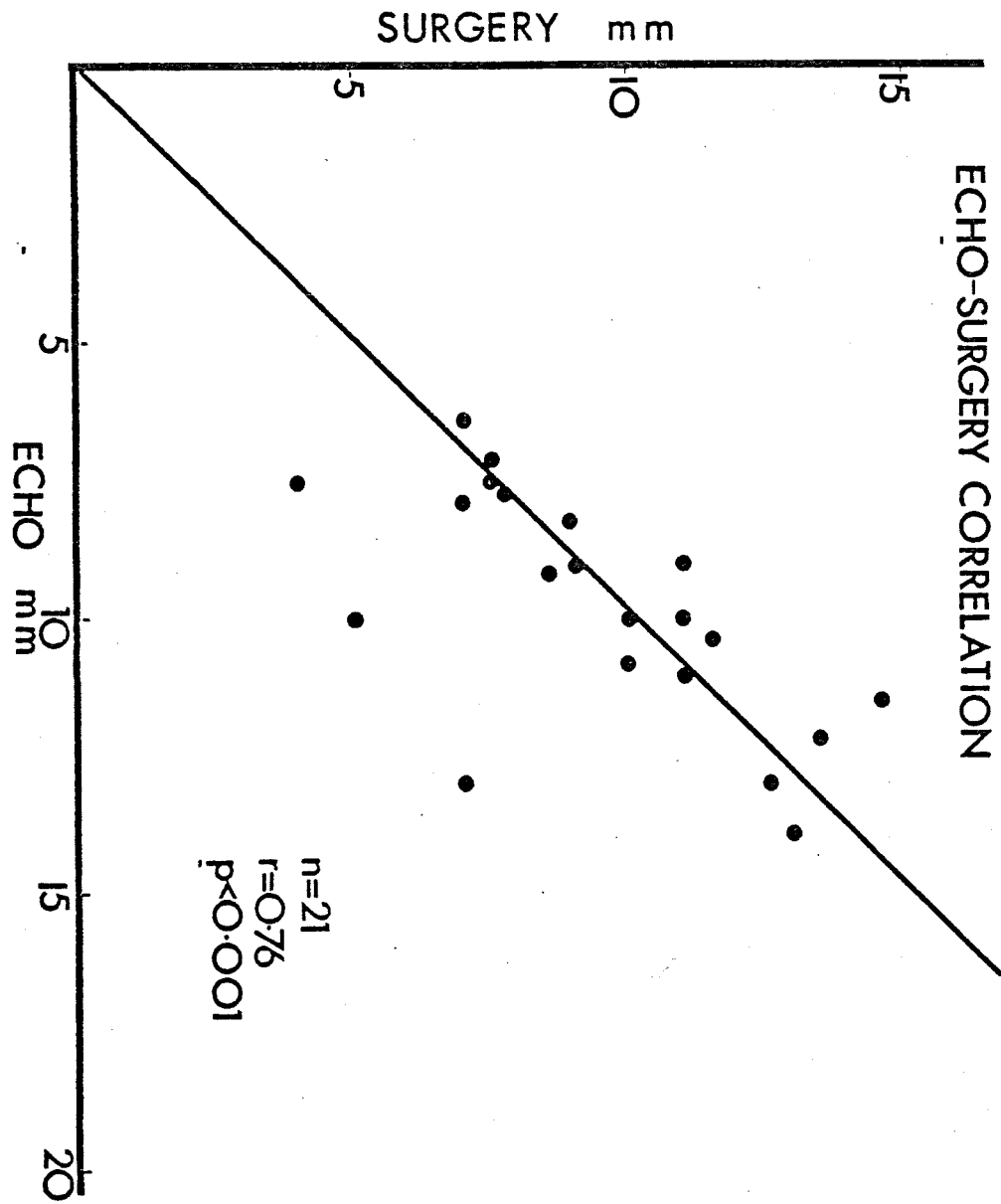
* Smith Kline Instruments, Inc. Sunnyvale, California 94086.

Surgery

Direct measurement of posterior left ventricular wall thickness was performed by the same surgeon upon hearts in asystole under the influence of hypothermic cardioplegia - a state corresponding to physiological diastole (Melrose, Dreyer, Bentall and Baker, 1955 and Hearse, Stewart and Braimbridge, 1975) with patients on cardio-pulmonary bypass. The heart was lifted and rotated medially in its long axis so that the area of the left ventricle just below the inferior border of the left atrium was visualised. A specialised measurement probe (fig 28) was then directed in a direction perpendicular to the epicardial surface. The sliding collar was advanced to rest lightly upon the epicardium and the adjusting screw tightened. The measurement of the gap between the lower surface of the collar and the upper aspect of the bulb by calipers was taken as the measurement of posterior left ventricular wall thickness.

The surgeon was unable to obtain optimal anatomic positioning for direct measurement in the hearts of subjects 5 and 9, who were both undergoing repair of atrial septal defect. An additional complication was the resumption of contractility during measurement, perhaps as a result of sub-optimum hypothermia. Despite achieving good anatomical positioning in the heart of subject 8, the exact point of endocardial contact could not be confidently felt. All other measurements were deemed satisfactory by the surgeon, who was unaware of echocardiographic dimensions. No complications resulted from the use of the measurement probe.

FIGURE 29



The probe was devised after a series of trials in the post mortem room using a modified venepuncture needle - initially with a rubber band wound around the tip and finally with a dot of solder. The latter modification allowed the needle to impinge on the endocardial surface of the left ventricle during slow withdrawal and appeared to cause no significant damage when fully withdrawn.

Specifications as shown in figure 28 were given to the New South Wales Institute of Technology who manufactured two probes from stainless steel. Between procedures probes were thoroughly washed in Cidex and then gas sterilised.

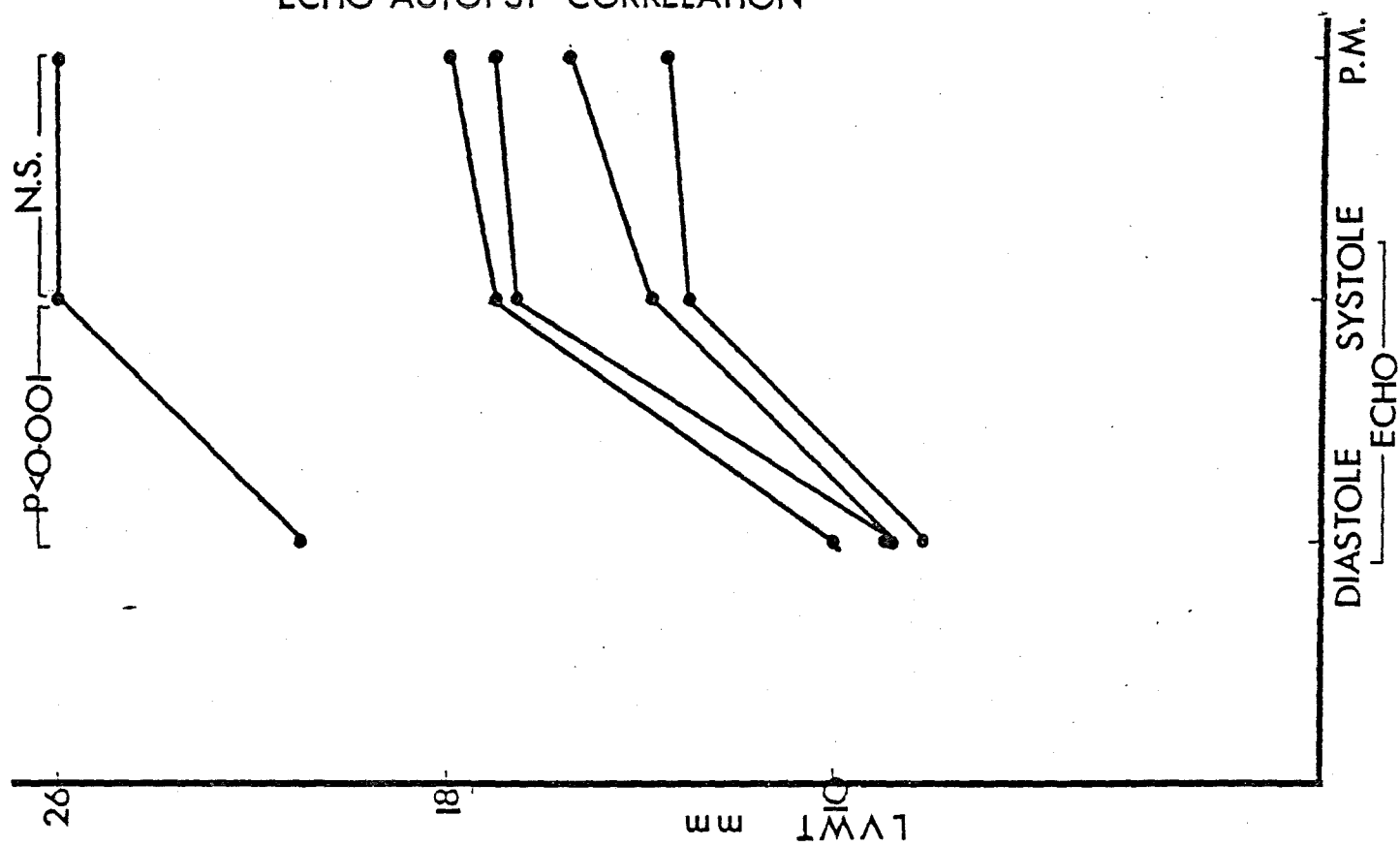
Post Mortem

Following removal of the heart at autopsy direct measurement of posterior left ventricular wall thickness was performed using the probe in similar fashion to that described at surgery. The average period from time of death to direct measurement at autopsy was 16 hours (range 10-22 hours).

Direct measurement of posterior wall thickness was also carried out at 19 consecutive, routine autopsies, in patients where no echocardiography had been performed, by two independent observers. This manoeuvre served as a modified test of reproducibility for the direct measurement technique.

FIGURE 30

ECHO-AUTOPSY CORRELATION



Statistical Analysis

Data were analysed by Student's t Test, with appropriate degrees of freedom, and least mean squares linear regression.

Data on patients 5 and 9 in the surgical group were not included in the final statistical analysis as diastolic/systolic separation was not possible during operative measurement.

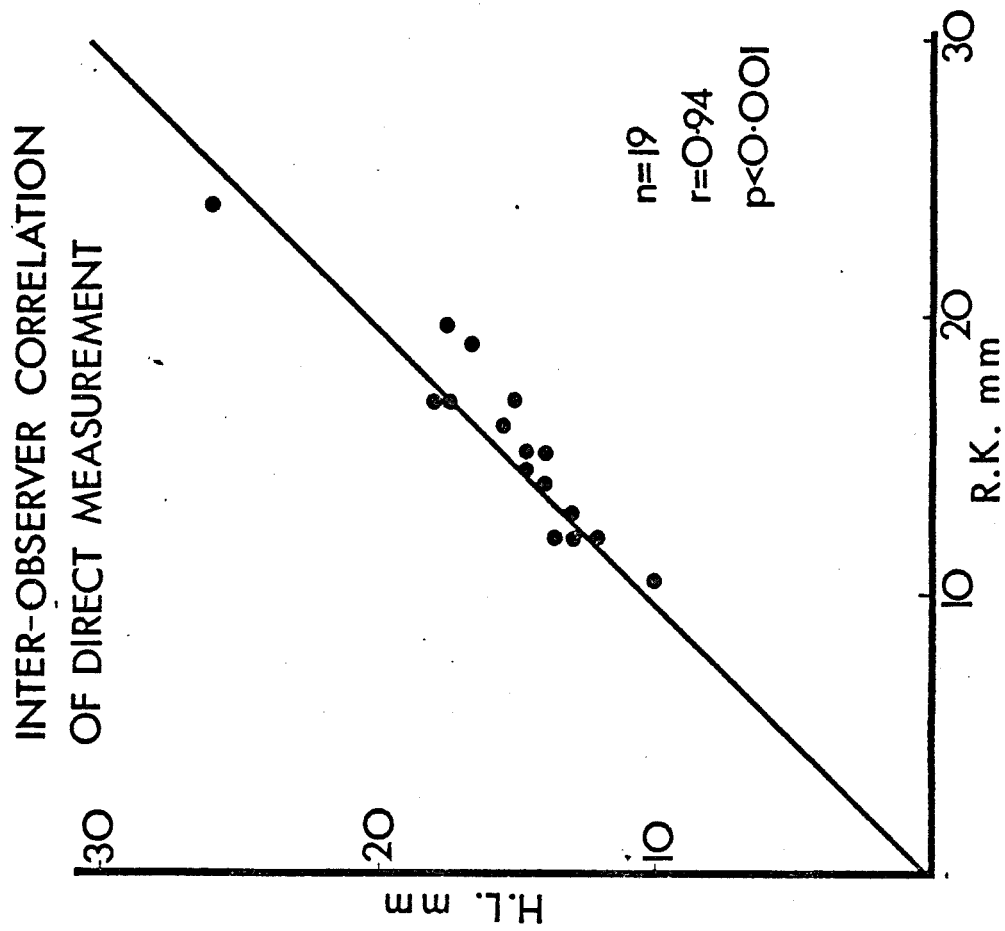
Results

The comparative data are represented in figures 29 and 30.

In the surgical group wall thickness ranged from 7-14.5 mm (9.9 ± 2.37 mm) upon direct measurement, while the end-diastolic echocardiographic range was 7.1 - 13.9 mm (8.9 ± 2.09 mm). The maximum difference between techniques was 4.8 mm, in subject 8 (table 20), where direct measurement difficulty was encountered. The results therefore show a close correlation ($r=0.76$; $P < 0.001$). Neither measurement technique consistently under or overestimated when compared to the other.

Post mortem left ventricular wall thickness ranged from 13.5 - 26 mm (17.8 ± 4.93 mm). This wide range perhaps reflects the diverse cardiac pathology present (table 21). The echocardiographic end diastolic range was 8.2 - 21 mm (11.4 ± 5.41 mm) and this was significantly less than autopsy figures ($P < 0.001$) (fig 30). There was no significant difference, however, between the systolic dimension range of values (13 - 26 mm; 17.3 ± 5.17) and those obtained at autopsy.

FIGURE 31



The values of posterior wall thickness obtained by two independent observers at routine autopsies displayed very close correlation ($r=0.94$; $P < 0.001$) (fig 31).

Discussion

It has been suggested that left ventricular mass may be a more reliable and useful predictor of anatomical left ventricular hypertrophy (Devereux and Reichek, 1977). The derivation of mass by echocardiographic criteria, however, requires a number of important assumptions, chief among these being that the left ventricular cavity is truly ellipsoid. Cardiac hypertrophy, however, is often associated with ventricular dilatation or asynergy, particularly in the mature hypertensive, and in these conditions extrapolation of one-dimensional data has been found to be inaccurate (Teichholz, Kreulen, Herman and Gorlin, 1976 and Bhatt, Isabel-Jones, Villoria, Nakazawa, Yabek, Marks and Jarmakani, 1978).

The measurement of posterior left ventricular wall thickness requires no assumptions or extrapolation and results presented here confirm the anatomical accuracy of the technique.

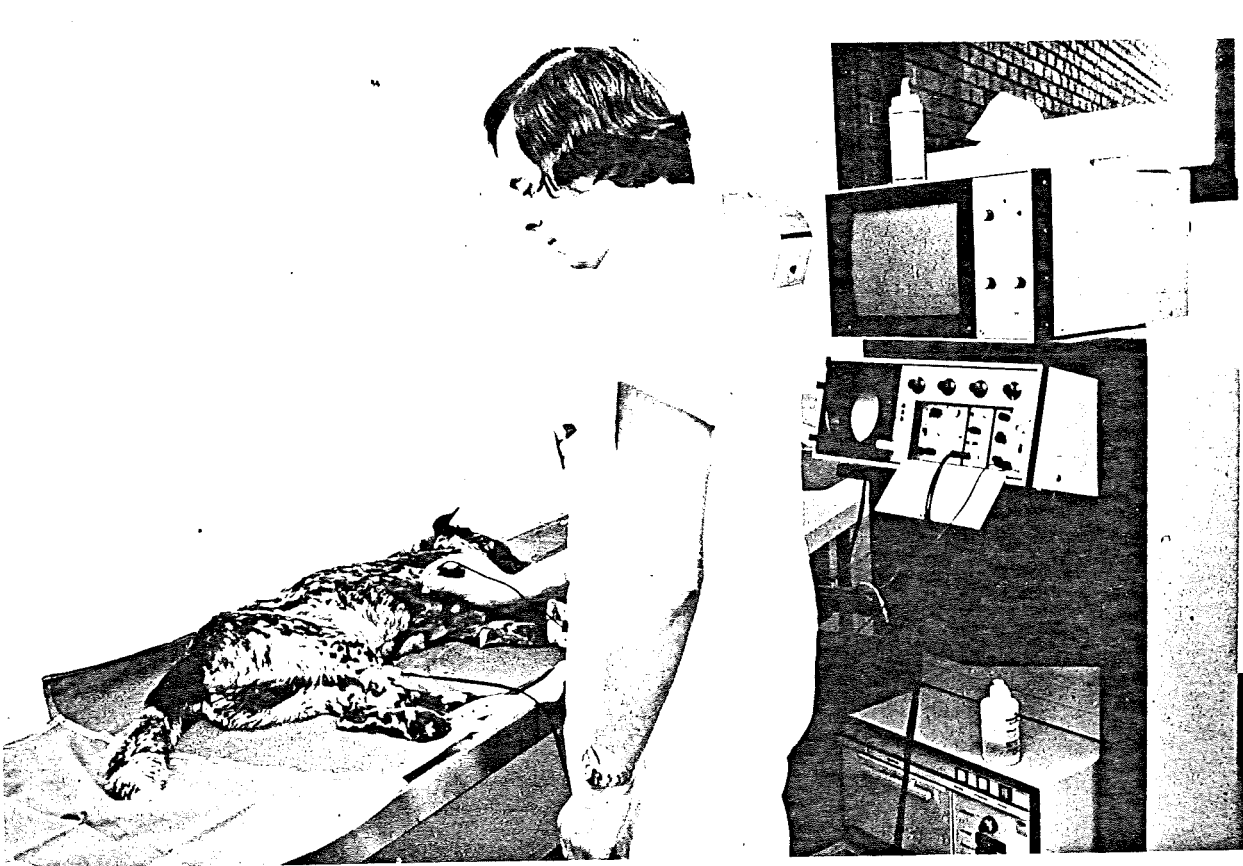
Measurement of Posterior Left Ventricular Wall Thickness in Dogs
by M-mode Echocardiography

Despite evidence presented attesting to the anatomical accuracy of the echocardiographic measurement of left ventricular wall thickness no previous study had attempted to examine the sensitivity of M-mode echocardiography in determining serial changes of left ventricular wall thickness in response to increasing blood pressure.

A dog model had a number of attractions in this area:

- 1 The small anteroposterior diameter of the dog chest allowed for the use of a higher frequency transducer - 5 MHz - with a corresponding increase in resolution of echo recordings.
- 2 The use of the dog allowed the placing of an epicardial marker, prior to the commencement of studies, ensuring that the same area of the posterior left ventricular wall was measured by echocardiography and direct measurement when the animal was sacrificed.
- 3 The animal could be rendered hypertensive.
- 4 It was hoped to answer the question: In what phase of the cardiac cycle does the heart stop at death? Feigenbaum, et al, (1968) and Schroeder, et al, (1969) had suggested that this was in the diastolic phase, while Maron, et al, (1977) found close correlation with the systolic dimension.

FIGURE 32



Methods

Echocardiography

M-mode echocardiography was performed using the equipment already described, but with the substitution of the 2.25 MHz transducer by a 5 MHz Smith Kline and French, non-focussed paediatric transducer.

To ensure good transducer contact an area over the right chest wall was shaved at the level of the third and fourth interspaces. The dog was placed on his left side with limbs extended and the transducer placed in the third or fourth interspace at the right sternal border (fig 32).

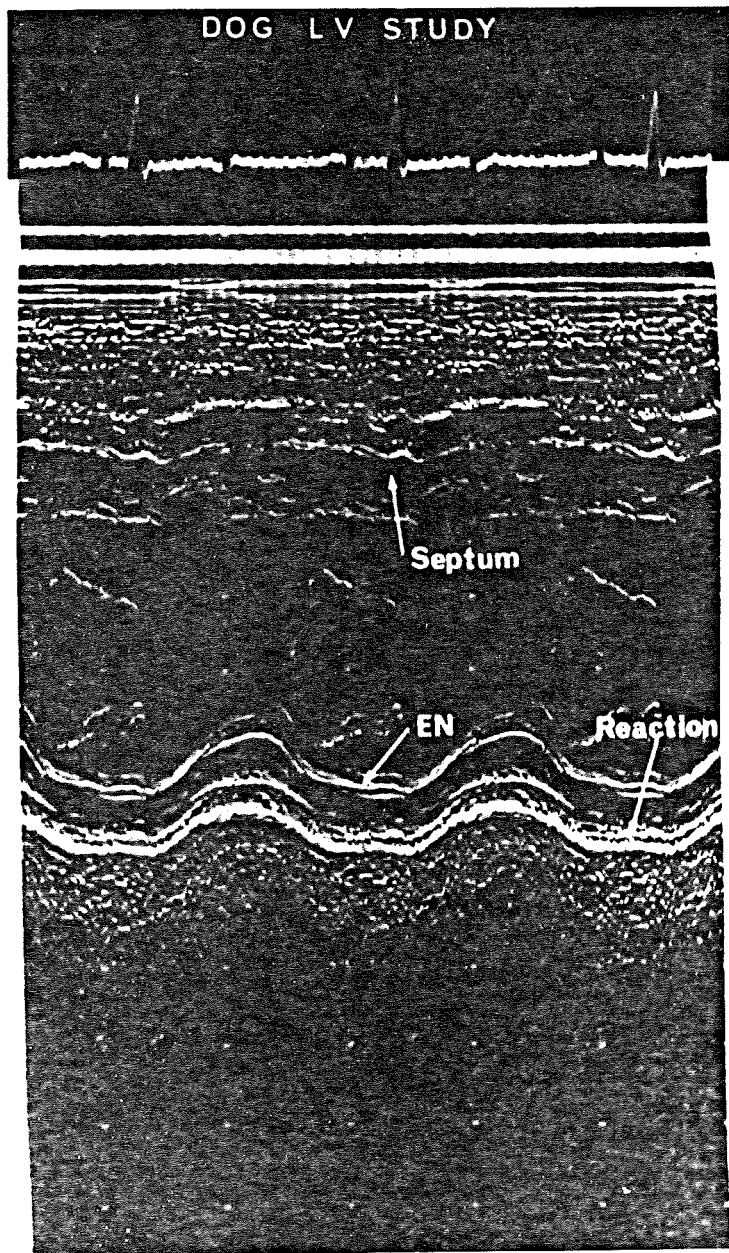
All animals were anaesthetised for the procedure with a small amount of intravenous sodium pentobarbitone. Echocardiography is possible to perform in conscious dogs, but as studies had to be carried out in a clinical area it was necessary to transport the animals whilst asleep.

Exceptionally high quality echocardiograms were readily obtained on all animals. Posterior left ventricular wall thickness was measured in end diastole and systole, (Sahn, et al, 1978), at the point where the epicardial marker was identified (fig 33).

Electrocardiography

Simultaneous electrocardiographic tracing was obtained via electrodes placed on shaved areas of three limbs.

FIGURE 33



Hypertension Induction

This procedure was performed under strict aseptic conditions with the animal anaesthetised by sodium pentobarbitone, 30 mg/kg, intravenously followed by tracheal intubation and subsequent respiration maintained via a respirator using an air/oxygen mixture.

Both kidneys were identified via a mid-line laparotomy. The right kidney was removed after appropriate haemostatic procedures. Following removal of perirenal fat and connective tissue and division of the capsular anastamotic vessels, the left kidney was wrapped in cellophane, which had previously been immersed in alcohol and then warm saline. This was then secured with a loose ligature, so that no compressive effect was exerted on the renal vessels or ureter. This procedure was based on the one-kidney, wrap-nephrectomy model of Page (1939).

Intra-arterial blood pressure was measured at all times with the animal in the anaesthetised state, recognising that this may have resulted in artificially high levels. Blood pressure was recorded from the femoral artery via a Statham transducer and a Grass multi-channel recorder.

Cardiac Surgery

Using the same anaesthetic procedure a left thoracotomy was performed. The pericardium was opened and a stainless steel disc (4 x 4 mm) was sutured on to the epicardial surface of the posterior left ventricle 5 mm below the inferior border of the left auricle. The pericardium was closed and the chest wound closed in layers after full lung inflation.

Apart from an accidental nick of the left anterior descending coronary artery in one dog, which responded to pressure - no intra-operative complications resulted, either in the chest or the abdomen.

Experimental Animals

Five, male, mongrel dogs obtained from Sydney University Animal House took part in the study.

Animals were sacrificed by an overdose of anaesthesia upon completion of the study and the chest immediately opened and the heart removed. The pericardium was opened and the metal marker identified. At this point wall thickness was measured, using the same measurement probe previously described (fig 28). The hearts, emptied of blood, were then wrapped in moist gauze swabs and the measurement was repeated after 6 hours.

TABLE 22

Blood Pressure and Echocardiographic Characteristics of Study Animals

DOG	Blood Pressure (mmHg)		Echo Measurement (mm)				Direct Measurement (mm)	
	(i)	(ii)	(i)	(ii)	(i)	(ii)	0	6 (Hours)
			S	S	D	D		
1	140/80	220/110	10.0	10.5	8.7	8.9	10	14
2	135/80	200/120	10.6	10.9	8.5	8.8	9.8	14
3	150/84	190/110	10.0	10.0	8.2	9.2	10	16
4	144/84	200/105	10.4	10.8	8.6	8.8	12	16.5
5	150/80	200/110	9.8	10.0	7.8	8.1	10	14.5

Blood pressure (i) and (ii) pre and post wrap nephrectomy; Echocardiographic measurement of posterior left ventricular wall thickness in diastole (D) and systole (S); (i) before wrap nephrectomy and (ii) immediately before sacrifice.

Results

Blood Pressure

The mean baseline blood pressure of $143.8/81.6 \pm 6.50/2.19$ mmHg rose to $202/111 \pm 10.95/5.48$ mmHg ($P < 0.001$) after a mean period of 6.6 ± 4.2 weeks. This rise in blood pressure was seen in all animals at the end of the first three days after wrap nephrectomy. One dog (4) had to be sacrificed after only eight days because of terminal uraemia.

Echocardiographic and direct measurements, together with blood pressure, are shown in table 22. Interestingly, the marked degree of systolic wall thickening during the cardiac cycle seen in humans is not present in the dog heart. The diastolic echo measurements were by and large about 10% less than the direct measurement, when the heart was empty of blood. The systolic dimension was between 5 and 10% greater.

An interesting finding and worthy of note was the increase in posterior left ventricular wall thickness during the six hour period after death. This increase - 4.7 ± 0.71 mm - was highly significant ($P < 0.001$).

Discussion

The degree of hypertrophy following hypertension induction was disappointing and this perhaps casts some doubt on the validity of assessing echocardiographic sensitivity in view of the small numbers presented here. Having said that, however, the absolute accuracy of the technique was again confirmed with results very similar to those of Mashiro, Nelson and Cohn, et al, (1976) and Salcedo, et al, (1979) who only reported end-diastolic echocardiographic measurements and

direct measurement immediately upon death.

In the human heart the left ventricular free wall thickens considerably during systole. Maron, et al, (1977), in an echocardiographic necropsy study of patients with asymmetric septal hypertrophy found that the abnormal septal free wall ratio of > 1.3 during life was not present at autopsy. This was explained by an increase in post mortem left ventricular wall thickness and it was concluded by the authors that hearts must therefore stop in systole. This increase in post mortem wall thickness and the close correlation with the echocardiographic systolic measurement has been confirmed by Larkin, et al, (1979). However, the findings in dogs suggest that the heart does not stop in systole, but rather that left ventricular wall thickening occurs in the first few hours after death in a rigor process.

The considerable systolic thickening in human hearts is not seen in the dog left ventricle and, for this reason, there is no correlation between the echocardiographic systolic measurement of left ventricular wall thickness and the post mortem measurement at six hours in the dog. In the human, however, it is suggested that the wall thickening which occurs after death quite coincidentally corresponds with the echocardiographic systolic measurement

CHAPTER TWELVE B - M - MODE ECHOCARDIOGRAPHY IN HYPERTENSION

"Echocardiography identifies anatomic and functional cardiac abnormalities in a large percentage of asymptomatic hypertensive subjects before abnormalities are detected by ECG or chest x-ray." Savage, et al, 1979.

"Hypertensive heart disease can be recognised by echocardiography as a continuum from an otherwise normal heart to left ventricular hypertrophy." Dunn, et al, 1977.

Echocardiographic Measurement of Posterior Left Ventricular Wall Thickness in Normotensives and Borderline Hypertensives

In established hypertension cardiac hypertrophy appears to have a close relationship with the level of the systemic arterial pressure and this later stage of the process has been extensively studied (Frolich, Tarazi and Dustan, 1971; and Frolich, 1977). By contrast there have been few studies of possible hypertrophy in the earlier stages of the condition, particularly in borderline hypertension.

The recent advent of non-invasive techniques, particularly echocardiography, has provided a reliable and accurate method for the measurement of ventricular wall thickness.

M-mode echocardiography was performed in normotensives and in borderline individuals before and upon completion of the six month placebo-controlled trial of atenolol.

FIGURE 34

RELATIONSHIP BETWEEN 24 HOUR SYSTOLIC AND DIASTOLIC ARTERIAL
PRESSURE AND ECHO SEPTUM AND WALL THICKNESS

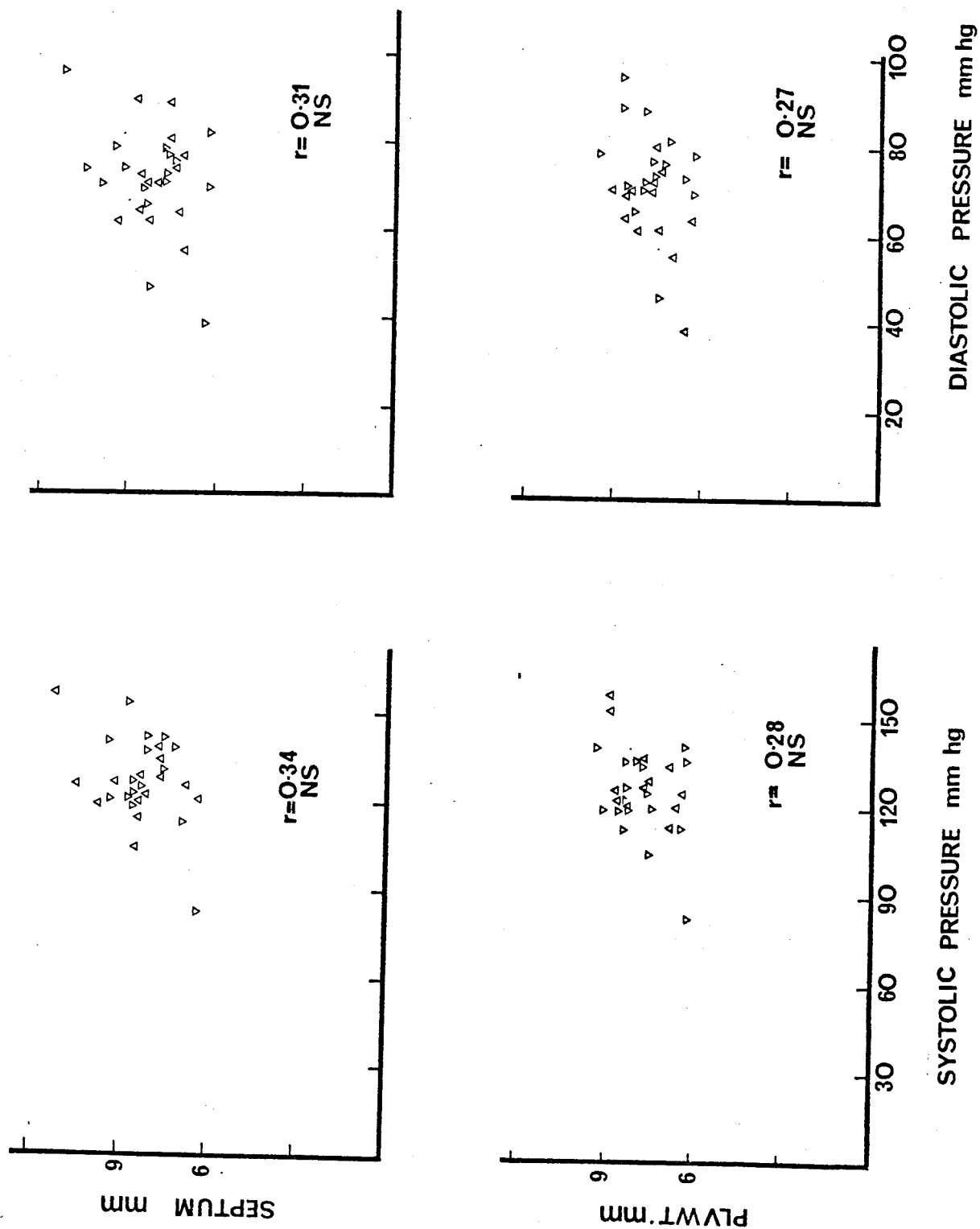
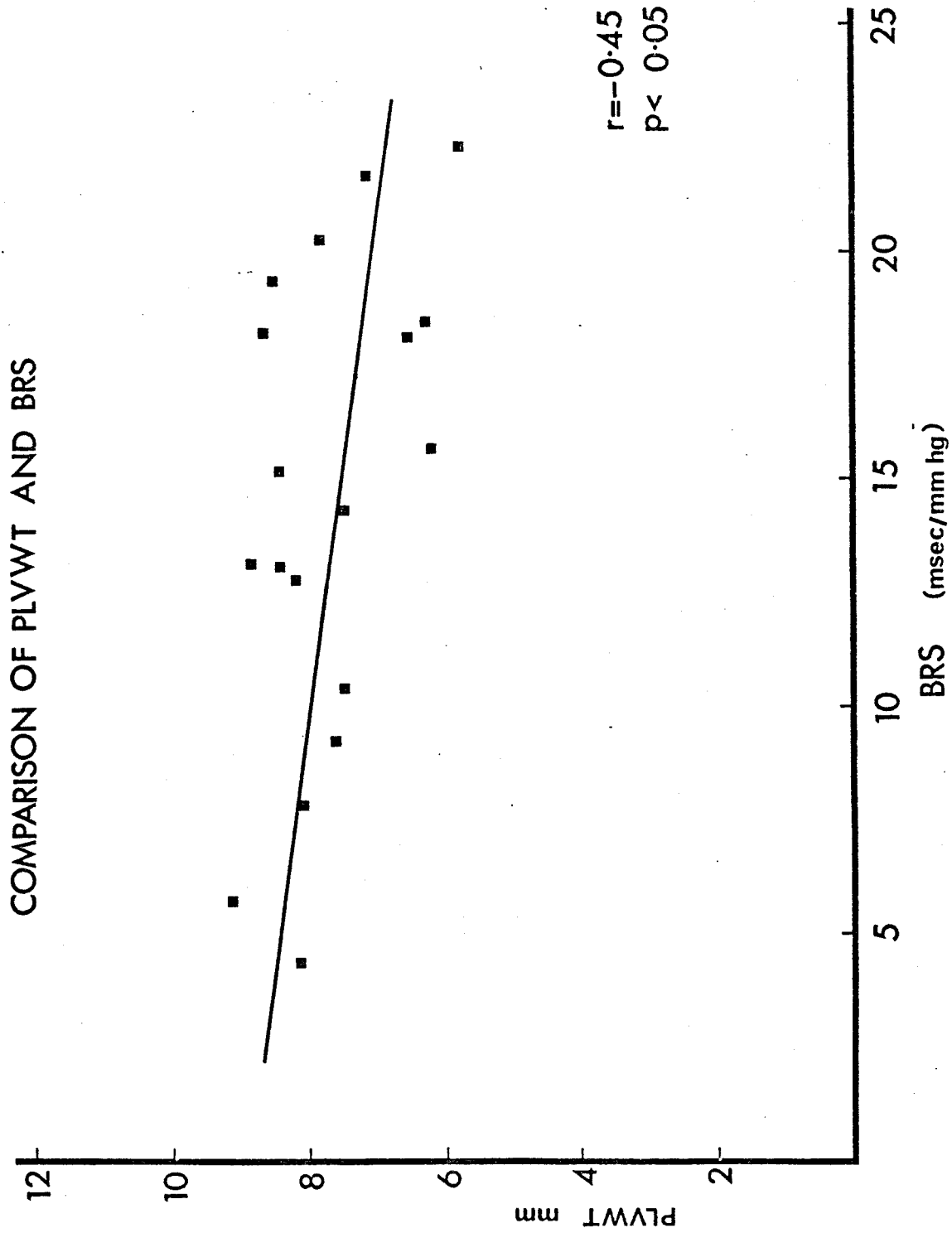


FIGURE 35



Methods

Echocardiograms were performed in the manner already described using the same equipment and measurement technique. Studies were repeated in hypertensive subjects after the six month placebo-controlled trial of atenolol.

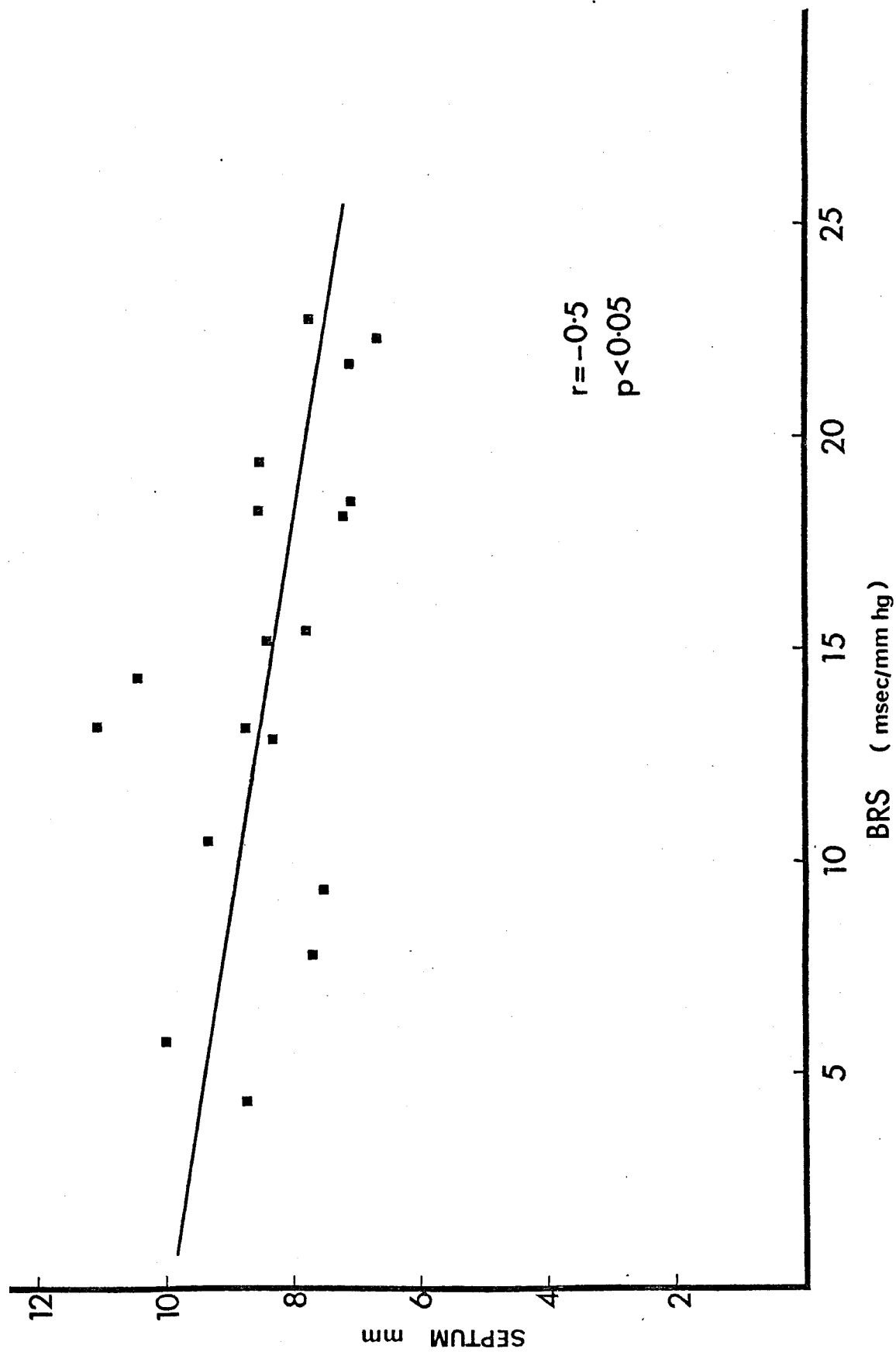
Results were analysed using Student t Test for paired and non-paired data and analysis of variance.

Results

Posterior left ventricular wall thickness was slightly increased in normotensive individuals, but this difference was not statistically significant (8.2 ± 0.65 mm vs 7.7 ± 0.87 mm; NS). Septal thickness, however, was significantly greater in normotensives (8.9 ± 1.49 mm vs 8.1 ± 1.04 mm; $P < 0.05$). The values for posterior wall and septal thickness were not significantly different in hypertensive individuals following randomisation for the six month placebo-controlled trial of atenolol. At the end of six months, however, posterior wall thickness was unchanged in atenolol-treated subjects (7.75 ± 0.92 mm vs 7.75 ± 1.18 mm; NS), but had increased in the placebo group (7.70 ± 0.84 mm vs 8.54 ± 0.83 ; $P < 0.01$). Similarly there was a significant increase in septal thickness in placebo subjects (8.08 ± 0.99 mm vs 8.94 ± 1.41 ; $P < 0.05$), but no increase in the actively treated group (8.17 ± 1.11 mm vs 8.21 ± 1.38 mm; NS).

No correlation was found between 24 hour intra-arterial systolic and diastolic arterial pressure and septal and posterior wall thickness. (Fig 34).

COMPARISON OF SEPTAL THICKNESS AND BRS



Data were further analysed by extracting echocardiographic values for ventricular and septal thickness of the 7 individuals with electrocardiographic evidence of left ventricular hypertrophy. Mean posterior wall thickness was 7.9 ± 1.06 mm in the group with electrocardiographic criteria but was not significantly different from the remaining 23 with non-hypertrophy (7.6 ± 0.80 ; NS). Findings were similar for septal thickness (8.1 ± 0.69 vs 8.1 ± 0.35 mm respectively; NS).

Influence of the Autonomic Nervous System on Posterior Wall and Septal Thickness

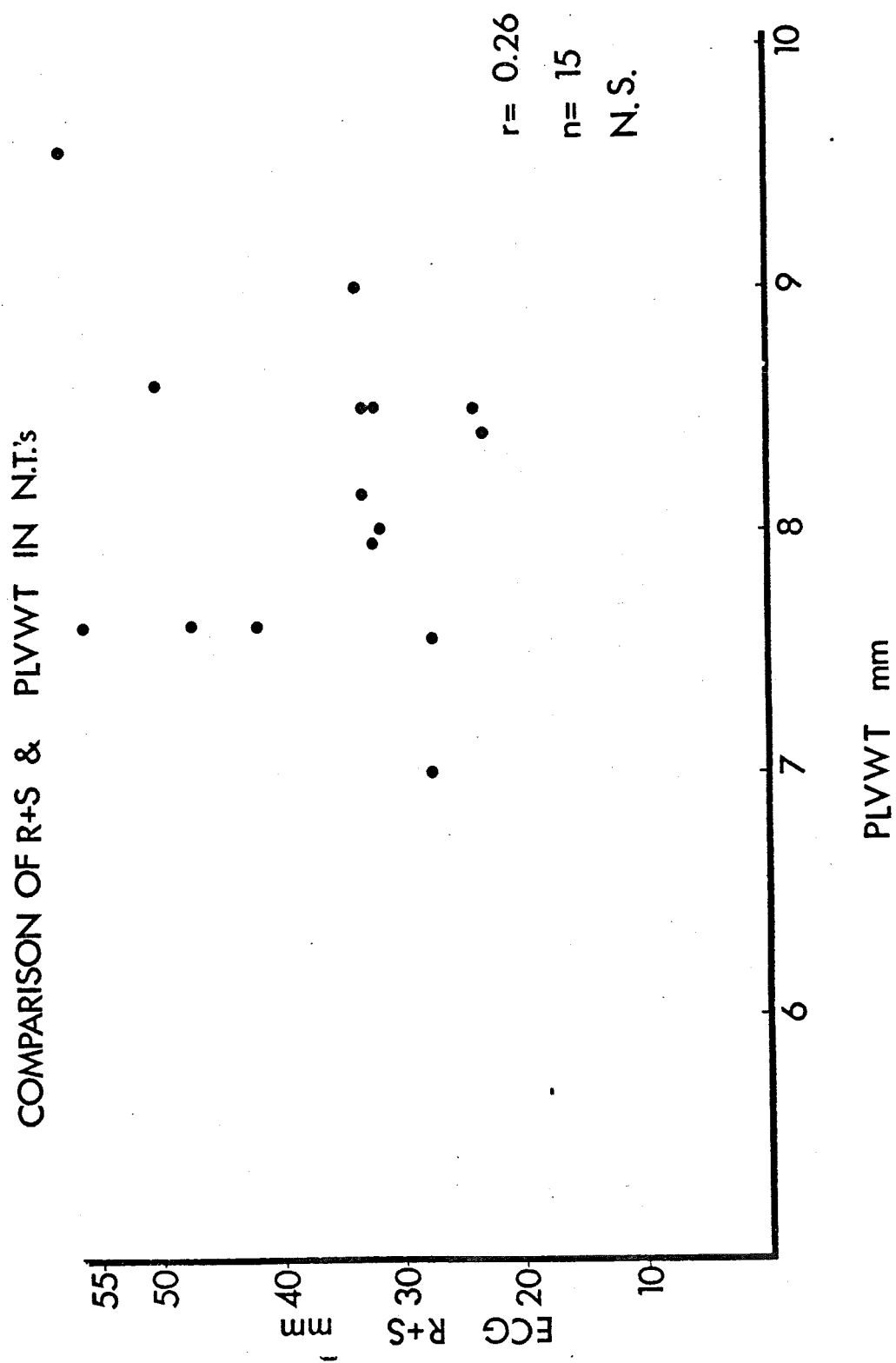
Studies in young spontaneously hypertensive rats have shown that cardiac and vascular hypertrophy occur before the blood pressure rise (Sen, Tarazi and Khairallah, et al, 1974 and Yamori, et al, 1979). The precise reason for these appearances is unclear, but Safar, et al, (1979), who found asymmetric septal hypertrophy in young borderline hypertensives, have suggested a possible abnormality of the autonomic nervous system as a contributory factor.

It was decided to examine the baroreflex sensitivity of borderline hypertensives and compare this with echocardiographically measured septal and posterior left ventricular wall thickness.

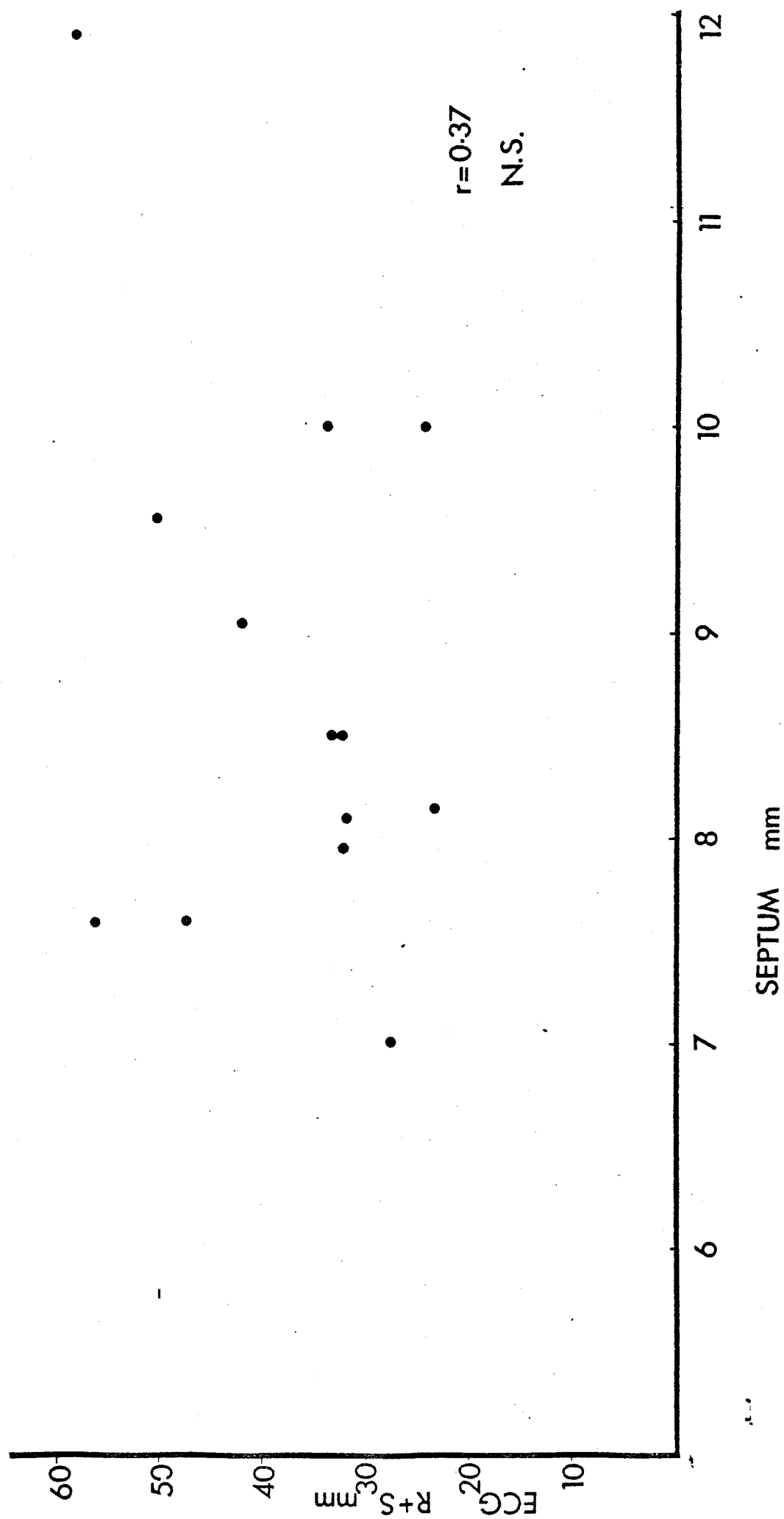
Results

Data were analysed by linear regression analysis and are displayed in figures 35 and 36. There was a significant inverse relationship between baroreflex sensitivity and septal and posterior wall thickness ($r=-0.50$, $r=-0.45$ respectively; $P < 0.05$).

FIGURE 37



COMPARISON OF R+S AND SEPTUM IN N.T.'s



COMPARISON OF ELECTROCARDIOGRAPHIC PRECORDIAL AND ORTHOGONAL
VOLTAGE WITH POSTERIOR WALL AND SEPTAL THICKNESS MEASURED
BY M-MODE ECHOCARDIOGRAPHY

Various authors have described conflicting findings in their comparison of electrocardiographic and vectorcardiographic determinants of left ventricular mass and hypertrophy with more direct methods such as biplane angiography or echocardiography. On balance, however, the relationship has been poor except in the presence of unequivocal left ventricular hypertrophy (Carter and Estes, 1964).

There are no reported studies in borderline hypertension regarding a possible correlation between electrocardiographic precordial and orthogonal voltage and echocardiographically determined septal and posterior left ventricular wall thickness.

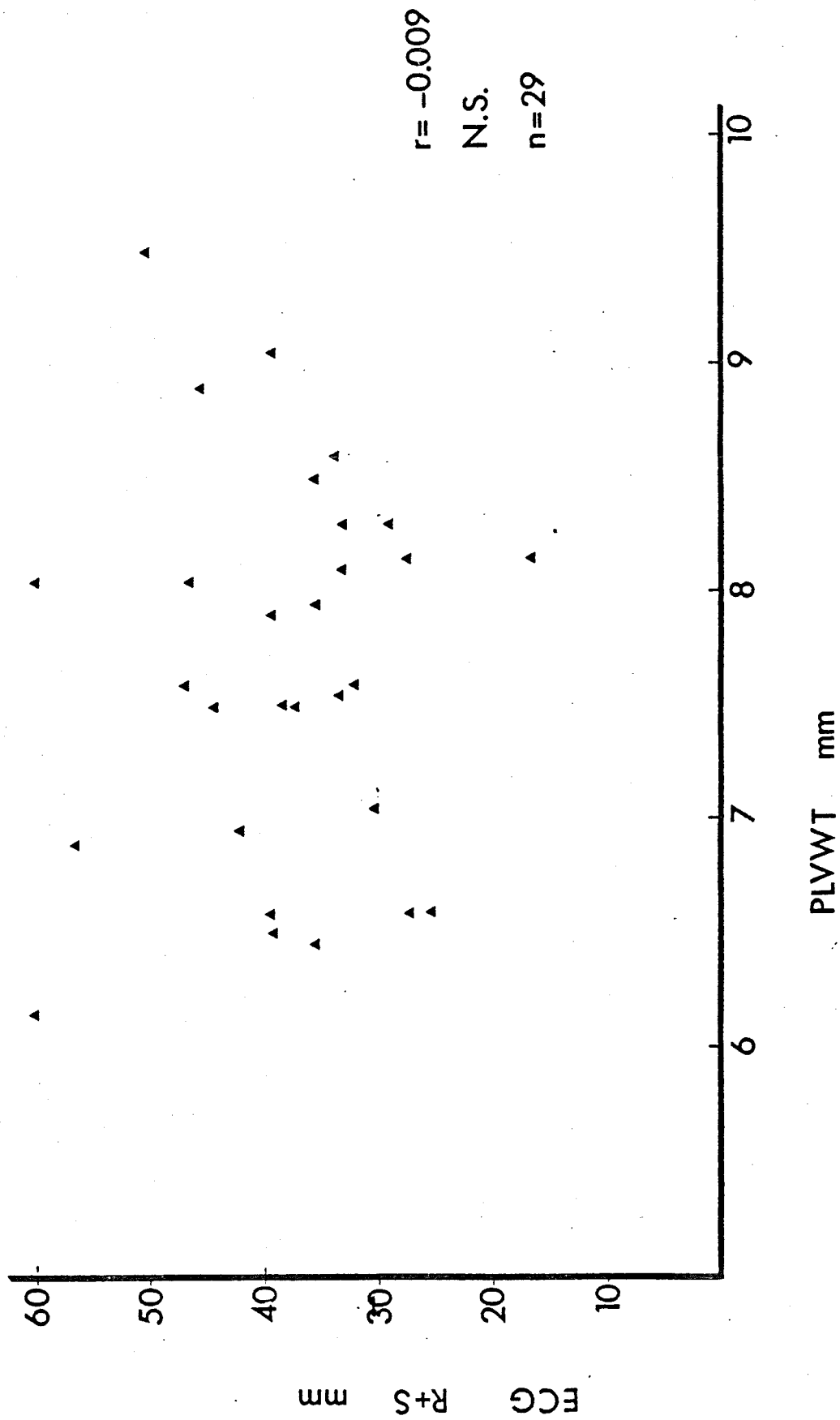
Results

Data were compared by linear regression analysis. No significant correlation was found between the sum of the maximum R + S in the precordial leads of the 12-lead electrocardiogram of borderline hypertensives when compared to the values for septal and posterior wall thickness ($r = -0.009$ and $r = 0.087$, respectively; figure 39 and 40) and this also applied to normotensives figure 37 and 38

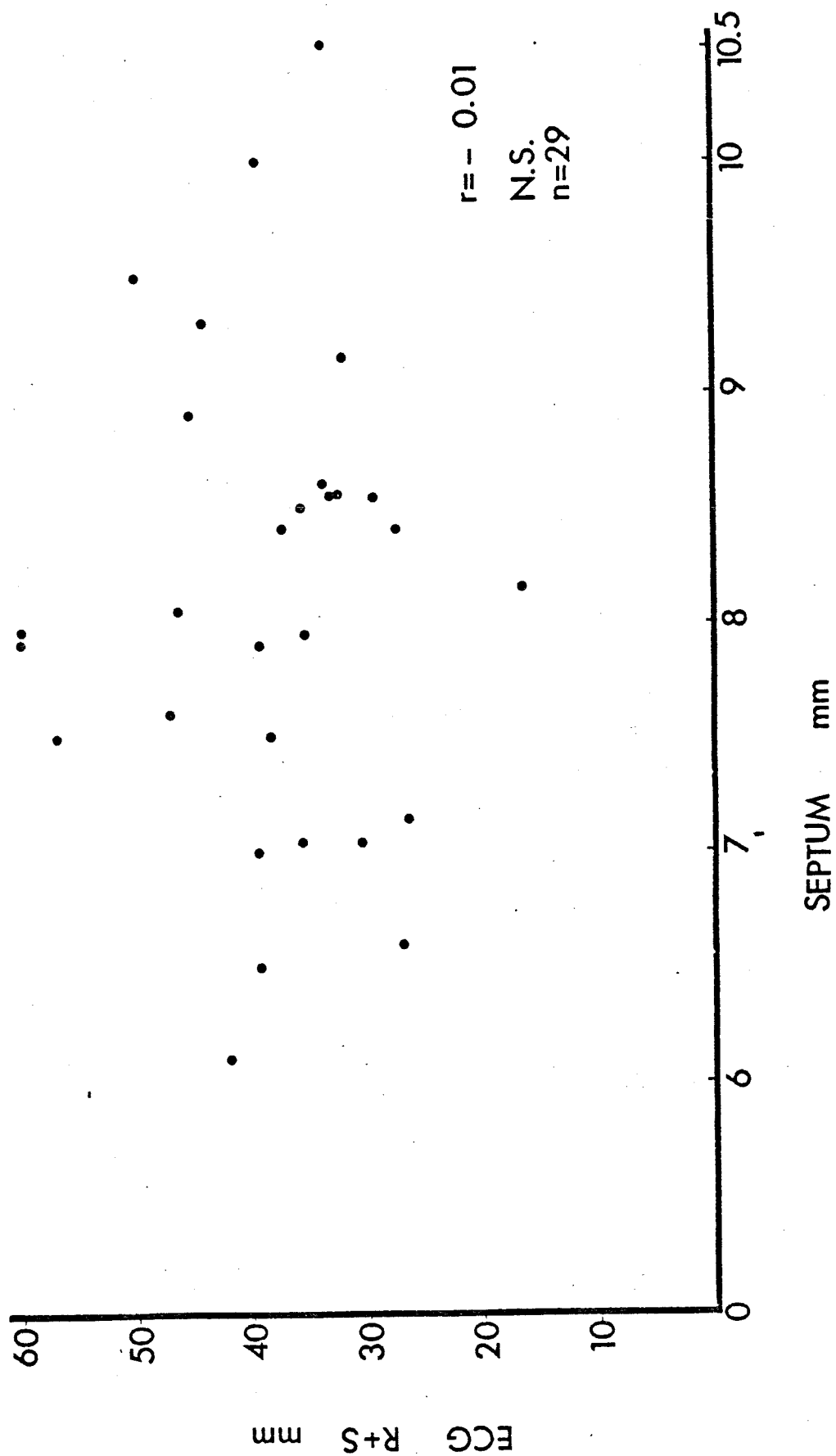
The maximum Frank lead QRS vector, V_f was also compared to the echocardiographic dimensions of septal and posterior wall thickness,

FIGURE 39

COMPARISON OF R+S & PLVWT IN B.H.T.'s



COMPARISON OF R+S & SEPTUM IN B.H.T.'s



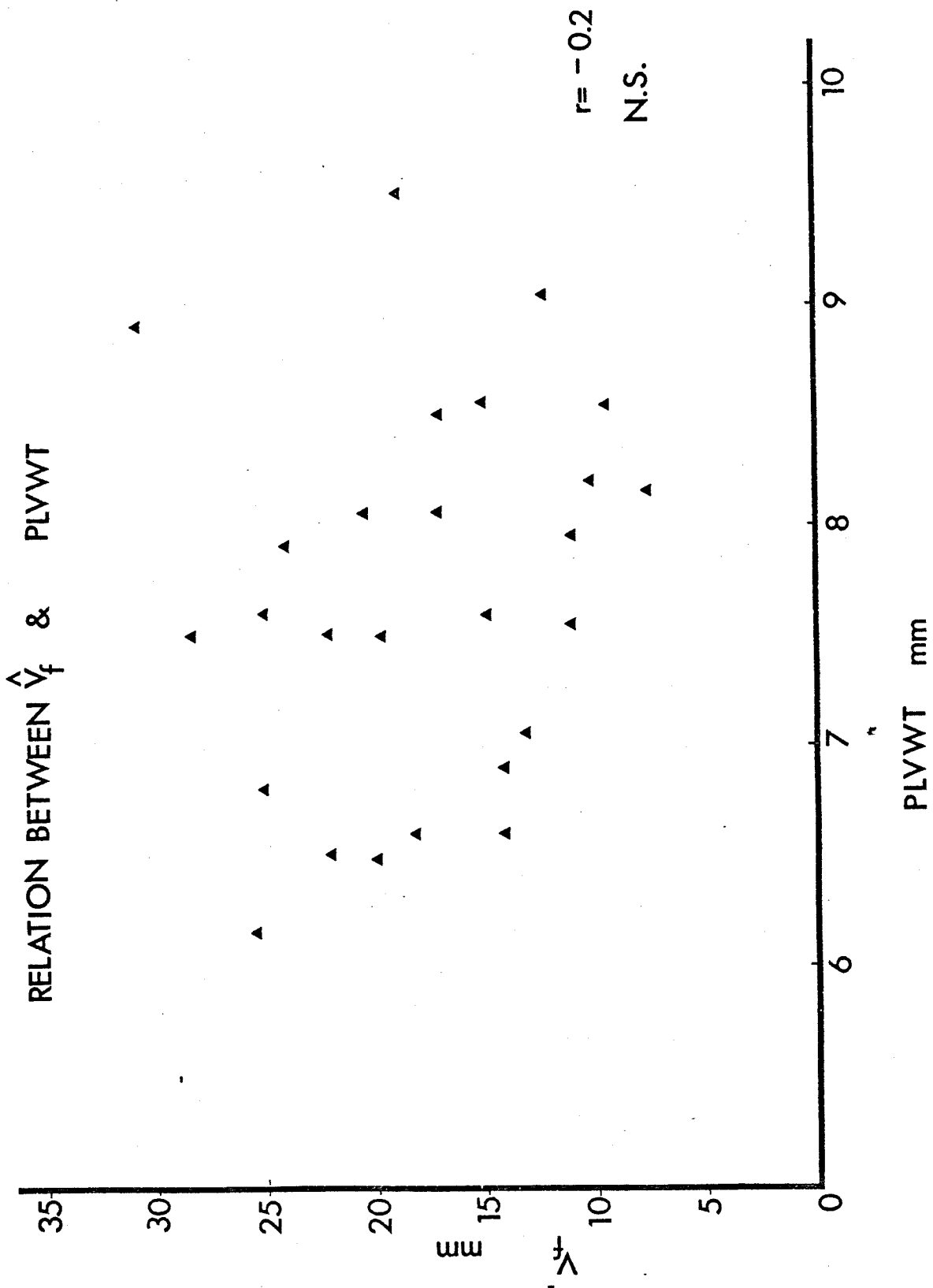
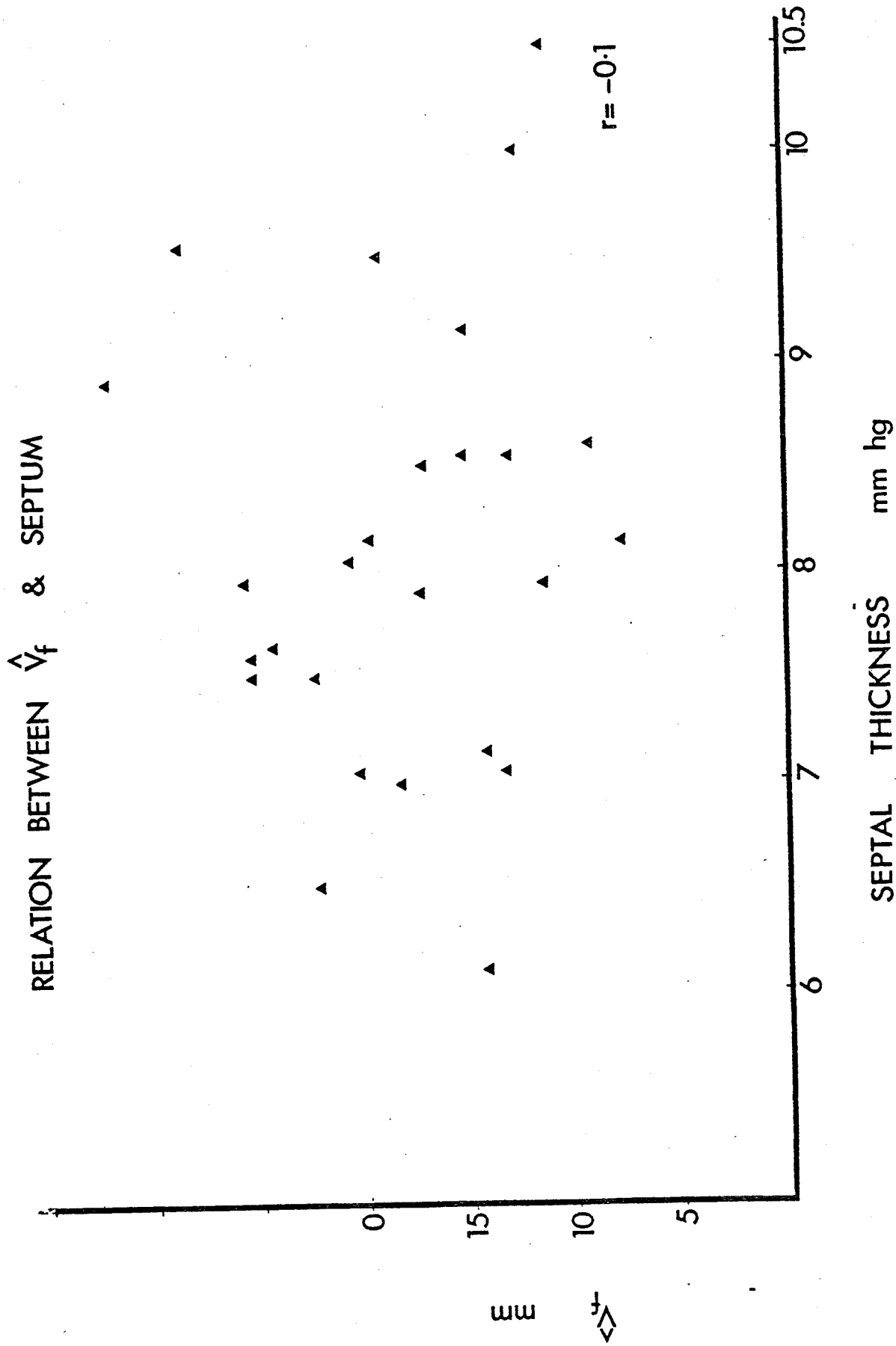


FIGURE 42



but results were similar to the electrocardiographic comparison
($r = -0.1$ and $r = -0.2$, respectively; figure 41 and 42).

APPENDIX I

BHT patients on NO therapy

Number of patients - 30

HOURS	SYSTOLIC	DIASTOLIC	HEART RATE
1	146 (15.43)	83 (10.24)	87 (12.97)
2	139 (15.92)	79 (10.54)	88 (19.7)
3	136 (17.21)	77 (12.25)	88 (20.54)
4	132 (17.02)	74 (12.55)	90 (24.35)
5	131 (19.19)	73 (13.88)	92 (25.51)
6	133 (19.43)	73 (14.4)	96 (27.03)
7	136 (18.83)	74 (13.96)	97 (26.99)
8	139 (18.58)	78 (13.11)	94 (21.3)
9	136 (22.01)	77 (15.3)	90 (19.09)
10	134 (20.51)	75 (15.88)	88 (18.86)
11	132 (18.83)	74 (14.26)	88 (18.17)
12	129 (17.9)	73 (12.8)	86 (19.09)
13	125 (16.39)	70 (12.06)	82 (18.87)
14	117 (19.83)	65 (14.66)	74 (16.61)
15	112 (22.47)	63 (16.24)	68 (13.97)
16	108 (20.77)	61 (15.18)	64 (13.93)
17	109 (17.78)	62 (13.71)	64 (11.77)
18	108 (18.25)	61 (15.28)	61 (12.16)
19	109 (19.99)	62 (16.16)	62 (10.47)
20	111 (18.69)	63 (14.95)	61 (11.29)
21	116 (18.08)	65 (13.46)	65 (12.72)
22	129 (17.68)	72 (12.65)	78 (15.6)
23	135 (19.5)	75 (14.15)	87 (20.35)
24	138 (18.25)	73 (15.14)	92 (27.14)

Normotensive patients

Number of patients - 15

HOURS	SYSTOLIC	DIASTOLIC	HEART RATE
1	132 (10.23)	72 (7.7)	88 (20.13)
2	126 (9.89)	69 (11.34)	93 (29.44)
3	124 (10.59)	67 (11.9)	91 (28.48)
4	123 (14.61)	65 (14.79)	93 (32.45)
5	121 (13.02)	62 (13.22)	97 (39.01)
6	120 (12.4)	63 (13.58)	95 (36.49)
7	124 (10.63)	66 (9.5)	94 (31.63)
8	127 (13.31)	67 (10.56)	95 (32.42)
9	121 (8.96)	66 (10.04)	90 (28.4)
10	121 (12.57)	65 (11.78)	90 (29.35)
11	119 (14.83)	64 (13.04)	90 (30.78)
12	118 (15.13)	63 (13.34)	91 (33.1)
13	116 (16.43)	62 (13.87)	86 (30.85)
14	108 (19.94)	56 (15.82)	80 (31.2)
15	100 (14.89)	52 (14.7)	75 (30.47)
16	101 (15.3)	53 (12.14)	73 (28.26)
17	97 (10.88)	51 (11.81)	69 (23.74)
18	95 (9.8)	51 (10.67)	65 (19.37)
19	97 (11.19)	53 (11.38)	65 (18.12)
20	101 (11.78)	55 (10.3)	64 (14.23)
21	101 (12.19)	54 (11.09)	65 (16.09)
22	108 (10.18)	57 (10.47)	73 (21.33)
23	119 (11.3)	62 (10.62)	89 (31.15)
24	122 (9.84)	64 (7.48)	86 (28.9)

COMPARISON OF

- 1 BHT standard deviations N=30
 2 Normotensives standard deviations N=15

HOURS	n-2	SYSTOLIC		P	DIASTOLIC		P	HEART RATE		t	P
		1	2		1	2		1	2		
1	43	8.9	8.6	NS	6.2	5.3	NS	11	13	-.49	NS
2	43	6.8	6.4	NS	4.7	3.8	NS	9.6	10	-.41	NS
3	43	6.7	5.4	NS	5.0	3.2	0.01	8.8	8.8	0	NS
4	43	5.5	5.8	NS	4.6	3.8	NS	8.6	9.6	-.52	NS
5	43	6.2	6.7	NS	4.7	3.7	NS	9.6	10	-.25	NS
6	43	6.9	6.2	NS	4.8	3.4	0.05	9.8	9.8	0	NS
7	43	8	8.6	NS	5.0	4.6	NS	10	13	-1.02	NS
8	43	7.8	9.4	NS	5.2	5.3	NS	11	17	-1.28	NS
9	43	7.4	7.1	NS	5.2	4.0	NS	9.4	9.1	.17	NS
10	43	7.2	6.0	NS	5.7	3.8	0.02	8.9	9.1	-.13	NS
11	43	6.7	6.3	NS	4.7	3.5	NS	7.3	7.9	-.46	NS
12	43	7.5	6.3	NS	5.0	3.6	0.05	8.3	7.6	.39	NS
13	43	6.8	5.5	NS	4.5	3.0	0.05	6.9	7.3	-.24	NS
14	43	7.5	6.4	NS	4.8	2.8	0.02	6.8	7.2	-.26	NS
15	43	6.1	5.4	NS	4.0	2.9	NS	6.0	5.8	.16	NS
16	43	6.6	5.9	NS	5.5	3.7	NS	6.6	5.8	.3	NS
17	43	5.3	4.7	NS	3.9	2.7	NS	5.2	5.7	-.49	NS
18	43	4.4	4.3	NS	3.6	2.6	0.05	5.0	5.1	-.03	NS
19	43	4.5	4.7	NS	3.7	2.7	NS	5.3	5.6	-.3	NS
20	43	4.8	5.1	NS	4.1	3.1	NS	4.7	6.5	-1.6	NS
21	43	7.6	4.2	2.71*	4.8	2.4	0.02	7.5	5.3	1.59	NS
22	43	8.4	7.9	.31	5.5	3.8	0.02	10	9.6	.47	NS
23	43	7.1	7.0	.19	4.5	3.7	0.02	10	10	-.22	NS
24	43	12	10	.5	8.3	5.1	0.02	14	9.6	1.47	NS

BHT patients, Group A, on NO therapy

Number of patients - 11

HOURS	No	SYSTOLIC	DIASTOLIC	HEART RATE
1	11	149 (13.09)	86 (10.59)	90 (11.06)
2	11	144 (9.88)	81 (8.66)	96 (18.73)
3	11	139 (12.31)	78 (11.47)	95 (21.98)
4	11	134 (11.6)	73 (11.69)	97 (31.24)
5	10	132 (14.05)	74 (12.83)	96 (27.98)
6	10	136 (15.71)	75 (12.6)	98 (26.1)
7	11	140 (14.67)	78 (12.68)	96 (23.65)
8	11	143 (9.23)	79 (10.91)	98 (23.18)
9	11	139 (11.81)	78 (10.89)	94 (19.8)
10	10	137 (17.55)	76 (15.48)	91 (20.46)
11	10	138 (12.76)	77 (10.76)	92 (18.19)
12	11	135 (14.86)	75 (11.09)	93 (23.61)
13	11	131 (14.16)	72 (11.65)	88 (22.77)
14	11	120 (18.55)	66 (14.66)	78 (18.6)
15	11	111 (15.11)	62 (11.67)	68 (10.48)
16	11	109 (14.29)	61 (10.5)	64 (9.04)
17	11	110 (12.7)	61 (10.71)	64 (7.36)
18	11	110 (13.86)	61 (11.46)	63 (8.01)
19	11	112 (14.91)	64 (13.04)	63 (8.03)
20	11	114 (14.83)	64 (12.84)	62 (8.11)
21	11	119 (20.95)	66 (15.35)	67 (12.66)
22	11	135 (17.26)	74 (12.38)	84 (17.26)
23	11	140 (11.18)	78 (11.36)	95 (23.96)
24	10	144 (10.23)	77 (12.61)	99 (25.07)

BHT patients, Group A, on ATENOLOL

Number of patients - 11

HOURS	No	SYSTOLIC	DIASTOLIC	HEART RATE
1	11	130 (10.51)	72 (6.07)	70 (8.52)
2	11	122 (9.12)	67 (5.4)	69 (13.09)
3	11	121 (10.01)	65 (8.22)	72 (14.52)
4	11	119 (12.4)	63 (9.17)	71 (13.44)
5	11	122 (7.78)	63 (4.83)	74 (16.95)
6	11	118 (5)	63 (4.76)	77 (20.98)
7	11	122 (7.57)	65 (6.79)	71 (15.55)
8	11	127 (12.01)	68 (7.73)	73 (12.76)
9	11	120 (15.61)	65 (9.25)	70 (11.63)
10	11	123 (12.49)	65 (10.65)	70 (10.49)
11	11	126 (12.86)	67 (9.47)	73 (13.7)
12	11	123 (13.63)	66 (6.98)	73 (15.23)
13	11	113 (15.44)	61 (8.35)	68 (15.9)
14	11	109 (17.29)	57 (11.14)	64 (11.74)
15	11	103 (15.41)	53 (10.74)	59 (11.51)
16	11	103 (12.54)	52 (9.67)	56 (10.43)
17	11	105 (11.5)	55 (7.4)	55 (10.01)
18	11	101 (9.24)	53 (6.56)	55 (9.28)
19	11	100 (8.44)	53 (8.26)	53 (8)
20	11	106 (7)	57 (7.96)	54 (8.23)
21	11	110 (11.63)	59 (8.64)	57 (7.44)
22	11	120 (14.5)	64 (10.25)	68 (15.73)
23	11	124 (10.19)	67 (7.22)	78 (18.98)
24	10	123 (10.36)	64 (7.83)	80 (22.72)

COMPARISON OF
 1 Group A NO therapy - STD Deviations N=12
 2 Group A ATENOLOL - STD Deviations N=12

HOURS	n-2	SYSTOLIC		P	DIASTOLIC		t	P	HEART RATE		t	P
		1	2		1	2			1	2		
1	22	7.9	6.4	NS	5.4	6.1	-1.79	NS	9.4	8.8	.28	NS
2	22	7.4	7.1	NS	4.6	5.6	.22	NS	10	7.2	1.28	NS
3	22	8.1	6.5	NS	5.8	5.8	1.39	NS	9.6	7.4	1.16	NS
4	22	6.2	6.4	NS	4.8	5.0	-.25	NS	10	7.4	.99	NS
5	22	6.7	5.7	NS	4.8	4.9	1.06	NS	9.2	8.2	.4	NS
6	22	7.1	6.5	NS	5.0	4.7	.48	NS	10	7.6	1.26	NS
7	22	7.6	9.2	NS	4.6	6.1	-.85	NS	9.4	15	-1.06	NS
8	22	6.7	7.4	NS	5.0	5.0	-.81	NS	9.3	7.6	.81	NS
9	22	7.2	6.4	NS	5.7	4.4	.61	NS	9.0	7.5	.64	NS
10	22	7.9	6.2	NS	6.3	4.8	1.6	NS	9.4	6.7	1.6	NS
11	22	7.5	8.1	NS	5.1	5.7	-.37	NS	7.9	8.1	-.13	NS
12	22	7.6	8.5	NS	4.9	5.9	-.64	NS	8.6	8.3	.21	NS
13	22	8.3	6.9	NS	5.5	4.8	.82	NS	8.3	5.3	1.78	NS
14	22	8.3	7.7	NS	5.3	5.4	.29	NS	7.4	7.1	.17	NS
15	22	6.2	6.4	NS	4.3	4.2	-.11	NS	6.2	5.2	.74	NS
16	22	4.5	3.9	NS	3.4	3.2	.93	NS	4.8	4.8	.01	NS
17	22	5.2	4.0	NS	3.6	3.6	1.4	NS	4.9	4.1	1.18	NS
18	22	4.1	4.1	NS	3.4	2.9	.04	NS	4.9	4.1	.66	NS
19	22	4.6	5.1	NS	4.0	3.2	-.69	NS	5.3	3.6	2.24	NS
20	22	4.6	5.8	NS	3.8	4.1	-1.24	NS	4.9	4.7	.37	NS
21	22	8.2	7.0	NS	5.2	4.3	.6	NS	8.0	7.2	.36	NS
22	22	-.7	7.7	NS	6.2	5.8	.85	NS	11	7.9	1.39	NS
23	22	7.3	7.5	NS	4.8	5.3	-.16	NS	11	9.7	.5	NS
24	22	9.4	6.4	NS	5.4	5.7	1.9	NS	11	8.7	.8	NS

Group A patients on NO therapy - averages of standard deviations

Number of patients - 12

HOURS	SYSTOLIC	DIASTOLIC	HEART RATE
1	7.98 (2.11)	5.45 (1.46)	9.48 (5.23)
2	7.42 (2.11)	4.65 (1.12)	10.06 (6.75)
3	8.12 (2.58)	5.8 (1.96)	9.69 (5.44)
4	6.23 (2.06)	4.84 (2.21)	10.13 (8.33)
5	6.74 (2.67)	4.83 (1.97)	9.28 (6.85)
6	7.14 (3.13)	5.05 (2.4)	10.73 (7)
7	7.63 (2.55)	4.6 (1.44)	9.46 (6.28)
8	6.7 (2.1)	5.07 (1.88)	9.38 (5.63)
9	7.2 (2.49)	5.78 (1.93)	9.09 (6.39)
10	7.93 (2.89)	6.31 (1.89)	9.45 (4.66)
11	7.53 (2.05)	5.16 (1.41)	7.98 (3.95)
12	7.65 (3.37)	4.96 (2.08)	8.68 (4.58)
13	8.39 (4.99)	5.51 (2.85)	8.36 (5.21)
14	8.33 (5.49)	5.36 (3.13)	7.46 (4.29)
15	6.21 (2.91)	4.39 (2)	6.28 (4.13)
16	4.57 (1.41)	3.41 (1.14)	4.89 (2.45)
17	5.27 (2.15)	3.65 (1.6)	4.99 (1.94)
18	4.13 (1.84)	3.42 (1.15)	4.91 (2.73)
19	4.66 (1.45)	4.06 (1.29)	5.38 (2.18)
20	4.61 (2.1)	3.88 (1.79)	4.97 (1.73)
21	8.23 (4.65)	5.2 (2.97)	8.05 (5.16)
22	9.76 (4.78)	6.26 (2.22)	11.68 (7.4)
23	7.39 (2.22)	4.85 (1.41)	11.56 (9.72)
24	9.47 (4.06)	5.44 (2.05)	11.41 (8.6)

COMPARISON OF

1 Group B on NO treatment N=11
 2 Group B on treatment (PLACEBO) N=11

HOURS	n-2	SYSTOLIC		P	DIASTOLIC		P	HEART RATE		P
		1	2		1	2		1	2	
1	20	142	142	NS	81	82	NS	85	85	NS
2	20	132	135	NS	75	78	NS	84	89	NS
3	20	131	130	NS	73	75	NS	85	88	NS
4	20	126	128	NS	71	73	NS	83	86	NS
5	20	126	131	NS	69	74	NS	87	86	NS
6	20	131	133	NS	72	75	NS	89	91	NS
7	20	133	137	NS	72	77	NS	93	95	NS
8	20	133	135	NS	75	78	NS	89	89	NS
9	20	133	134	NS	74	76	NS	87	86	NS
10	20	132	133	NS	74	76	NS	86	86	NS
11	20	128	130	NS	73	75	NS	83	81	NS
12	20	126	130	NS	71	74	NS	80	80	NS
13	20	124	123	NS	70	70	NS	79	74	NS
14	20	116	117	NS	65	67	NS	71	68	NS
15	20	113	115	NS	64	67	NS	69	64	NS
16	20	110	111	NS	62	64	NS	64	62	NS
17	20	109	111	NS	63	65	NS	66	63	NS
18	20	106	108	NS	61	64	NS	62	59	NS
19	20	108	110	NS	61	65	NS	63	60	NS
20	20	110	112	NS	64	66	NS	62	60	NS
21	20	115	117	NS	66	67	NS	65	64	NS
22	20	123	129	NS	70	72	NS	72	79	NS
23	20	127	138	NS	72	76	NS	77	91	NS
24	20	134	133	NS	70	73	NS	82	96	NS

t 0 -0.54 -0.35 -0.36 .1 -0.2 -0.17 0 .12 0 .27 0 .69 .47 .74 .3 .44 .5 .52 .33 .19 -1.04 -1.59 -1.02

BHT patients, Group B (placebo), on NO therapy

Number of patients - 11

HOURS	No	SYSTOLIC	DIASTOLIC	HEART RATE
1	11	142 (15.01)	81 (9.49)	85 (14.78)
2	11	132 (15.83)	75 (12.15)	84 (16.89)
3	11	131 (19.1)	73 (14.21)	85 (17.45)
4	11	126 (18.33)	71 (13.89)	83 (18.67)
5	11	126 (19.96)	69 (14.68)	87 (23.1)
6	11	131 (18.35)	72 (13.2)	89 (24.71)
7	11	133 (20.64)	72 (14.8)	93 (27.32)
8	11	133 (16.14)	75 (9.36)	89 (20.47)
9	11	133 (22.28)	74 (14.08)	87 (18.74)
10	11	132 (17.18)	74 (12.78)	86 (18.68)
11	11	128 (19.72)	73 (14.06)	83 (17.39)
12	11	126 (15.75)	71 (10.27)	80 (13.04)
13	11	124 (12.53)	70 (9.31)	79 (15.36)
14	11	116 (18.69)	65 (12.65)	71 (14.77)
15	11	113 (26.5)	64 (18.92)	69 (15.63)
16	10	110 (27.05)	62 (20.35)	64 (16.02)
17	9	109 (22.41)	63 (17.2)	66 (13.73)
18	9	106 (22.17)	61 (17.71)	62 (13.77)
19	8	108 (26.77)	61 (19.92)	63 (12.7)
20	8	110 (23.07)	64 (17.21)	62 (14.88)
21	9	115 (14.23)	66 (10.15)	65 (11.21)
22	9	123 (15.71)	70 (9.49)	72 (12.08)
23	10	127 (22.45)	72 (14.74)	77 (15.51)
24	9	134 (22.53)	70 (16.62)	82 (26.3)

BHT patients, Group B (placebo), taking PLACEBO

Number of patients - 11

HOURS	No	SYSTOLIC	DIASTOLIC	HEART RATE
1	11	142 (19.29)	82 (12.19)	85 (16.82)
2	11	135 (20.95)	78 (12.57)	89 (25.74)
3	11	130 (17.34)	75 (11.18)	88 (22.71)
4	11	128 (15.01)	73 (11.95)	86 (21.01)
5	11	131 (14.96)	74 (11.63)	86 (20.16)
6	11	133 (15.12)	75 (11.15)	91 (23.43)
7	11	137 (17.69)	77 (9.48)	95 (28.59)
8	11	135 (17.12)	78 (11.74)	89 (22.91)
9	11	134 (17.36)	76 (10.43)	86 (20.3)
10	11	133 (14.69)	76 (10.88)	86 (19.82)
11	11	130 (11.17)	75 (10.1)	81 (17.07)
12	11	130 (14.78)	74 (10.4)	80 (18.05)
13	11	123 (12.73)	70 (9.68)	74 (18.4)
14	11	117 (12.26)	67 (8.41)	68 (15.15)
15	11	115 (14.94)	67 (10.46)	64 (15.74)
16	11	111 (17.53)	64 (13.36)	62 (14.34)
17	11	111 (17.42)	65 (13.01)	63 (16.08)
18	11	108 (12.54)	64 (9.92)	59 (12.77)
19	11	110 (14.43)	65 (9.98)	60 (12.06)
20	11	112 (12.22)	66 (8.24)	60 (11.51)
21	11	117 (12.74)	67 (8.31)	64 (11.14)
22	11	129 (15.15)	72 (9.89)	79 (17.14)
23	11	138 (16.75)	76 (10.88)	91 (23.66)
24	10	133 (13.02)	73 (9.48)	96 (33.15)

BHT patients with no ECG evidence of LVH

Number of patients - 23

HOURS	No	SYSTOLIC	DIASTOLIC	HEART RATE
1	23	142 (14.86)	81 (9.08)	87 (14.71)
2	23	134 (13.87)	76 (9.87)	87 (22.17)
3	23	130 (15.05)	74 (11.27)	86 (23.66)
4	23	126 (15.69)	70 (11.71)	89 (28.75)
5	23	125 (17.32)	69 (13.6)	91 (29.27)
6	23	128 (19.56)	70 (14.82)	96 (31.03)
7	23	132 (18.74)	71 (13.54)	97 (30.73)
8	23	135 (19.51)	75 (13.27)	94 (24.18)
9	23	132 (22.35)	73 (15.75)	89 (21.24)
10	23	128 (19.59)	71 (15.43)	87 (22.43)
11	23	128 (19.57)	71 (14.8)	87 (21)
12	23	125 (17.3)	70 (12.81)	86 (21.79)
13	23	122 (16.98)	68 (12.42)	83 (21.92)
14	23	113 (19.17)	62 (14.37)	74 (19.07)
15	23	108 (23.47)	61 (17.39)	68 (15.13)
16	23	107 (22.46)	60 (16.38)	65 (13.77)
17	23	107 (18.76)	60 (14.56)	65 (12.71)
18	23	104 (18.43)	58 (15.84)	61 (13.01)
19	23	105 (20.15)	59 (15.99)	61 (10.94)
20	23	107 (18.43)	60 (14.78)	61 (11.8)
21	23	113 (16.41)	63 (12.75)	64 (12.55)
22	23	126 (17.28)	70 (12.26)	78 (17.89)
23	23	131 (19.69)	72 (14.17)	88 (24.01)
24	23	136 (19.54)	71 (15.57)	95 (31.18)

BHT patients with LVH

Number of patients - 7

HOURS	SYSTOLIC	DIASTOLIC	HEART RATE
1	157 (11.42)	91 (10.61)	90 (8.31)
2	152 (14.59)	88 (7.86)	92 (12.12)
3	153 (9.94)	88 (7.9)	93 (7.95)
4	146 (11.28)	84 (8.59)	91 (9.5)
5	147 (14.71)	83 (8.65)	95 (14.63)
6	147 (11.12)	83 (8.2)	95 (17.65)
7	149 (12.52)	84 (10.67)	96 (18.32)
8	150 (9.28)	85 (10.39)	94 (12.94)
9	151 (13.87)	86 (9.23)	94 (13.42)
10	150 (13.56)	87 (10.76)	91 (7.83)
11	143 (11.02)	84 (7.59)	89 (11.53)
12	143 (12.93)	82 (8.2)	87 (12.33)
13	135 (10.27)	77 (8.51)	81 (9.54)
14	129 (17.91)	74 (12.42)	74 (12.16)
15	122 (15.91)	69 (10.51)	68 (13.06)
16	111 (16.08)	63 (11.9)	62 (16.17)
17	118 (11.44)	70 (5.57)	64 (14.12)
18	120 (12.81)	71 (8.04)	63 (14.45)
19	121 (14.46)	73 (12.33)	64 (14.77)
20	126 (12.17)	75 (9.25)	63 (15.53)
21	126 (21.11)	75 (12.28)	67 (16.86)
22	138 (17.25)	79 (12.36)	77 (9.41)
23	148 (13.41)	85 (9.1)	85 (8.18)
24	145 (12.75)	78 (13.17)	81 (16.91)

APPENDIX IISIDE EFFECTS QUESTIONNAIRE

Please ring appropriate answer, or insert required number,

eg Age 23 years

1 Age last birthday years

2 Have you recently been bothered by unsteadiness,
lightheadedness or faintness?

YES

NO

3 Do you now feel more sleepy during the day?

YES

NO

4 Do you sleep right through the night?

YES

NO

If yes, proceed to question 6.

5 Have you always had trouble sleeping?

YES

NO

6 Do you feel depressed?

YES

NO

7 Have you recently noticed any weakness in the
limbs?

YES

NO

8 Do you often have any discomfort in the chest?

YES

NO

9 Do you feel short of breath?

(Please ring only one)

- 1 On walking or other exertion
- 2 While resting
- 3 Both at rest and on exertion
- 4 Not at all

10 Do you find that your bowel habit has changed?

YES,

- 1 The bowels open more frequently
- 2 The motions are often loose or liquid
- 3 They are both loose and frequent
- 4 The motions are harder and more difficult to pass

NO,

- 5 There has been no change

11 Do you find that you have to rise at night to pass urine?

YES

NO

12 Do you suffer from a dry mouth?

YES

NO

13 Are you often troubled by a blocked or runny nose?

YES

NO

14 Within the last few months, have you often been troubled by vivid dreams or nightmares?

YES

NO

15 Within the last few months, have you often felt sick or vomited?

YES

NO

16 During the last few months, have you had a rash?

YES

NO

17 How often do you suffer from headache?

(Please ring only one)

- 1 Never
- 2 Less than one each month
- 3 Less than one per week
- 4 1 - 6 per week
- 5 One or more per day

- 18 Please insert details below of tablets, powders, or medicines you are taking, eg aspirin, APC, laxatives, vitamins, or other tablets from your own doctor, NOT blood pressure tablets:

NAME (if known)	COLOUR	Amount taken per day
1		
2		
3		
4		
5		
6		

- 19 Have you been bothered recently with sore, irritated or gritty eyes?

YES

NO

During sexual intercourse are you troubled:

- 20 by failure to sustain an erection?

1 YES

2 NO

3 UNKNOWN

- 21 by failure to ejaculate?

1 YES

2 NO

3 UNKNOWN

- 22 Has your inclination for sex during the last few months been:

1 UNCHANGED

2 INCREASED

3 DECREASED

APPENDIX III

The data comprised R + S values for individual subjects on various occasions.

The study design was such that values were replicated on the various days, so that the value for subject i on period k of day j was represented symbolically by x_{ijk} .

An additive model

$$x_{ijk} = \alpha + \beta_i + \gamma_{ij} + \xi_{ijk}$$

provided an adequate description, where:

α = overall constant level for all subjects on all occasions,

β_i = adjustment of subject i,

γ_{ij} = further adjustment for subject i on day j,

ξ_{ijk} = residual effect, further adjusted for period k, for subject i, on day j.

Thus the model involved successively adjusting for the effect of:

- a) Overall average (for all subjects at all times),
- b) Subject effect (at all times),
- c) Subject/day interaction.

DISCUSSION

It was Sir George Pickering who said, when discussing hypertension, that you never define, but describe the quantity. He, with others (Kannel, et al, 1969 and Kannel, et al, 1970), also emphasised that blood pressure is a continuous physiological variable without any dramatic cut-off point at which morbidity and mortality suddenly increase and at which juncture the term hypertension can be safely used.

The most commonly used definition for the term is that described by Peart (1981) as a blood pressure level which is associated with increased morbidity and mortality at some future time compared with the whole population. This definition is eminently suitable for the epidemiologist, depending as it does on large numbers and usually based on one casual cuff blood pressure reading. It has, however, little application in the clinical setting where the prognostic significance of a single, casual recording of blood pressure must be balanced against the repeat reading which has settled with rest, or when the doctor has left the room. Although Smirk, Veal and Alstad (1959) reported that life expectancy was more closely related to basal, rather than casual, blood pressure the overwhelming epidemiological opinion is that the casual reading is all important, (Kannel, Sorlie and Gordon, 1980). It is possible, however, that by virtue of the large numbers involved in most epidemiology studies that those with blood pressure "lability" are submerged in the statistical analysis by the large numbers who have established elevation of blood pressure. It should also be stressed

that for the number of patients whose blood pressure falls on re-checking an equal number sustain a subsequent rise (Hawthorne, Greaves and Beevers, 1974), so that the average blood pressure of the community is unchanged on re-checking. Subjects who display so-called "lability" of blood pressure have been found to have little evidence of significant end-organ effects or electrocardiographic left ventricular hypertrophy (Stokes, MacCarthy and Frost, 1981) and many of these people in future years do not achieve blood pressure levels that are normally treated (Julius, 1977). However, Harlan, Oberman and Mitchell, et al, (1973) in a 30 year longitudinal study of United States Navy airmen found that the higher the baseline blood pressure then the higher it was 30 years on. Despite this somewhat obvious observation, however, the 30 year pressure relationship only applied to those with baseline systolic pressures of greater than 160 mmHg. The borderline individuals provided a difficult prognostic problem.

Borderline hypertension in the young has attracted wide investigative interest as many workers believe that this period of "labile" blood pressure with its attendant features of tachycardia, raised cardiac output and autonomic dysfunction may herald the onset of the hypertensive process (Julius and Schork, 1971), while others have dismissed the concept as being a manifestation of the defence reaction (Pickering, 1972). It should be remembered that all previous studies of the condition have by and large measured blood pressure indirectly, and if direct measurement has been employed this has been in the somewhat frightening environs of physiology laboratories. There is therefore little information on blood pressure behaviour at times in the day when the doctor is not present, although Julius, et al, (1974) found

that blood pressure of borderline hypertensives did fall when measured at home. Similarly, apart from the normotensives in Julius' home blood pressure study (1974) little information is available regarding the behaviour of blood pressure in the normotensive throughout a 24 hour period.

In view of these controversies and inconsistencies a study of 24 hour, continuous, intra-arterial ambulatory monitoring in young normotensive and borderline hypertensive men was undertaken in this study in order that blood pressure patterns and levels might be determined and so that blood pressure variability might be examined.

Obsessional care was taken to accurately categorise subjects according to their blood pressure status. Indirect, office blood pressure was measured by a random zero sphygmomanometer according to recommendations of the Australian National Blood Pressure Study (Abernethy, 1974) over a three month lead-in period. The office blood pressure readings were complemented by home blood pressure recordings after a period of intensive training.

As far as possible therefore subjects were accurately labelled as either normotensive or borderline hypertensive according to criteria already described. The 24 hour systolic and diastolic arterial pressure of borderline hypertensives was greater than their normotensive counterparts. Despite the relative mildness of office blood pressure elevation in borderlines the difference in global 24 hour intra-arterial levels between them and normotensives was statistically highly significant.

On analysis of the data on an hourly basis throughout the 24 hour period the bimodal pattern of blood pressure was identical for both groups. The dramatic fall in night-time blood pressure during sleep was also apparent in both normotensive and hypertensive alike, as was the pronounced early morning rise.

Blood pressure was lowest around 0200-0300 hours and began to rise before waking. The controlling mechanism for this apparent circadian blood pressure rhythm is unknown, but it is well recognised that adrenal cortico-steroids and mineralocorticoids exhibit a diurnal variation. The information on plasma catecholamines is less clear.

The further rise in blood pressure around the time of waking has been attributed to the arousal or defence reaction. It is extremely difficult to determine when the precise moment of waking occurs. Subjects in the study were asked to press their event marker button on waking and again on rising. Not surprisingly most omitted to do this immediately on coming to, so that the waking and getting up events were often very close together. The analysis technique used in this study did not permit substantial separation of these events in most instances. It is now generally agreed that awakening probably is a gradual process in most individuals, beginning in the period of rapid eye movement sleep. A combined study of electroencephalography and continuous intra-arterial blood pressure recording might contribute to further understanding, but may also potentiate the defence reaction, as any such study would naturally have to be performed in a hospital environment.

Day-time blood pressure for both groups was significantly higher than night-time levels and corresponded closely to office and home blood pressure readings although displaying no actual correlation. Despite the significant blood pressure difference between normotensives and hypertensives it has recently been found that in a 24 hour period normotensives may exceed pressure levels that are normally regarded as hypertensive. Using an improved analysis technique, employing beat to beat recognition, Hunyor, Larkin and Roffe, et al, (1982) demonstrated that systolic pressure of 160 mmHg and diastolic pressure of 100 mmHg was exceeded by most normotensives at some point in the 24 hours, but for significantly shorter periods than borderline hypertensives. This finding is entirely consistent with the findings of Watson, et al, (1979) who found that physical activity strongly influenced arterial pressure variability. Peaks of blood pressure were observed in this study in which normotensives and borderline hypertensives engaged in normal everyday pursuits, thereby strengthening the belief that all blood pressures are indeed labile.

The finding of blood pressure lability was not entirely unexpected, but excessive blood pressure variability has been described in borderline hypertension (Birkenhager, et al, 1968). The difficulty in determining blood pressure variability is illustrated by examining data from the Framingham Study in which the coefficient of variation of blood pressures measured in triplicate showed almost no correlation with subsequent measurements (Gaylarde, 1982). The authors of the study, however, (Kannel, et al, 1980) found that variability rose with increasing mean blood pressure, although this has not been confirmed by others.

There is thus uncertainty regarding the best index of blood pressure variability and that which is statistically most relevant and powerful. Few studies have been done of intra-arterial pressure variability, but Watson, et al, (1979) and Ogawa, et al, (1981) employed standard deviation of the mean. Obviously standard deviation is directly correlated to the value of the mean in any gaussian distribution, but it was felt to be a suitable index of variability for this study in view of the relatively small difference in mean blood pressures between groups.

Despite some isolated periods of increased variability in the 24 hours, by and large systolic and diastolic arterial pressure variability of borderline hypertensives was not significantly different from normotensive controls in this study.

The observation of widely fluctuating blood pressure in the baroreceptor denervated dog (Cowley, et al, 1973) has reinforced the view that the baroreflex arc is important in buffering excessive swings of blood pressure. Although blood pressure in the dogs was extremely labile none subsequently developed hypertension, thereby suggesting that the baroreceptor mechanism had little or no role in the initiation of hypertension. There is now, however, accumulating evidence that baroreceptor denervation in man does result in hypertension after a period of blood pressure fluctuation (Sleight, 1979). Despite some reservations and doubts it is now generally accepted that baroreflex function is impaired in established hypertension (Gribbin, et al, 1971 and Korner, et al, 1974), while more recent evidence suggests that impairment is also present in young, borderline

hypertensives (Takeshita, et al, 1975 and Eckberg, 1979). The latter finding, however, has been disputed by others (Julius, et al, 1975) and even by Eckberg (1979) who found normal baroreflex sensitivity in "milder" borderline hypertension.

In view of these inconsistencies and controversial findings baroreflex sensitivity was measured in normotensives and borderline hypertensives using the universally accepted method of Smyth, et al, (1969). Baroreflex sensitivity was found to be diminished in borderline hypertensives compared to normotensives and results were in close agreement with those of Takeshita, et al, (1975). There was no correlation in this study between systolic arterial pressure and baroreflex sensitivity as reported by other workers (Watson, et al, 1979). This may be due to the fact that subjects in this study were comparable to Eckberg's milder borderline hypertensives.

The finding of reduced baroreflex sensitivity was not reflected by significantly increased blood pressure variability in borderline hypertensives and this is perhaps not altogether surprising bearing in mind the relative mildness of blood pressure elevation and the young age of the individuals. Long-term longitudinal studies are obviously desirable in this area as data presented here do not permit any firm pronouncement on the role of the baroreflex arc in the initiation of the hypertensive process. The discovery, however, of a close negative correlation between baroreflex sensitivity and thickness of the interventricular septum and posterior left ventricular wall, in the absence of left ventricular hypertrophy, does tend to support Eckberg's hypothesis (1979) that borderline subjects with

depressed baroreflex responses are more likely to develop hypertensive cardiovascular disease.

It is no great consolation to a young man to be told that the biggest benefits in hypertension at any stage of treatment are to be found in those subjects over 50 years and with diastolic pressures in excess of 100 mmHg, who already have signs of end organ damage. On purely theoretical grounds lowering of the blood pressure before hypertension develops offers the strongest possible approach to prevent future hypertension. This policy would, of course, entail a considerable financial burden on any health service, not to mention the possible psychological problems encountered by treated individuals. The question of possible long-term, harmful drug side effects in an otherwise healthy young individual would also loom large. At the present time most hypertensive risk factors are weak and as yet unproven, although a recognised major predictor is the initial blood pressure level itself.

In order to assess the effectiveness and efficacy of antihypertensive therapy in a young, borderline hypertensive population, the β -adrenoreceptor blocker, atenolol, was employed during a six month placebo-controlled trial in this study.

It was hoped to examine a number of questions:

- 1 Can effective blood pressure lowering be achieved in mild, borderline hypertensives?
- 2 What is the incidence and nature of side effects encountered?
- 3 Does the β -adrenoreceptor-blocker, atenolol, indeed have an effective 24 hour antihypertensive action?

- 4 Is the blood pressure lowering action of β -blockers achieved by modification of the baroreflex mechanism?
- 5 Do borderline hypertensives have hypersensitive B-adrenergic receptors?

The antihypertensive effectiveness of atenolol was amply demonstrated by office and home blood pressure readings during the six month trial period. There was a significant fall in both systolic and diastolic arterial pressure compared to both pre-treatment and placebo levels. Although there was also a reduction of blood pressure in the placebo group this did not reach statistical significance. Interestingly, this fall in placebo-group blood pressure was not evident when the record of 24 hour intra-arterial blood pressure was examined. This observation lends support to the view that the fall in blood pressure during repeated cuff measurements is not due to regression towards the mean or a placebo effect, but rather results from damping down of the defence reaction (Pickering, 1972).

The results of this study therefore demonstrated, for the first time, quite conclusively, that significant lowering of the blood pressure can be achieved by β -adrenoreceptor blockade in young, borderline hypertensives.

With the prospect of life-long drug therapy, any metabolic consequences of long-term administration assume great importance. The need for additional drug therapy for hypokalaemia and hyperuricaemia in certain instances of diuretic therapy and the recognised side effects of methyl dopa made these agents less than ideal and prompted the use of a β -adrenoreceptor blocking agent. This decision, however, does

not imply a belief that β -blockers are free of side effects. The fact that this is not the case is illustrated by results from the MRC Working Party on Mild to Moderate Hypertension (1977) in which patients treated with propranolol had an increased incidence of symptoms of Raynaud's phenomenon, dyspnoea, skin disorders and lethargy, and impotence in males, compared to placebo controls.

The numbers in this study were, of course, small, but there were no drop-outs and drug compliance was excellent. A side-effects questionnaire was administered upon completion of the therapeutic period. This was based on that used in the Australian National Blood Pressure Study (Bauer, et al, 1978). There were no complaints of Raynaud's phenomenon - although it should be stressed that the trial was conducted in a warm climate with a cardioselective β -blocker. Dyspnoea, with wheeze, was reported by two individuals on atenolol, both of whom had suffered from childhood asthma. In one there was a slight reduction from his baseline FEV₁, but this did not necessitate him stopping therapy. It was not the remit of this study to assess physical fitness, but many of the subjects participated in regular sports and none volunteered symptoms of exercise limitation. Importantly in young, healthy men there were no reports of interference with sexual function.

The reasons for using a β -blocker in the study have already been described. It was felt that a cardioselective agent with a once-a-day dose would be desirable and atenolol (ICI 66.082, Tenormin) was selected in a dose of 100 mg. In brief, the important properties of the compound are (a) cardioselectivity, (b) lack of intrinsic

sympathomimetic properties (c) lack of membrane-stabilizing effect and (d) inability to cross the blood-brain barrier.

Atenolol has been reported to have an effective 24 hour antihypertensive action with a once daily dose (Floras, 1979), but this was not confirmed by Millar-Craig, Kenny and Mann, et al, (1979). The effective 24 hour antihypertensive action of atenolol was quite striking in this study of borderline hypertensives for both systolic and diastolic arterial pressure. There was no effect on blood pressure variability, however. Despite an effective 24 hour antihypertensive action, the effect on heart rate slowing was not maintained until the end of the 24 hour period.

These results indicate that atenolol is an effective antihypertensive drug in borderline hypertension, with a full 24 hour action, in a once-a-day dose and with an extremely low incidence of side effects. The lack of complete 24 hour reduction of heart rate perhaps calls into question its possible once-a-day effectiveness in the control of anginal symptoms.

The antihypertensive mechanism of β -blockade is not fully understood, but Pickering, Gribben and Peterson, et al, (1972) and Eckberg, Abboud and Mark (1976) have demonstrated that intravenous propranolol increased the sensitivity of the baroreceptor reflex. This raises the possibility that this mechanism may have a role in the antihypertensive action of β -blocking agents.

It had already been demonstrated that baroreflex sensitivity was decreased in borderline hypertensives when compared to age-matched normotensive controls. After chronic β -blockade repeat assessment of baroreceptor function in borderlines showed that there had been a significant increase in sensitivity, reaching normotensive values. These observations are consistent with those of Watson, et al, (1979) who found increased sensitivity with chronic propranolol, but only in hypertensive subjects below the age of 40. Results from these authors are also in agreement with this study regarding the lack of correlation between fall in blood pressure and alteration of baroreflex sensitivity. This observation does not lend support to the theory that increased baroreflex sensitivity is a major contributor to the antihypertensive action of β -adrenoreceptor antagonists. It seems likely that the apparent increase in sensitivity after β -blockade is a function of the achieved heart rate, as Pickering, et al, (1972) have demonstrated that baroreflex sensitivity is inversely related to pulse interval. These observations point to a critical balance between parasympathetic tone at the sino-atrial node in determining baroreflex sensitivity and the response to β -adrenoreceptor blockade.

Julius and Esler (1975) have postulated that borderline hypertensives have hyperresponsive β -adrenoreceptors as part of a "hyperkinetic" state. Takeshita, et al, (1978) assessed β -adrenoreceptor responsiveness to intravenous propranolol in young, tachycardic, borderline hypertensives and decided that there was no evidence to support a theory of β -receptor hypersensitivity in borderline hypertension. A similar conclusion can be drawn from this study, where

at no time did heart rate differ significantly between normotensives and borderline hypertensives and although β -blockade increased baroreflex sensitivity to normotensive values it did not significantly exceed those values. These findings support the opinion that there is no firm evidence to suggest a hypersensitivity of β -adrenoreceptors in borderline hypertension.

Increased arterial pressure is obviously the major stimulus to cardiac hypertrophy in hypertension. However, it has been suggested that other factors may precipitate the process and this has been demonstrated by Yamori, et al, (1979) in the pre-hypertensive stage of spontaneously hypertensive rats. In human, borderline hypertension Safar, et al, (1979) have reported an increased incidence of asymmetric septal hypertrophy - findings corroborated by Culpepper, Hutcheon and Arcilla, et al, (1979) in hypertensive children.

There is little doubt that although the major responsibility for cardiac hypertrophy in hypertension is the increased pressure load, the findings, both in animal and human studies, of hypertrophy at an early borderline phase of the condition raise the possibility that neurohumoural and genetic factors may have a role and that muscular hypertrophy may only be part of a generalised phenomenon in systemic hypertension involving the vasculature and the myocardium. This theory poses the interesting question: Can myocardial hypertrophy be prevented by blood pressure lowering at an early stage, and does it regress with treatment?

Despite obvious limitations of sensitivity, and to a lesser extent specificity, (Romhilt, et al, 1969), the electrocardiogram is a valuable tool for the diagnosis of left ventricular hypertrophy.

Although close correlation has been reported between electrocardiographic voltage criteria and hypertrophied hearts at post mortem, no correlation has been demonstrated in the absence of hypertrophy (Sjogren, 1970).

The majority of electrocardiographic criteria of left ventricular hypertrophy are based on precordial voltage amplitude (Sokolow and Lyon, 1949 and McPhie, 1958), but in the young male increased precordial voltages are often found (Manning and Smiley, 1964 and Kilty and Lepeschkin, 1965), although it should be stressed that concurrent blood pressure data is sadly lacking.

The relationship between body build and electrocardiographic voltage hypertrophy in the young male is controversial. In the clinical setting the finding of high precordial voltages in the electrocardiogram of the young asthenic individual is well recognised, but Simpson, et al, (1978) found no correlation between electrocardiographic appearances and body habitus.

Physical fitness is also known to result in a variety of electrocardiographic changes, including voltage left ventricular hypertrophy, in athletes (Zoneraich, Zoneraich and Rhee, et al, 1979).

Despite the difficulties alluded to, the electrocardiogram, with proper and careful use, can perform an unique role in screening large numbers for left ventricular hypertrophy. The importance of early hypertrophy detection has already been discussed and for this reason it was decided to determine the prevalence of electrocardiographic

left ventricular hypertrophy in a young male population in whom accurate blood pressure and body build data was available.

A striking feature of the survey was the sheer number of young men with a blood pressure "abnormality" - 26% of the total 913 individuals. This figure is in close accord with those found by others (Julius, et al, 1974) and illustrates the size of the problem of mild hypertension in the young, emphasising the need to determine identification parameters for those who will ultimately go on to established hypertension.

Electrocardiograms were coded according to the Minnesota Code (Blackburn, et al, 1960) with electrocardiographic left ventricular hypertrophy being represented by MC3-1, and, or MC3-3. Blackburn, Parlin and Keys (1966) have found that these criteria compare favourably with other voltage criteria which have been more extensively studied. Approximately 14% of all individuals fulfilled Minnesota Code criteria for hypertrophy. Only 11% of normotensives fulfilled criteria, but almost one in three hypertensives were found to have electrocardiographic evidence of left ventricular hypertrophy. Findings in the borderline group were comparable to those of Stokes' (1981) study of labile hypertension where no increase in hypertensive end organ effects was noted.

No significant difference in blood pressure was found, within blood pressure categories, between hypertrophy and non-hypertrophy groups. No correlation was found between body habitus, measured by quetelet index, and electrocardiographic criteria, except in the borderline group. Overall hypertensives were significantly heavier than

normotensives, but in the borderline category hypertrophy subjects were significantly more asthenic than their non-hypertrophy counterparts. This finding raises the possibility that in only this group did body habitus influence electrocardiographic appearances.

The discovery of a significantly increased incidence of electrocardiographic left ventricular hypertrophy in young hypertensives, with comparatively mild blood pressure elevation is of considerable importance. It adds support to the view that in a population study cardiac hypertrophy may already be present in the earliest stage of hypertension. The absence of a difference in arterial blood pressure between hypertrophy and non-hypertrophy groups is consistent with the theory that factors other than height of arterial pressure may contribute to the development of cardiac hypertrophy.

Population study data showed no difference in blood pressure between hypertrophy and non-hypertrophy hypertensives. Although there was a difference in office blood pressure readings between hypertrophy and non-hypertrophy borderline hypertensives in the laboratory this just failed to reach statistical significance. However, when an analysis of 24 hour intra-arterial blood pressure recordings was performed it was found that there was a highly significant difference between groups, with hypertrophy individuals maintaining higher arterial pressures for considerably longer periods in the 24 hours compared to non-hypertrophy counterparts.

This exciting discovery may, at least in part, explain the observation of lack of significant difference in indirectly measured blood pressure

between electrocardiographic hypertrophy and non-hypertrophy groups. It is clear that the hearts of subjects in this study with electrocardiographic evidence of left ventricular hypertrophy were exposed to increased afterload for a considerably longer period in any 24 hours period. Perhaps these are the individuals who proceed to established hypertension and anatomical myocardial hypertrophy. These data may also help explain the many discrepancies between the level of arterial pressure and the occurrence of signs of cardiac hypertrophy, or their reversal by therapy (Helmcke, Schneckloth and Corcoran, 1957 and Farmer, Gifford and Hines, 1963).

The appearance of electrocardiographic left ventricular hypertrophy in the established hypertensive is an ominous harbinger of future cardiovascular events (George and Dollery, 1972). The prevention, or reversal of the process at an early stage offers the best theoretical grounds for subsequent reduction of morbidity and mortality. In this study electrocardiograms were performed before and upon completion of a six month period of placebo-controlled antihypertensive therapy. As previously mentioned there was no significant difference in precordial voltages of borderline and normotensive groups. At the end of six months antihypertensive therapy precordial voltage was significantly reduced in subjects treated with atenolol and had remained unchanged in the group given placebo. The possible significance of these findings will be discussed together with echocardiographic data overleaf.

In assessing any hypertensive individual's response to antihypertensive therapy it is desirable, and indeed important, to be aware of the

normal variability present in the electrocardiogram, particularly in the R and S voltages of the precordial leads. Although significant repeat variability had been shown by early workers (Simonson, et al, 1949), no study had been undertaken since the introduction of high impedance buffer amplifier equipment. These amplifiers effectively eliminated skin-electrode resistance which had previously been recognised as the major source of variability (Berson and Pipberger, 1968).

The presence of significant intra-individual variability has been demonstrated in this study, despite stringent efforts to minimise all known, remediable causes. The extent of variability was surprisingly large, even on a same-day basis and was only reduced by precordial electrodes remaining in position between recordings. This has demonstrated that the major source of precordial voltage variation is due to inaccurate sequential electrode positioning. These findings pose further difficulty in the assessment of the hypertensive's electrocardiogram and in the interpretation of possible response to antihypertensive therapy. The effects of repeat variation, however, would be expected to cancel out in group data.

As previously mentioned a number of authorities have postulated the existence of β -receptor hypersensitivity in borderline hypertension. This supposed increased adrenergic drive, with effects on the heart of tachycardia and increased cardiac output has resulted in the introduction of the term "hyperkinetic heart syndrome" (Guazzi, et al, 1975). These authors detected a number of electrocardiographic changes in such individuals, but it should be pointed out that the small number of subjects had initially been referred because of a

supposed cardiac abnormality or the finding of an already abnormal electrocardiogram. It was presumed that increased sympathetic stimulation resulted in T-wave inversion and these changes could be reversed by β -blockade.

Certainly, T-wave inversion was common in this study, with 30% of borderline subjects displaying inverted T-waves in lead III. Unlike reports from others (Guazzi, et al, 1975) long-term β -blockade had no effect on these appearances in this study, further reinforcing the view that borderline hypertensives were not exposed to increased sympathetic drive.

Orthogonal electrocardiography, by virtue of its simultaneous 3-lead display, offers a number of advantages to the cardiologist. Chief amongst these is probably the relative ease whereby the system can be adapted for computer analysis by virtue of the reduced information required to be stored compared to the conventional 12-lead system. Despite this attraction, however, it is little used, although since its introduction by Frank (1956) a number of varying claims have been made regarding the accuracy of the technique in the diagnosis of left ventricular hypertrophy.

Recently MacFarlane, Melville and Horton, et al, (1981) in a comparative computer evaluation of 12-lead and orthogonal 3-lead systems, found that the performance of both was very similar in the detection of left ventricular hypertrophy in a hospital population. Bahler, et al, (1977) in a study of apparently normal young subjects found a close correlation between echocardiographic septal thickness and the absolute value of the Frank Lead QRS vector (Vf).

In this study a close correlation was found between Vf and maximum precordial voltage of borderline hypertensives. In addition the value of Vf was significantly greater for hypertensives when compared to normotensive controls.

The correlation between Vf and precordial voltage is not unexpected as both reflect the spatial magnitude of the heart vector. The increased value of Vf in borderline hypertensives is of considerable interest, however, as it suggests a possible relationship with the level of arterial pressure. This latter observation was reported by Gamboa, Hugenholtz and Nadas (1959) who found a close correlation between systolic pressure and the maximum QRS vector, albeit at considerably higher levels of pressure than seen in this study.

Little is known about normal orthogonal electrocardiographic appearances in the young and there are no previous studies in borderline hypertension. Results from this study suggest that more information is required as the technique may have a role in the investigation of the young hypertensive, with or without computer analysis.

Despite a number of interesting findings it is clear that the established electrocardiographic criteria for left ventricular hypertrophy are only loosely correlated with blood pressure in borderline hypertension. These results are consistent with the observation of McPhie (1958) that lesser degrees of left ventricular hypertrophy cannot be accurately diagnosed by any criteria described to date. It is perhaps somewhat naive however to expect that electrocardiographic hypertrophy is purely a function of muscle bulk. There are

suggestions that the process may begin at a cellular electrical level with an alteration in the depolarisation pulse through the fibres which will subsequently hypertrophy. This is borne out by computer analysis of precordial voltage waveforms where a relationship has been demonstrated between R and S wave rise time and left ventricular wall thickness in borderline hypertensives (Fischhof and Larkin, 1980). The rise time is a difficult parameter to measure, both from chart records, because of the small times involved (corresponding to about $\frac{1}{2}$ mm), and by computer, because of the difficulties involved in establishing the starting point. Despite this technicality, however, the computer analysis of electrocardiographic waveforms may have a particular role in the detection of the myocardium's earliest initiation of the hypertensive process.

At best the electrocardiogram is still an indirect method of assessing cardiac anatomy. Echocardiography, however, provides a safe, non-invasive and direct method for the measurement of various cardiac dimensions. Examination of the left ventricle is of particular interest in the area of hypertension as any increase in systemic arterial pressure exerts a direct effect on the left side of the heart by virtue of an increased after-load. The description of the anatomical accuracy of the echocardiographic measurement of posterior left ventricular wall thickness by Feigenbaum, et al, (1968) heralded the possible alternative to the electrocardiogram for the diagnosis of left ventricular hypertrophy.

This assumption was premature as no conclusions about anatomical accuracy could be drawn from the Feigenbaum (1968) study because of

its serious limitations. Further studies on anatomical accuracy were controversial (Schroeder, et al, 1969 and Maron, et al, 1977), with the main area of disagreement surrounding the phase of the cardiac cycle which corresponded most closely to the echocardiographic measurement of left ventricular wall thickness.

Results of this study support the view that the measurement of echocardiographic end diastolic posterior left ventricular wall thickness corresponds closely to the direct measurement performed upon hearts in a state of hypothermic, cardioplegic arrest at open-heart surgery. The echocardiographic end systolic measurement, not diastolic, corresponds with that obtained in the post mortem room. Maron, et al, (1977) also reported this finding and concluded that the heart must stop in a systolic phase at death. This is not supported by the data obtained in the study of dogs' hearts, however, which point to the heart stopping in diastole, but progressive muscle thickening occurring over a period of hours after death.

It had originally been intended to use the dog heart as a model for assessing the accuracy of echocardiography in detecting serial changes of left ventricular wall thickness in response to surgically-induced hypertension. Unfortunately, the project was not a complete success owing to the high mortality rate among animals. Echocardiography could only be performed in a clinical area and as a result dogs had to be transported by wheelbarrow in an anaesthetised state. As a result a number succumbed from respiratory arrest during transport either to or from echocardiography, leaving few for statistical analysis. Although there was a rise in absolute blood pressure, it should be pointed out that femoral intra-arterial pressure in the dog rises in

the anaesthetised state and no blood pressure data was available on the post-operative conscious animal and it may well be that these levels were not quite so high. This would be consistent with Page's findings (1938) whose animals did not develop hypertension until at least three weeks after renal wrapping. The slow development of hypertension probably explains the generally small change in posterior left ventricular wall thickness in the hypertensive phase. The study, however, did confirm, once again, the anatomical accuracy of echocardiography and also helped explain the intriguing question of the phase of cardiac cycle at death.

The availability of an accurate method of measuring cardiac dimensions prompted a comparison between electrocardiographic precordial voltage and measurements of septum and wall thickness. Previous studies have demonstrated an extremely poor relationship between the electrocardiogram and measurements of wall thickness during biplane angiography, echocardiography and post mortem, except in the presence of established left ventricular hypertrophy (Carter and Estes, 1964).

In this study of borderline hypertension the comparison between electrocardiogram and echocardiograph was disappointing with no statistical correlation apparent. The situation was similar when the orthogonal maximum spatial vector was compared to septal and posterior left ventricular wall thickness.

Geva, Elkayam and Frishman (1979) in a study of patients with chronic systemic hypertension found the sensitivity of electrocardiographic criteria for left ventricular hypertrophy to range from 52% to 69%

when compared to echocardiographic measurements of left ventricular wall thickening but six patients who had increased left ventricular wall thickness and normal electrocardiograms were categorised as showing mild left ventricular wall thickening. In view of these results, and others, it is perhaps not surprising that no electrocardiographic/echocardiographic relationship was present in borderline hypertension. This observation does not however, attempt to diminish the importance of either technique in the investigation of the young hypertensive. Electrocardiographic appearances in early hypertension may be independent of muscle mass and it should be stressed at this point that uncertainty still surrounds the exact mode of production of electrocardiographic phenomena in ventricular hypertrophy. Differences in ventricular activation time in borderline hypertension may herald the onset of the earliest hypertrophy process.

No borderline hypertensives in this study fulfilled the commonly accepted echocardiographic criteria for left ventricular hypertrophy - i.e. wall thickness in excess of 11 mm (Feigenbaum, 1976). Indeed there was no significant difference between left ventricular wall thickness of hypertensives and normotensive controls, while the septal thickness of the latter group was actually greater than hypertensives. At first sight this might appear to indicate that wall thickness was independent of arterial pressure, but after six months of placebo-controlled antihypertensive therapy there was a significant increase in both septal and posterior wall thickness while these dimensions remained unchanged in the group treated with β -blocker.

These results are consistent with the view that cardiac hypertrophy is only slowly progressive and there must obviously be a baseline value. Measurement of wall and septal thickness may be important only as a comparison for future sequential studies, with left ventricular wall thickening indicating hypertrophy in progress and requiring urgent blood pressure lowering.

Baseline results from this study do not support Safar, et al's, (1979) findings of increased septal thickening in borderline hypertension compared to normotensive controls. In this French study, however, subjects were older with higher levels of systemic arterial pressure. Septal measurement by echocardiography is not without difficulty and false reports of asymmetric septal hypertrophy are commonly seen where incorrect transducer positioning has been employed (Kotler, Segal, Mintz and Parry, 1977).

These variables may explain the discrepancies between Safar's (1979) findings and those of this study. However, the results of the longitudinal study are in accord and indicate that cardiac hypertrophy is in progress, while at the same time being countered by blood pressure lowering in this phase of borderline hypertension. It will be remembered that a similar situation was witnessed with regard to the electrocardiogram.

These findings add further weight to the belief that cardiac hypertrophy is already present at the earliest stage of hypertension. A number of authors have already reported alterations in cardiac performance by echocardiography in established hypertension, before the appearances of electrocardiographic appearances, (Dunn, et al, 1975

and Savage, et al, 1979) and in pregnancy hypertension (Larkin, Gallery and Hunyor, et al, 1980). Many of these parameters, however, rely on the extrapolation of one-dimensional M-mode information into 3-dimensional form, which of course requires assumptions on the true ellipsoid character of the heart.

The effect of hypertrophy on myocardial performance has long been controversial, but quite recently Marcus, Mueller, Gascho and Kerber (1979) have demonstrated that the coronary circulation is adversely affected. It was previously proposed that the vascular hypertrophy of hypertension is a generalised process involving not only the vasculature, but also the myocardium. The inverse relationship between baroreflex sensitivity and septal and posterior left ventricular wall thickness is consistent with this view and suggests that possible structural changes may be present in the carotid body as part of generalised vascular hypertrophy in borderline hypertension. Reversal of this structural hypertrophy after prolonged β -blockade may be the mechanism which resulted in increased baroreflex sensitivity and this is in agreement with the findings of Jennings, Korner and Esler (1979) who found complete restoration of structural changes after one year of antihypertensive therapy.

Blood pressure reduction in established hypertension reduces future morbidity and mortality, but all too often at a stage when the process has been long-standing and end organ effects are already present. Far better that the condition be identified in the young, asymptomatic individual, free of all target organ damage. This study has shown that borderline hypertension is a sizeable problem and of course not all individuals will proceed to later, established blood pressure

elevation. These young people should therefore be screened intensively by office and home blood pressure readings over a period of time, while having serial electrocardiography and echocardiography performed. In those whose blood pressure does not settle with time, or who show evidence of developing cardiac hypertrophy by electrocardiographic or echocardiographic criteria assessment of baroreflex sensitivity and, if available, 24 hour continuous ambulatory, intra-arterial monitoring may help to decide those in whom long-term blood pressure lowering therapy is indicated.

CONCLUSIONS

- 1 Hypertension is a common finding in young males. This study found a prevalence of 28% of whom 19% fell into the borderline hypertension category.
- 2 Borderline hypertensives were heavier than their normotensive counterparts.
- 3 Heart rates of normotensives and hypertensives did not differ significantly.
- 4 Contrary to the findings of previous studies home blood pressure did not significantly differ from office readings.
- 5 Throughout continuous monitoring of 24 hour intra-arterial systolic and diastolic pressure there was a significant difference between normotensives and borderline hypertensives for the greater part of the day-long period.
- 6 The circadian variation of blood pressure was identical for both groups with night-time levels significantly lower than those of the waking hours.
- 7 Day-time ambulatory, intra-arterial blood pressure corresponded closely, but did not correlate with, office and home blood pressure.
- 8 All blood pressures were noted to be labile, but borderline hypertensives did not demonstrate increased variability.
- 9 Baroreflex sensitivity was reduced in borderline hypertension, but there was no correlation between this impairment of the control mechanism and blood pressure variability.
- 10 Effective blood pressure lowering was achieved by the β -adrenoreceptor blocker, atenolol, in borderline hypertensives with minimum side effects.

- 11 Atenolol effectively reduced systemic arterial pressure throughout the 24-hour period in a once-a-day dose.
- 12 Baroreflex sensitivity increased after six months β -blockade, but the increase was unrelated to the fall in blood pressure.
- 13 One in three young men with mild hypertension satisfied electrocardiographic criteria of left ventricular hypertrophy.
- 14 The relationship between body habitus and electrocardiographic criteria of left hypertrophy is weak.
- 15 Significant repeat variation of precordial voltage in the normal electrocardiogram is of sufficient magnitude to interfere with the accurate assessment of serial changes in the individual.
- 16 Maximum precordial voltage did not differ between the electrocardiograms of borderline hypertensives and normotensives, but the 24-hour blood pressure of seven hypertensives who fulfilled electrocardiographic criteria of left ventricular hypertrophy was consistently greater throughout most of the 24-hour period.
- 17 During the six month period of placebo-controlled atenolol therapy precordial voltage increased in the placebo group, while remaining unchanged in actively treated individuals.
- 18 Orthogonal electrocardiography correlated closely with conventional 12-lead electrocardiography, but neither technique's criteria for left ventricular hypertrophy displayed any correlation with echocardiographic septal and posterior left ventricular wall thickness.
- 19 There was no evidence of borderline hypertensive sympathetic overactivity based upon heart rate, baroreflex sensitivity and electrocardiographic appearances.
- 20 M-mode echocardiography is an accurate method for the measurement of posterior left ventricular wall thickness when compared to direct measurement at open heart surgery and autopsy.

- 21 Septal and posterior wall thickness did not differ between borderline hypertensives and normotensive controls, but during the six month period of antihypertensive therapy there was a significant increase in these dimensions in the placebo group, while remaining unchanged in the actively treated group.
- 22 The finding of an inverse correlation between baroreflex sensitivity and septal and posterior wall thickness supports echocardiographic and electrocardiographic data of developing cardiac hypertrophy in borderline hypertension.

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pressure, while the point at which they were suppressed represented systolic pressure.

Out of the two lines of evolution have developed the modern methods of measuring the blood pressure. The first important advance was in 1896 by Riva-Rocci, who inflated a pneumatic cuff on the upper arm to a pressure sufficient to obliterate the pulse at the wrist. Later v. Recklinghausen (1901) showed that Riva-Rocci's arm band gave erroneously high readings and recommended a cuff 10-15 cm. wide. In 1905, Korotkoff, a Russian physician, suggested that the sounds heard over the artery distal to the cuff should be used as indices of systolic and diastolic pressure. Subsequent work showed that those sounds passed through four successive phases as the arterial pressure was reduced.

Phase I : Sudden appearance of a clear, but often faint, tapping sound growing louder.

Phase II : The sounds are prolonged into a murmur.

Phase III : The sounds become clearer and increase in intensity.

Phase IV : The sounds quickly decrease in intensity and finally disappear.

It is of considerable interest that the two papers on which contemporary methods of estimating blood pressure are based, are inaccessible to most readers in the English-speaking world. W. Hall Lewis (1941) states that in the United States the only copy of Riva-Rocci's paper is in the Army Medical Library, and the only copy of Korotkoff's report is in the Slavonic Division of the New York Public Library. With the assistance of Miss Gallagher, Librarian to St. Mary's Hospital Medical School, I have been unable to trace a single copy of either of these papers in the libraries of Great Britain.

Lewis obtained translations of both papers, and I quote him as follows :

Riva-Rocci first recorded the purpose of his research on arterial pressure and then set forth the simpler aspects of hydraulics involved. He gave a fairly voluminous review of the literature and described the three types of the von Basch sphygmomanometer available commercially at the time. He preferred the first, or mercurial, model completed in 1881, to the non-mercurial manometer produced in 1883. Riva-Rocci adopted a modification of von Basch's instrument, which was similar to that proposed in 1881 by Rabinowitz, of which Riva-Rocci was not aware. Riva-Rocci's instrument was a "sphygmomanometer likewise based on the principle established by Vierordt and improved on by Marey and von Basch in turn. In other words, it is an instrument affecting manometric measurement of the force necessary to impede the progression of the undulation of the pulse. Sphygmomanometry is then applied to one of the large aortic branches, to the humeral. Since the humeral is the direct continuation of the axillary (since the region contains no collateral large enough to be considered as a branch of the bifurcation), the measurement gives the total charge of a point fairly close to the aorta, or, if you like, of the charge of pressure either in the aorta itself (if the left humeral is concerned) or of the brachio-cephalic trunk (if the right humeral is concerned)." Riva-Rocci considered that his instrument was easy to apply, rapid



in action, precise, and innocuous. It was composed of two parts, one for exerting pressure, one for measuring the pressure exerted. The compressor apparatus was represented by a tubular "muff" with walls soft, non-extensible, and impermeable to air. It consisted of a rubber tube 4 or 5 cm. in diameter, lined with a cloth sleeve to prevent undue dilation of the tube. One end of the tube was open, while the other was attached to a piece of metal made in two parts. The patient's arm was tested with this tube plus an insufflator. The intercalation of a manometer revealed the pressure on the "muff" at all times, and hence the pressure exerted on the arm.

Riva-Rocci stated: "The most reliable manometer is still the mercury manometer, but it is necessary to facilitate its reading by adopting a single branch, as in the manometers of Marey and of François-Franck, and the original model of von Basch. In order to render the apparatus easier to handle and transport, I, too, have adopted the metal manometer. So far, I have been able to obtain only the holosteric kind, since the aneroid kind is of more delicate construction."

... Korotkoff's observations were given at a meeting of the Imperial Military Academy in St. Petersburg, December, 1905 and reported in the bulletin of the Academy, "*Izvestiya Voennomeditsinskoi Akademii*," page 365. The original report occupies only a portion of one page in the bulletin, with the title: "On methods of studying blood pressure (from the Clinic of Prof. Feodoreff)." A translation in full reads:

"On the basis of his observation, the speaker came to the conclusion that a perfectly constricted artery, under normal conditions, does not emit any sounds. Taking this fact into consideration, the speaker proposes the sound method for measuring blood pressure on human beings. The sleeve of Riva-Rocci is put on the middle third of the arm; the pressure in this sleeve rises rapidly until the circulation below this sleeve stops completely. At first there are no sounds whatsoever. As the mercury in the manometer drops to a certain height, there appear the first short or faint tones, the appearance of which indicates that part of the pulse wave of the blood stream has passed under the sleeve. Consequently, the reading on the manometer when the first sound appears corresponds to the maximum blood pressure; with the further fall of the mercury in the manometer, there are heard systolic pressure murmurs which become again sounds (secondary). Finally all sounds disappear. The time of the disappearance of the sounds indicates the free passage or flow of the blood stream; in other words, at the moment of the disappearance or fading out of the sounds, the minimum blood pressure in the artery has surpassed the pressure in the sleeve. Consequently, the reading of the manometer at this time corresponds to the minimum blood pressure. Experiments conducted on animals gave positive results. The first sound tones appear (10-12 mm.) sooner than the pulse which (l. ar. radialis) can be felt only after the passage of the major portion of the blood stream."

There were now available three methods of determining the arterial pressure from the inflation of a cuff on the upper arm; the suppression of the pulse as felt at the wrist, the Korotkoff sounds, and the pulsations of the air contained in the cuff. Many papers have been written on these methods and their variations, their sources of error, accuracy, and convenience (see for example v. Recklinghausen's series in 1906 and 1930). In the English-speaking world the auscultatory method has come to be almost the only method used. Von Recklinghausen pointed out that the use of too small a cuff gave erroneously high readings, while the use of too large a cuff gave erroneously low readings.

¹ This should read *Izvestiya Imperatorskoi Voenno-Meditsinskoi Akademii*.

SUMMARY

This study was concerned with the measurement of blood pressure and the assessment of its patterns and variability in the young borderline hypertensive and normotensive male. The effects of prolonged β -adrenergic blockade were also studied in a placebo-controlled trial of atenolol in 30 borderline hypertensives in whom echocardiographic and electrocardiographic parameters were examined for possible evidence of early hypertensive cardiac hypertrophy.

Borderline hypertension was defined on the basis of blood pressure variation about the arbitrary limits of 140 mmHg systolic and/or 90 mmHg diastolic during at least three separate office readings with random zero sphygmomanometry during a three month baseline period. The 15 normotensives in the study at no time exceeded these limits during a similar time period.

Office and home blood pressure levels were significantly greater for borderline hypertensives compared to controls. Home blood pressure, however, was not significantly different from that recorded in the "stressful" hospital environment and this is contrary to the findings of previous studies.

The significant difference in blood pressure between normotensives and hypertensives was apparent for the majority of 24 hours when continuous ambulatory, intra-arterial records were analysed. Both blood pressure categories demonstrated profound night-time falls

in blood pressure, with an early morning rise. Day-time continuous arterial pressure corresponded closely to indirect office and home readings.

β -adrenergic blockade effectively lowered blood pressure in borderline individuals and although a non-significant fall in pressure was seen in office recordings in placebo-treated subjects this was not demonstrated in 24 hour recordings. The use of atenolol was accompanied by minimal side effects and was well tolerated.

Baroreflex sensitivity was found to be reduced in borderline hypertensives, but after chronic β -adrenergic blockade there was a return of sensitivity towards the normotensive range. There was no correlation between the degree of blood pressure reduction and increase in sensitivity, so it seems unlikely that β -blockers exert their antihypertensive action by a direct effect on the carotid baroreceptor mechanism.

Despite reduced baroreflex sensitivity there was no evidence of increased blood pressure variability, measured by the standard deviations of the hourly means, from analysis of continuous ambulatory blood pressure records of borderline hypertensives.

In a study of epidemiological data 27% of 913 young males aged between 16 and 35 years were found to have a blood pressure abnormality and 18% of these fell into the borderline category. Thirty per cent of young men of the remaining 9% with mild hypertension satisfied criteria for electrocardiographic left ventricular hypertrophy.

Despite this observation there was no significant difference in electrocardiographic maximum precordial voltage between normotensives and borderline hypertensives in the main area of this study. However, after identifying seven borderline hypertensives who fulfilled electrocardiographic left ventricular hypertrophy criteria it was found that their 24 hour intra-arterial blood pressure was significantly elevated throughout most of the day-time period when compared to non-hypertrophy individuals. These findings indicate a possible relationship between prolonged elevation of left ventricular afterload and electrocardiographic appearances of ventricular hypertrophy.

Blood pressure reduction had no effect on precordial voltage of the electrocardiogram, but at the end of six months there had been a significant increase in this measurement in the electrocardiograms of placebo-treated individuals.

Echocardiographic measurement of posterior left ventricular wall thickness was found to be anatomically accurate, but no correlation was found between electrocardiographic maximum precordial voltage and septal and posterior wall thickness. At the same time no difference between the echo measurements was seen when normotensive and borderline hypertensive values were compared, but blood pressure lowering prevented the increase in septal and left ventricular wall thickness which was found at the end of six months in the placebo-treated group.

The finding of a significant inverse relationship between baroreflex sensitivity and posterior wall and septal thickness suggested that early structural changes involving the vasculature and myocardium might already be operative and this observation is supported by the electrocardiographic and echocardiographic findings in this study of borderline hypertension.

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