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HAEMODYNAMIC PROFILING FOR DIAGNOSING AND TREATING HYPERTENSION

by

©G.S.H.DANIEL

Submitted in partial fulfillment of the requirement for the Degree of Doctor of Philosophy at Dalhousie University, Halifax, Nova Scotia, Canada, Spring 1984.

DEDICATED

To all who have nurtured me along the path of independent thought and academic excellence, beginning with my parents.

CONTENTS

Abstract

A method for haemodynamic profiling by noninvasive measurements was developed. Its repeatability was tested by comparing profiles determined 24 hours apart in 21 subjects. Significant correlations were obtained, with r values at least 0.80 ($p<.001$).

The method was then applied to a group of 25 treated hypertensives aged 29 to 68 years, and 11 normotensive subjects aged 26 to 60 years. It was found that despite being treated at higher levels of a stepped care treatment scheme, nonresponders to antihypertensive therapy, (13 subjects), had higher peripheral resistances (2702±171 dyne.cm.sec-5) compared to responders (2030±211 $p<.05$) and normotensive control subjects (1935±185 $p<.01$).

A prospective study of a group of 31 male hypertensive subjects aged 40-64 years, randomised into diuretic and beta-blocker treatment groups, showed a higher response to monotherapy for the diuretic treated group, 84% versus 55%. Beta-blocker monotherapy was most effective in a subgroup of hypertensives with low peripheral resistance and high cardiac output. Monotherapy subjects (in particular diuretic treated) showed improved cardiac contractile function with therapy.

Finally, a cardiovascular system model, regulated by baroreceptors, cardiopulmonary receptor mechanisms, autoregulation and renal control functions, was used to assess various possible factors determining nonresponse of arterial blood pressure to drug interventions. A theoretical study of the longterm cardiovascular responses to drug intervention with diuretics, vasodilators and beta-adrenergic blockers was carried out. The indications of this study are, that cardiovascular adaptation (i.e. reduced cardiovascular responsiveness) to the antihypertensive drug may be a more important factor than adaptation of the cardiovascular control systems, in determining nonresponse to antihypertensive drug therapy.

List of Abbreviations and Symbols

...ACP	- cardiopulmonary control function
...ANS	- autonomic control function
...ARL	- renal control function
...ATR	- autoregulation control function
...B	- unregulated value of variable or parameter
...E	- volume excess of circulatory bed
...M	- control function multiplier
...Q	- adapted 'set point' value of regulated parameter
...T	- time derivative
...X	- initial value of regulated parameter
ANG	- angle in radians
AOD	- aortic dimension
BSA	- body surface area
C...	- compliance of vascular space
CA	- arterial compliance
CC	- compliance of the systemic vascular bed
CIS	- compliance of the interstitial space
CRA	- right atrial compliance
CV	- compliance of the systemic venous bed
D...	- derivative
EF	- left ventricular ejection fraction
ELV	- left ventricular elastance
F...	- vascular flow rates
FC	- total capillary blood flow
FCO	- left heart output into systemic bed

FIN	- rate of fluid intake
FIS	- transcapillary fluid flow
FUO	- urine output
FVI	- venous blood flow
G...	- gain of control function
HR	- heart rate
HT	- body height
IVS	- inter-ventricular septal thickness
LAD	- left atrial dimension
LVED	- left ventrivular end diastolic dimension
LVES	- left ventricular end systolic dimension
LVPW	- left ventricular posterior wall thickness
P...	- pressure variable
PA	- arterial blood pressure
PC	- capillary hydrostatic blood pressure
PD	- diastolic blood pressure
PDA	- mean arterial blood pressure during diastole
PDR	- pressure drop across renal arterial tree
PIS	- capillary filtration equilibrium pressure
PMS	- mean circulatory filling pressure
PRA	- right atrial pressure
PS	- end systolic arterial blood pressure
PSA	- mean arterial blood pressure during systole
PSP	- systolic blood pressure
PV	- venous blood pressure
R...	- resistance variable
RA	- arterial resistance

RFAC	- ratio of venous to arterial resistances
RIF	- capillary leakage resistance
RTP	- total peripheral resistance
RVL	- total venous resistance
RV	- venular resistance
RVR	- resistance to venous return
SCF	- velocity of circumferential fiber shortening
SEM	- standard error of the mean
SL	- renal function parameter
SV	- stroke volume
T...	- time intervals, time constants of adaptation
TCP	- computer central processing time
TD	- diastolic time period
TRC	- RC decay time constant
TS	- systolic time period
V...	- volume
VA	- arterial blood volume
VB	- total systemic blood volume
VECF	- extracellular fluid volume
VIF	- volume of interstitial fluid
VLVD	- left ventricular diastolic volume
VLVS	- left ventricular systolic volume
VPL	- plasma volume
VRA	- right atrial volume
VV	- venous volume
WT	- body weight
X...	- cardiovascular drug input

XBL	- beta blocker
XHH	- diuretic
XVL	- vasodilator

Acknowledgments

I take this opportunity to express my many thanks to my supervisor Dr. Herman Wolf for his initiative and guidance in the completion of this study. I will also like to acknowledge the invaluable assistance of Dr. C.R.T. Dean and Dr. P.M. Rautaharju, both members of my supervisory committee.

Many other individuals have provided valuable assistance at critical phases of my research, namely: Dr. K. Mukelabai, Dr. T. Montague and Dr. G. Klassen.

To my friends and fellow graduate students of the department, my deep appreciation for being there to share the peaks, and for support over the troughs. A special 'thank you' to my colleague Janet Gregory.

Also my thanks for financial support to the Faculty of Graduate Studies, and the Heart Disease Research Centre. Clinical portions of this study were supported by grants to Dr. Rautaharju and to Dr. Wolf.

Chapter 1

1.1 INTRODUCTION

The present study sets out to determine haemodynamic features of the cardiovascular system which may be useful in the prior determination of anti-hypertensive drug regimens.

There are two major objectives of this study namely:

To design a simple model of the circulation which allows for the calculation of haemodynamic parameters from non-invasively recorded data, with possible application towards differentiating between hypertensive patient groups, and as an aid in the prior selection of anti-hypertensive drug therapy.

To simulate the haemodynamics of the circulation in an effort to provide assistance in the understanding of the interrelationships of the various cardiovascular control systems, and to study the possible responses to therapeutic interventions.

To this end, we set out to look at several hypotheses with regards to the cardiovascular system, the control of blood pressure and the hypertensive state, namely:

(H1) Hypertensives form a heterogeneous group.

(H2) Haemodynamic differentiation of hypertensives is possible, and provides for a rational and effective assignment of hypotensive drug therapy.

(H3) The cardiovascular system controllers adapt to the prevailing level of the sensed variable with varied time constants.

These views will be developed with reference to the literature on hypertension and blood pressure control, and from our data and digital computer simulations of the cardiovascular system. A review is given in Chapter 1.2 of the concept of, and previous attempts to classify hypertensive subject groups. The haemodynamic and circulatory control factors with possible relevance to the hypertensive state are reviewed in Chapters 3 & 4 respectively. In chapter 4.1 previous attempts at applying haemodynamic modelling of the circulation to the hypertensive state is reviewed, while section 4.2 discusses the estimation of circulatory parameters.

In carrying out our first objective, a simple Windkessel model of the circulation is presented in Appendix 2. This model uses non-invasively recorded data on systolic and diastolic blood pressures, left ventricular systolic and diastolic dimensions, heart rate and left ventricular ejection time, to calculate parameters of arterial compliance, degree of arterial filling, total peripheral resistance and ventricular elastance. The application of this model to the analysis of data from two different study groups of hypertensive subjects is carried out in chapter 5. Assessment is made of haemodynamic differences between responders and non-responders to anti-hypertensive therapy in one study, and between diuretic and beta-blocker treated patients in the second study.

In meeting our second objective, a more detailed analysis of the haemodynamic and control aspecects of the circulation is required. Previous haemodynamic studies of the hypertensive state have demonstrated that essential hypertension represents a spectrum of physiological alterations expressing varying combinations of pressor and depressor mechanisms, constituting what Page (1) calls a 'mosaic.'

Hypertension is today recognised as a disease of regulation which results because the mechanisms for keeping the blood pressure within the normal range have gone awry. There are several systems involved in blood pressure control, hence there are several abnormalities that can result in hypertension, and in some cases one system mechanism may be dominant.

The interactions between participating blood pressure control systems, and the relative importance of the haemodynamic changes they produce, may vary in early and established stages of the hypertension and in the differing expressions of the disease.

Under steady state conditions of constant blood flow, mean arterial blood pressure (PA) is given as a function of the total systemic blood flow (FCO) and the total resistance to blood flow (RTP) through the parallel peripheral circulations. This can be expressed as an equation:

$$PA = FCO \times RTP .$$

Hence, although a great variety of factors can produce elevated blood pressure, a longterm steady state increase in pressure can only occur due to factors resulting in an increase in cardiac performance or vascular resistance or both. Hence, determining the haemodynamic state is a logical first step towards the differentiation of high blood pressure states.

The hypertensive condition may be viewed as a pyramid, where the bottom of the pyramid represents the various pathological conditions which lead to the condition (presently largely unknown), and the top of the pyramid is the final outcome of all these pathologies in the form of elevated blood pressure (Fig 1.1-1).

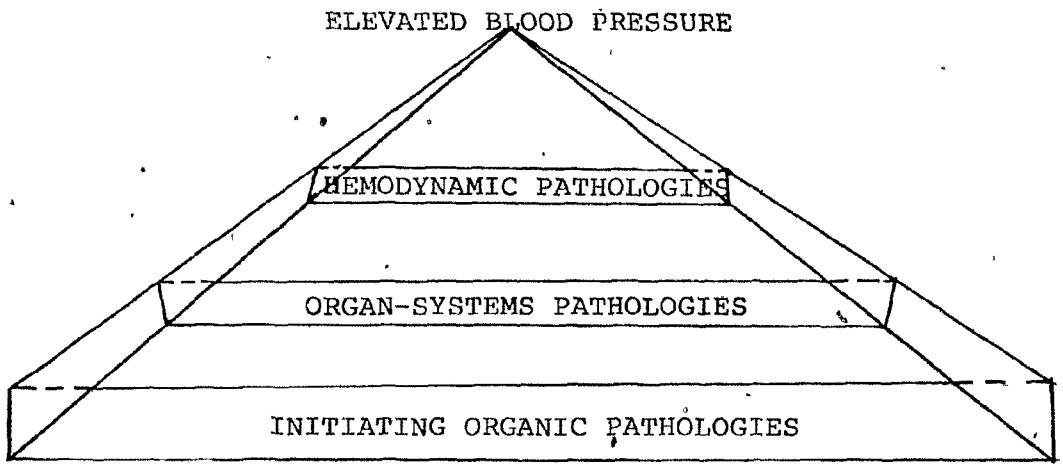


FIG 1:1:1 Hypertension Pyramid

Analysis at the top of the pyramid is limited to the

differentiation of severe, mild and borderline hypertensives. The level below the top could be assigned to the haemodynamic parameters which determine blood pressure.

For the longterm simulation of our cardiovascular model, the system is assumed to move from one steady state to another (iteration time steps varying from ten minutes to ten hours). Hence, use is made of the above pressure-flow relationship in our simulation of the longterm effects of cardiovascular drug therapy (section 6.2).

However, in order to better account for the shortterm non-steady state dynamics of the circulation, compliance properties of the arterial system must be incorporated in the model (further analysis of the energetics of the circulation would require the inclusion of inertial properties). The dynamical arterial pressure PA(t), results from the interplay of the rate of blood flow into and out of the vascular bed and the compliant properties of the bed. Because of the relationship between cardiac output and the degree of filling of the circulatory system (2), the haemodynamic factors evidenced to play important roles in maintaining elevated arterial blood pressure may be stated as: arterial overfilling and arteriolar constriction, or an inappropriate interaction of these two factors. Hence, blood pressure may be expressed (3) as:

PA ≈ Effective Arterial Volume x Vasoconstrictor Component, (where the effective volume refers to the circulating blood volume in relation to its unstressed vascular capacity). The effective volume depends on the relative distribution of total blood volume between the various intravascular spaces. This distribution depends on the total blood volume load and the relative capacitances of the intravascular spaces.

The two contributors to blood pressure, indicated above, may be amplified by other cardiovascular factors which 'fine tune' the system, e.g. factors affecting vascular reactivity. Hence the nervous, renovascular and neurohormonal systems are implicated in such a simple haemodynamic model.

If this model is correct we might then predict two kinds of chronic essential hypertension: one due to excess effective arterial blood volume and the other largely related to excessive arteriolar vasoconstriction. Between these two extremes more common forms may exhibit the whole spectrum of abnormal effective blood volume and vasoconstrictive combinations.

1.2 HYPERTENSION: CLASSIFICATION AND COMPUTER RECOMMENDED THERAPY

In view of the heterogeneity of essential hypertension and its possible varied expression in terms of haemodynamic conditions of volumic and vasoconstrictive functions, the control of the hypertensive state would therefore require different interventions, different treatment regimens (4).

Drug therapy should ideally be based on a regime which is designed to treat specific pathophysiological abnormalities. However, since the pathophysiological abnormalities underlying essential hypertensive disorders have not been fully unravelled, drug therapy is still largely empirical.

The recommended (5) and widely accepted treatment regimen do not differentiate between patients except by blood pressure, and response to therapy. It is designed to progress from mild to powerful drugs in order to achieve control of blood pressure, and applies equally to all patients with essential hypertension. In these 'stepped care' programs, the choice of drug is made on the basis of efficacy determined through trial and error, rather than on specific features in the patients clinical profile.

It is well established that not all patients with essential hypertension respond to the 'recommended' treatment, and the fact that they have to be treated at a higher level in the step care system may not be due to the severity of the condition but to the set of circumstances in that particular patient.

The pharmacotherapy of hypertensive disorders is based on the use of a wide variety of drugs, not only differing in chemical composition but also in their mode of action. These agents share only one common property: their ability to decrease blood pressure in hypertensive patients. However, the changing haemodynamic conditions leading to these effects often remain unknown, namely because of lack of knowledge of the detailed dynamics of antihypertensive drug action, and lack of insight into the longterm interactions of these drugs with blood pressure control mechanisms.

Although the major haemodynamic, neural and endocrine characteristics of the hypertensive disorder are now known, the complexity of the multifold responses of the cardiovascular control system to changes in cardiovascular parameters makes the unravelling of dynamic cause-effect difficult. A reflex increase in sympathetic activity, and plasma volume due to renal fluid retention, following vasodilator drug therapy, may for instance reduce the

effectiveness of the original hypotensive effect of the vasodilator.

Efforts have been made to individualize hypertensive treatment regimens by differentiating the hypertensions. Laragh (3,6,7) has advocated the use of plasma renin activity as an indicator for the choice of antihypertensive therapy. The renin subgroups can be subdivided according to various abnormalities in aldosterone secretion so that there are theoretically, nine different subgroups of essential hypertensives. (8). Buhler (9) has considered age as an additional factor in the analysis of this classification scheme. In this differentiating hypothesis, hypervolumic and vasoconstrictive patients are distinguished, with one group responding better to diuretic therapy and the other to adrenergic blockers. However, studies from other groups (10,11) have failed to confirm the therapeutic benefits of Laragh's hypothesis.

Another approach based on the use of haemodynamic profiles for the differentiation of hypertensive patients into different treatment classes has been suggested (11). This approach is based upon the assumption that patients with a relatively high cardiac output would respond better to beta-blocker therapy than patients with normal or low cardiac output. However, the results of the study by Guazzi (12), did not confirm this particular treatment hypothesis.

Efforts at differentiation have not however, penetrated into the primary care system where the vast majority of hypertensive patients are being treated. Possible explanations are cost-benefit considerations and the complicated nature of the tests. In addition, there are questions as to whether differentiation or generalized stepped care is the most efficacious.

We propose the development of an alternative to these classification hypotheses for differentiating patients with respect to their treatment regimens. While attempting to maintain the hypervolumic-vasoconstrictive dichotomy, we replace complicated renin tests with non-invasive haemodynamic investigations supplimented by haemodynamic systems modelling of the dynamics of the circulation.

The model will be based on a relatively uncomplicated lumped parameter system of reservoirs and resistances for arterial, capillary and venous beds, with a contractile heart source. A patient is then characterized by his model parameters. Such a model will provide a framework within which intervention results can be described and monitored.

From the results of the studies of Guazzi and others (11,12), we recognize that some degree of differentiation of hypertension with respect to haemodynamic parameters is

indeed possible. Guyton (13) has made an analysis of the blood pressure control systems and the concepts he uses are based on haemodynamic variables of flows, resistances, capacitances and volumes, and he has applied computer models to the control systems analysis of the longterm regulation of blood pressure. Struykerboudier (4), using the systems analysis of Guyton et al. has attempted to analyse the dynamics of antihypertensive drug action. It was shown that it is possible to quantify the dynamics of drug action if the primary pharmacodynamic effects of these drugs, as well as the response to their primary effects, were taken into account.

The hope is that if the models are proven to be reasonable representations of reality, then they may not only aid in drug therapy, but may also be used as a tool in the design of new drugs (4).

Other approaches to computer assisted antihypertensive therapy have been published. Coe (14) has used an adaptive statistical treatment algorithm for guiding drug therapy. To the extent that the algorithm predicts future long term experience, it is described as having the potential to "guide nonphysicians in drug treatment of hypertension in a manner compatible with prevailing standards for such treatment among consultants." Smith (15), on the basis of a

discrete state transition disease model, has produced an interactive computer program to determine the prognosis of patients on antihypertensive therapy. These studies indicate that there is a desire to make the computer behave as physicians might in making diagnoses and recommending therapy.

Of the various classification procedures, the haemodynamic approach has been used here, since the vast body of experience with haemodynamic models surpass that in any other hypertension model and the system description can be complete without the inclusion of many unproven assumptions.

In order for computer recommended therapy, based on the dynamics of the individual hypertensive state, it becomes necessary to tailor the model parameters to the given patient, (16), hence critical unmeasurable parameters can be tracked and monitored. Such a patient to model comparison is not only mandatory to validate the model but is also necessary in order to achieve one of the primary goals of the model: to be a diagnostic tool for the clinician.

Chapter 2

2.1 ROLE OF CARDIAC OUTPUT IN HYPERTENSION

Increased cardiac output with normal peripheral resistance, has been reported by many investigators to occur in the early stages of some forms of hypertension in humans. This pattern is often reversed in older patients with well-established essential hypertension, who show normal or below normal levels of cardiac output, and a marked increase in peripheral resistance (17).

For many years, established hypertension has generally been characterized by normal cardiac output and elevated peripheral resistance (18). However, most forms of mild essential hypertension show elevated cardiac output at some stage of the hypertension (19,20).

An early increase in cardiac output has been suggested as a necessary condition for the later rise in total peripheral resistance (21,22). However, more recent studies of clinical hypertension due to sodium loading (23) and increased mineralocorticoid secretion (24) have demonstrated that a primary rise in resistance occurs more often than not. Other clinical conditions have shown persistently elevated cardiac output without any tendency for resistance to increase (25).

Coleman (26), views these latter observations as being explainable in terms of accepted patho-physiological mechanisms often related to increased metabolic needs or decreased oxygen delivery. Other clinical and experimental models show transitions from increased cardiac output with normal resistance to normal output and increased peripheral resistance (27,28). Generally, in conditions of established hypertension cardiac output seems to fall while peripheral resistance is increasing (29,30).

In approximately one-third of patients with borderline hypertension, total peripheral resistance was shown not to contribute directly to an increase in blood pressure (31). Because cardiac output appeared to be elevated, the suggestion was made that this represented the initial stage of the hypertension. If hypertension did not begin with an increase in resistance; did the increase in cardiac output reflect a primary disturbance of fluid volume? This question posed many years ago is still a subject of controversy (32,33).

No significant relationship has been found between blood volume and cardiac output in either normal (34), or hypertensive (20,30,32,35) individuals. In most instances the increased cardiac output of essential hypertension is associated with normal (36) or decreased (34,37) blood

volume. In contrast, a significant direct correlation was found between cardiac output and cardiopulmonary blood volume, and between cardiac output and the ratio of cardiopulmonary to total plasma volume (20,32,35). Hence, cardiac output depends mainly on the distribution of blood volume between peripheral and cardiopulmonary areas, rather than on the magnitude of volemia. This relationship is improved when differences in sympathetic drive in patients are reduced by cardiac autonomic blockade (38), and by the administration of isoproterenol (20).

Plasma volume has been found to increase in the face of increased cardiac output (34) and increased mean circulatory pressure (20), suggesting venoconstriction. Similar conclusions have been drawn from the studies of cardiopulmonary blood volume in established (20,35) and borderline (20,35,39) essential hypertension; cardiac output for a given cardiopulmonary volume level being lower in hypervolumic than in hypovolumic essential hypertensives (32).

In several studies the increased cardiac output state can be attributed to an increase in heart rate (20,36,40), stroke volume being normal. When excess cardiac function is mainly determined by heart rate, the underlying disorder has been attributed to a combination of sympathetic overacting and parasympathetic inhibition (41).

One major shortcoming of studies on the role cardiac output may play in chronic rises in blood pressure is the inadequacy and diversity of the methods used to determine stroke volume and cardiac output. Results obtained with different techniques may not be directly comparable. Also, normotensives do show wide variations in cardiac output, and these deviations from the mean include increases in cardiac output which have been considered a haemodynamic abnormality in the early phases of some hypertensions. These wide variations have only served to further demonstrate the heterogeneity of the haemodynamics of hypertension.

2.2 VOLUME FACTOR IN HYPERTENSION

Blood volume studies carried out by many reseachers have provided additional evidence (37,39) that hypertension cannot be considered a homogeneous entity. The spectrum of volume alterations and their haemodynamic correlates in hypertension appear too wide to be forced under a single physiological construct. These studies show that hypovolemia occurs in most types of hypertension for example: high and normal renin essential hypertensives (42), pheochromocytoma (43), and renovascular hypertension (44).

However, hypervolemia is the rule in other forms of hypertension, namely: primary aldosteronism (25,45), volume dependent low renin essential hypertension (46), and in renal parenchymal disease (47).

Studies in essential hypertension show that the weekly average diastolic pressure is inversely proportional to the volume of circulating plasma (34,48), contrasting the positive correlation shown in patients with renal parenchymal disease (49,50).

With the exception of the initial phase of experimental renal hypertention of the one kidney, one-clip type, and of mineralocorticoid hypertension, the various established

forms of hypertension are not associated with an increase in the intravascular volume to a degree which could explain the elevated blood pressure state. In mineralocorticoid hypertension, which responds with an increase in cardiac output, the intravascular volume may become normal or even reduced, with progressive hypertension (24), especially if total vascular compliance is reduced.

Most studies indicate that extracellular fluid volume in essential hypertension is normal (51), with expanded volume occuring mainly in specific conditions such as: renal parenchymal disease (47), cardiac impairment (52), increased exchangeable sodium (53), and in primary aldosteronism (45).

It should be noted that elevated blood volume does not necessarily lead to the development of hypertension (49). This may indicate the interference of some additional factor (with haemodynamic expression) in the translation of hypervolemia to hypertension. Luetscher (54) in his mathematical analysis of the circulation, has shown convincingly, that haemodynamically our biological system can accomodate without a rise in blood pressure, volume alterations of the degree usually seen in hypertensive patients. This may in part be due to changes in vascular compliance. Hence, it can be noted that in exploring the relation between volume and hypertension, neither absolute

increases nor decreases in volume can be fully interpreted without added information about the compliance within the circulation, and hence an estimate of the effective degree of filling of the vascular system

As with cardiac output, the methods of volume measurement are very inexact, with high variability in the results. There is also the problem of a comparative volume index in the comparison of individuals of differing body sizes. Whether body mass, height or body surface area provides the most suitable index is yet to be determined (32).

2.3 VOLUME DISTRIBUTION AND CAPILLARY FILTRATION

The control of total body fluid volume and hence blood volume is determined over the long term by fluid intake and fluid loss mainly by the kidneys. The kidneys therefore serve a unique role in the maintainance of blood volume and thereby arterial blood pressure. The kidneys have therefore been implicated by Guyton (13) in almost all forms of hypertension. However, changes in blood and plasma volumes in relation to total fluid volume depend on transcapillary filtration, capillary filtration pressures and the fluid shift system.

The finding of decreased plasma volume in patients with normal extracellular fluid volume has suggested that there is a disturbance in the partition of intravascular (VPL), and interstitial (VIF) components of the extracellular fluid volume (VECF).

$$VECF = VIF + VPL.$$

The ratio VPL/VIF in men with essential hypertension has been found to be reduced (55), while in renoprival hypertension it is found to be increased (56).

Hypertensives with reduced plasma volume have been found to have a significantly lower VPL/VIF ratio than normal or hypervolumic hypertensive individuals. The latter have

ratios which are only slightly reduced and are not significantly different from normal (32). Since the relation between plasma and extracellular fluid volumes is particularly stable in normal subjects (57), the alteration in the ratio VPL/VIF in hypertensives suggests a disturbance in the forces regulating extracellular fluid distribution.

The distribution of the total peripheral resistance between pre- and post capillary vessels (RA, RV respectively), affects capillary hydrostatic pressure (PC), thus modifying capillary filtration. The relationship between the various systemic pressures and resistances may be given by the equation:

$$PC=(PV+PA*RV/RA+PIS*RV/RIF)/(1+RV/RA+RV/RIF).$$

(where PA, PV - arterial and venous hydrostatic pressures; RIF - transcapillary impedance to plasma flow; PIS - net arterial and interstitial osmotic pressures and interstitial hydrostatic pressure). A similar, and simpler, relationship has been given by Landis & Pappenheimer (58) for the condition of no net transcapillary fluid flow.

An increased capillary filtration rate has been observed in essential hypertensives (59), with an increased transcapillary rate of albumin escape (48,60), which is directly related to the mean arterial pressure. This suggests the possibility of an inadequate protection of the

capillaries by the precapillary sphinctor (i.e., reduced precapillary resistance), or an increased venous tone.

Changes in venous resistance and compliance have a major effect on capillary hydrostatic pressure and on venous return to the heart and therefore on body fluid distribution and cardiac output. It has also been observed that the compliance of the interstitial space may be decreased in experimental renal hypertension (56). Decreased interstitial compliance, as well as decreased venous compliance would tend to increase venous return.

The literature on hypertension is sprinkled with reports which suggest significant changes in venous distensibility in hypertensive individuals. The decreased VPL/VIF ratio has been attributed to an increase in venous tone (35,61). The increased venous tone is offset by the decreased volume, resulting in the finding that cardiac output and right atrial pressure are normal in most essential hypertensives. These conclusions have also been supported by the finding of decreased venous distensibility in hypertensive patients (62). Also the fact that the ratio of cardiopulmonary to total blood volume is increased in some hypertensives with reduced blood plasma volume, suggests a decreased reservoir function of the large veins (20,35,39), which would be associated with a slight increase in venular tone. Decreased

venous compliance in the presence of decreased blood volume could leave cardiac filling unchanged or increased and thus cardiac output would adjust accordingly.

Leth (61) reports that the ratio VPL/VIF was further diminished by propanonlol and hydrochlorothiazide therapy, suggesting venoconstriction as the most probable cause of the shift in fluid volumes. Other studies with guanethidine have shown that neural control of the veins could play an important role in the distribution of extracellular volumes (63).

Kettel (64) found no evidence for increased venous resistance in the large veins of men with essential hypertension. There have been reports however, suggesting altered capillary filtration and shifts in fluid from the intravascular to the interstitial space (37).

Studies in isolated vascular beds have suggested that an increased pressure at the venular end of the capillary bed could lead to vasoconstriction (65), and since the small veins and venules contain the largest proportion of blood volume , their functional relationship to the haemodynamics of the distribution of body fluids should provide valuable insights into the hypertensive volume abnormalities.

2.4 RESISTANCE AND AUTOREGULATION

Established hypertension has generally been characterised by elevated arterial pressure due to increased vascular resistance. The search for a vasoconstrictor mechanism to explain the increased total peripheral resistance has focused on humoral factors such as renin, and on the overactivity of the autonomic nervous system. But in many instances, changes in these suspected variables are small in relation to the increased resistance observed, hence additional factors such as highly increased vascular reactivity, have been postulated. However, such explanations have not proved entirely satisfactory.

The observation of a progressive rise in total peripheral resistance above normal, over several days, in certain forms of hypertension (for example, volume expansion with an initial increase in cardiac output), has given rise to the use of the term autoregulation in hypertension (27).

Autoregulation refers to the local tissue mechanisms which act intrinsically to control vascular resistance and thereby the flow through a particular tissue (27). The underlying mechanisms in this process are not completely understood, but by definition they act independently of the central nervous system or circulating hormones.

Nearly all of the individual organ systems locally adjust their vascular resistance to some degree in order to maintain an appropriate level of blood flow, hence total peripheral resistance is determined by the spectrum of these autoregulatory capacities. The overall regulation results in what is called ' whole-body autoregulation' (65).

The autoregulatory response varies in different tissues. In the kidneys, increased perfusion pressure quickly produces a rise in resistance, but in the skin resistance quickly falls due to passive vasodilation resulting from increased transmural pressure. As a result of this varied mixture of active vasoconstriction and passive vasodilation, no effect of increased tissue perfusion pressure on total peripheral resistance may be observed over several minutes (66).

Local factors adjust the level of resistance so that the ratio of tissue blood flow to tissue metabolism tends to remain constant for a given tissue (67). This ratio however, varies among the peripheral circulations, being highest in the kidneys and lowest in the heart (67). In some organs, notably the heart and skeletal muscle, shifts in the site of principal resistance are known to occur. The evidence indicates that acute sympathetic stimulation shifts the site of principal resistive pressure drop towards smaller arterioles (68). This could alter the flow pattern, for

example, metarteriolar constriction could decrease capillary density thereby increasing diffusion distances and hence change the setting of the flow/metabolism ratio.

If autoregulation controls blood flow via resistance changes in hypertension, then we would expect hypertension to be characterised by increased resistance and normal blood flow; if humoral or neural vasoconstrictors adjust resistance independent of the metabolic needs of the tissues, then we would expect flow derangements to often be a part of the overall haemodynamic description of hypertension.

It has not been clearly demonstrated whether the rapid autoregulatory response in the various tissues might persist indefinitely in hypertension, or if there might be further development of vasoconstriction and a gradual substitution of longer-term mechanisms. The most striking long term adjustment is the gradual alteration of the vascular architecture by changes in wall thickness and length, and by the growth or decline of new and existing vessels (69). Evidence has been provided by Folkow (69,70), supporting a gradual substitution and transformation to longterm structural mechanisms.

These slowly developing structural changes appear to contribute to the changes in total peripheral resistance

observed in established hypertension, though some change in resistance may be directly induced by the high pressure. However, in situations of chronic volume overload (or a prolonged alteration in tissue metabolic rates), the needs of the tissues appear to be best met by a more or less longterm autoregulatory mechanism with permanent vascular alterations.

The potency of autoregulation is cited by Cowley (27), who states that fluid retention over a period of weeks or months leading to a 10 per cent increase in cardiac output can sustain a 100 per cent increase in arterial blood pressure.

The most dramatic illustration of this longterm tissue autoregulation is the adjustment in blood flow observed in patients with coarcation of the aorta. Measurements have shown that despite an increased arterial blood pressure in the upper extremities, the blood flow per unit mass of tissue is nearly normal in both upper and lower extremities (71).

Based on the work of several investigators (13,21,72), a well structured concept of autoregulation has now evolved. Increases in extracellular fluid and blood volumes resulting from: renal disease or dysfunction, excess salt intake or increased steroids, leads to high cardiac output and

hypertension. Eventually longterm autoregulatory processes return the cardiac output to normal after a number of days, and the hypertension is maintained by an increased peripheral resistance.

Changing haemodynamic patterns after therapeutic intervention offer further support for the concept of longterm autoregulation (73,74). Wenting (24) found that in patients with primary aldosteronism, discontinuation of spironolactone therapy resulted as expected, in a gradual increase in arterial blood pressure. This increased pressure was at first associated with an increase in plasma volume, but the latter returned towards normal, presumably as autoregulation produced vasoconstriction.

Other studies have suggested that in patients who respond to diuretic therapy, the initial haemodynamic effect is a decrease in plasma volume and cardiac output. Over the next several weeks plasma volume and cardiac output return towards normal, while the reduction in blood pressure is maintained by the progressive fall in peripheral resistance (73,75).

The link between volume and hypertension cannot always be described in terms of autoregulation (49,76). Some clinical observations are difficult to reconcile with the

autoregulatory hypothesis; these include the persistence of elevated cardiac output in primary aldosteronism (25), as well as in some anephric patients (49,77), and some patients with long standing essential hypertension (78).

There are essentially no studies of the time course of changes in resistance to blood flow during the development of hypertension. Only the steady state values, separated in time, are available. Thus it has not been determined whether the time course of the resistance changes in individual tissues is compatible with the phenomenon of classic autoregulation and/or vascular restructuring.

Autoregulatory vasoconstriction is definitely not required to explain resistance increases in situations where high levels of circulating vasoconstrictors are present, for example, hyperreninemia with advanced renal disease, and increased catecholamine concentration in pheochromocytoma. However, these cases account for only a very small percentage of the total incidence of hypertension.

Autoregulation of cardiac output and peripheral resistance, two haemodynamic variables which control arterial blood pressure, is a pivotal mechanism connecting these two parameters with each other. However, a rise in cardiac output, which is the consequence of hypervolemia caused by

excess fluid or salt intake, and by reduced renal mass, is haemodynamically not comparable with an increased cardiac output subsequent to cardiac sympathetic stimulation. In the latter case (as shown in the dog), no effect on resistance may occur (66), or persist after stimulation ceases (79).

The function of the circulation is to satisfy the metabolic needs of the tissues, so that in the long term, blood flow is more important than pressure. Autoregulation is only one of many overlapping parallel control systems concerned with the delivery of the proper blood flow to the tissues. Its basic purpose is the control of blood flow and hence, generally, it disregards blood pressure, and as such, can alter the equilibrium state of arterial blood pressure. Although autoregulation cannot be used to explain all the haemodynamic changes observed in hypertension, it is important to understand those situations in which autoregulation does influence observed haemodynamic changes.

Chapter 3

3.1 HAEMODYNAMIC CONTROL SYSTEMS

> Old concepts are being reinvestigated and new fields are being explored. As is usually the case in physiology, many are following a reductionist approach and studying the minutia of structure and function ... Others are approaching the totality and dealing with the autonomically controlled cardiovascular components of reaction and behaviour.
>
> C. McC. Brooks (1981).

There are several mechanisms which determine the stability of arterial blood pressure. Each of these mechanisms differs in their capability and speed to return pressures towards their control levels. Each mechanism also differs in the range of pressures over which it can effectively operate, and the duration of time over which it is effective (80,81).

In the analysis and understanding of the hypertensive process, it is useful to consider arterial blood pressure as being regulated by two major mechanisms:

(i) rapid acting mechanisms which provide short term and intermediate control, and which usually exert their effects through hormonal and neural regulators.

(ii) long-term regulation which is invested in a renal-fluid-volume-pressure mechanism.

Guyton (82) has suggested that it is this latter mechanism which ultimately dominates the regulation of blood pressure and determines the value around which the blood pressure stabilizes.

In this analysis of the control of blood pressure we shall be assuming that:

(i) blood pressure control is vested in closed feedback loops.

(ii) in the adaptable blood pressure controlling system control dynamics occur at a level of analysis 'below' the level of the controlled haemodynamic system.

The several mechanisms which are of primary importance in the control of blood pressure in the hypertensive state includes: baroreceptors, cardiopulmonary receptors, renal system, numerous circulating hormones and other vasoactive compounds, and local regulatory processes (e.g. autoregulation).

3.2 BARORECEPTORS

Arterial baroreceptors respond to changes in arterial blood pressure by changing afferent nerve activity originating from the receptors in the aortic arch and carotid sinus (83,84,85). The normal arterial pressure pulsations are important in the activity of the baroreceptors as decreased pulsations have the same effect as a decrease in mean arterial pressure (86). The static gain of the overall baroreflex was found to attenuate mildly with an increase in pulse pressure, whereas the effect of changing pulse rate was minimal (87).

The change in afferent nerve activity influences efferent sympathetic and parasympathetic nerve activity via the CNS. However, local reflexes mediated at the spinal level, have been known to occur via cardio-cardiac sympathetic ganglions (88). The afferent signals via the vagal and sympathetic nerves appear to converge into a common final neuron pool and the individual reflex effects are in an approximately additive manner (89), the two autonomic arms acting reciprocally (90). However, nonreciprocal reflexes have been observed on distension of cardiac chambers (90). The reflex efferents include control signals to the heart (both rate and contractility), resistance and capacitance vessels and some endocrine systems. Signals from higher level of the

brain can however, alter the performance of the reflex system, for example as in exercise.

These reflexes provide the cardiovascular system with fast and potent mechanisms to adapt blood pressure to meet its many and varied challenges. These baroreceptor mechanisms possess a limited duration of activity since they adapt, over one to two days, to the level of blood pressure to which they are exposed (91,92), accompanied in some cases by structural changes in wall of the arteries. Recent studies however, have indicated that a substantial amount of adaptation (baroreceptor resetting) may occur within minutes after the baroreceptors are subjected to acute hypo- and hypertension (93,94,95). The baroreceptor reflex can therefore serve only to buffer the rate at which blood pressure changes, while the longterm levels are set by other mechanisms, as indicated in the dog (96,97).

The arterial baroreceptor reflex is a typical example of biological control based on negative feedback. It is also an example of a multi-input, multi-output, multi-level control system, as both the carotid and aortic receptors sense multiple components of the input pressure.

In the early phase of interaction between physiology and classical control theory, the baroreceptor reflex system was

often envisaged as a constant reference pressure servo-control mechanism. The system thus schematized attempts to equalize the actual arterial pressure with a desired reference pressure. However, no neural definition nor representation of the reference or error signal has been documented. As a result a different scheme has been presented, in which blood pressure equilibrium is determined by the interaction between competing dynamic processes, tending to decrease or increase the blood pressure (87). The experimental evidence also indicates that the arterial baroreceptors provide the baroreflex with a 'floating' rather than a fixed set point determined by the prevailing arterial pressure (95), as the adaptive baroreceptor mechanism 'unfolds'. Experimental evidence, mainly in the rabbit, indicates that the baroreceptors are nonlinear in their operation, showing a threshold, a linear range and the saturation (98). Curves have been produced relating heart period to vagal efferent activity. At low levels of activity the curve is linear but saturation flattens it when heart period is approximately three times its resting value (95,99).

There are question as to where on the nonlinear baroreflex curve normal and hypertensive indiviuals operate (100,101). The prevailing clinical and experimental evidence indicates that normal individuals operate at mid-range (below for very

low blood pressures), whereas hypertensives tend to be found closer to their saturation levels (95,101). This latter finding would agree with the often made interpretation of a decreased baroreflex gain in hypertensives.

Experimental evidence has also indicated that the threshold, operating range and saturation level adapt to the prevailing level of blood pressure (95,98). In chapter 6 the model representation of this and other controls will be given.

Cardiopulmonary reflexes are elicited from the so-called low pressure receptor areas in the atria and in the pulmonary arteries, due probably to changes in the degree of filling of the cardiopulmonary system. These reflexes appear to serve to primarily regulate blood volume (102,103). The reflexes act mainly through changes in sympathetic nerve activity and the subsequent effect on the secretion of vasopressin (104,105), and on the renin-angiotensin system (106). The reflexes have been shown in the dog to compete more effectively with the arterial baroreceptors in the kidneys than they do in the hindlimb (107). As much as 50% of the renal vascular autonomic tone has been attributed to the cardiopulmonary reflex (107). However, when the arterial baroreceptors are fully active cardiopulmonary receptors exert little effect on cardiac contractility and blood pressure responses (108,109).

The concept of a low pressure autonomic reflex, sensitive to pulmonary or central vascular filling must be introduced for the following reason: - If the only input to autonomic activity is from arterial pressure receptors, then arterial pressure must decrease on standing in order to provide the signal for an increase in autonomic activity and to initiate the central movement of blood necessary for counteracting the pooling of blood in the lower limbs (110). However, there is evidence of increased arterial pressure on standing (110). Results of one study suggests that this tonic inhibitory influence of cardiopulmonary baroreceptors is augmented in humans with borderline hypertension (111).

The above neural reflex mechanisms provide for the rapid control of the cardiovascular system, in contrast to the intermediate and longer-term control mechanisms discussed below.

3.3 CIRCULATING SUBSTANCES

Circulating catecholamines can influence the haemodynamic state of the circulation by their direct effect on the heart and the vasculature system, and indirectly by promoting the release of renin or by influencing the tubular reabsorption of sodium by the kidney (112). Norepinephrine released from sympathetic nerves forms the primary catecholaminergic control of the cardiovascular system. However, catecholamines released from the adrenal medulla can influence parts of the circulation which lack a sympathetic nerve supply e.g.- metarterioles of several vascular beds (113).

The renin-angiotensin-aldosterone system is one hormonal mechanism involved in the control of blood pressure. A decrease in renal filtration rate and glomerular pressure, or a reduction in tubular fluid sodium concentration, or increased renal sympathetic activity can cause renin to be released from the juxta-glomerular cells of the kidneys (114). Renin catalyses the conversion of renin substrate into angiotensin I. This substance is converted into the more powerful angiotensin II by a converting enzyme that is found mainly in the lungs. Angiotensin II exerts a number of effects on the cardiovascular system including:

(a) constriction of arterioles and veins

(b) intrarenal effects causing retention of both sodium and water.

(c) enhancement of sympathetic activity both by peripheral-presympathetic and CNS effects.

(d) stimulation of adrenal aldosterone secretion.

Aldosterone affects blood pressure control through its effects on body fluid volumes. Its primary effect is to increase renal tubular reabsorption of sodium. At the same time potassium excretion is enhanced. The reabsorption of sodium promotes the increased water reabsorption, thereby raising the level of extracellular fluid volume (115,116).

The control of vasopressin release is another mechanism involved in the regulation of blood pressure. Vasopressin is released by the posterior pituitary gland in response to a change in osmolarity of blood plasma or a change in blood volume. The two primary effects of vasopressin are: increasing tubular permeability to water (promoting water reabsorption), and causing strong vasoconstriction (117).

3.4 KALLIKREIN-KININ AND PROSTAGLANDIN SYSTEMS

Kinin peptides- namely bradykinins, have long been known as potent vasodilator substances, being linked to structures and processes that appear to control systemic vascular resistance and blood pressure, though their exact role has as yet to be determined. Kinins are rapidly activated by kininases, the best known of which is kininase II or angiotensin I converting enzyme, which links the kallikrein-kinin system to the renin-angiotensin system. The systems are also reported to be linked due to effect of kallikrein in converting inactive plasma renin to active renin (118); in vivo however, the importance of kallikrein in activating renin is yet to be determined. However, a significant positive correlation between plasma renin and kinin has been reported (119). Also, angiotensin, aldosterone and ADH can stimulate renal kallikrein release either directly or indirectly through an alteration of water and electrolyte metabolism (120).

Other studies suggest that the renal kallikrein-kinin system may be involved in the regulation of water and electrolyte excretion and hence effect blood volume and pressure, with increased kinin levels leading to diuresis and naturesis. The presence of the kallikrein-kinin system in the kidneys is also especially important in circulatory regulation since

the kidneys are essential in the longterm control of blood pressure.

In essential hypertension and most experimental forms of hypertension urinary kallikrein excretion is decreased, with the exception of mineralocorticoid induced hypertension, in which it is increased (121,122).

Once activated, kallikrein is rapidly inhibited by several plasma proteinases and hence only prekallikrein is normally found in blood plasma. Kinins are also rapidly inactivated by kininases in the blood and tissues. Therefore it appears that the direct regulatory effect of the kallikrein-kinin system may be limited to relatively short term control , of duration intermediate between baroreceptors and the renal system.

Although the role of the kallikrein-kinin system in the regulation of the circulation is not completely understood, the evidence is that it is involved in regulation of local blood flow, water and electrolyte excretion, and consequently affecting blood pressure (123).

Prostaglandins are a family of compounds of high biological activity, synthesized by virtually all body cells. They comprise numerous vasoactive compounds which are mainly

potent vasodilators, while some others are vasopressors. Recent studies have suggested that even within a single organ prostaglandins effect a wide spectrum of regulatory mechanisms that influence blood pressure (124). These mechanisms include: the renin-angiotensin system, renal sodium and water excretion, and vascular smooth muscle tone/autoregulation (124); the prostaglandins acting as local mediators of the various hormonal actions (125). Metabolism of prostaglandins are very rapid, and the metabolites are excreted in the urine (126). Prostaglandins may therefore play an important role only in regulatory phenomenon of intermediate duration, unless, however, prostaglandin synthesis is permanently disturbed.

The endocrine mechanisms controling blood pressure are not as potent or as fast as the nervous reflexes. The primary importance of these mechanisms seems related more to the regulation of body fluid volumes and content, rather than the direct control of arterial blood pressure. However, both through their direct effects on the cardiovascular system and indirect effects via changes in renal function, these mechanisms play an improtant role in the control of blood pressure.

3.5 THE RENAL SYSTEM

The kidneys serve an essential role in the control of blood pressure. An increase in arterial pressure causes the kidney to excrete increasing amounts of salt and water (127). The pressure gradient providing glomerular filtration depends on the ratio of afferent arteriolar and post-afferent renal resistances. In the dynamics of renal function, the afferent renal arteriolar resistance is regulated by renal nervous activity (to which the afferent arteriolar smooth muscle is quite sensitive). Renal blood flow and glomerular filtration rate are regulated by an intrinsic vascular control mechanism (autoregulation) which stabilizes glomerular filtration pressure over a broad range of arterial blood pressures.

Changes in salt and water excretion results in a change in both extracellular and intravascular volume. The change in blood volume influence arterial pressure via changes in cardiac output and peripheral resistance. Guyton (13) has proposed that in the normal day-to-day control of arterial pressure this mechanism is relatively unimportant since nervous reflexes provide potent and much faster control mechanisms. Guyton further proposes that the long-term control of blood pressure is determined primarily by the steady-state relationship between arterial pressure and renal urine output.

The concept that has been widely reviewed and discussed is that renal disfunction is the initiating event in hypertension (8,72,82); high blood pressure being considered to occur only when the kidneys are incapable of excreting sufficient salt and water to normalize the pressure (82).

The renal dysfunction-autoregulation theory postulates that when other controlling factors are disturbed or are unable to maintain fluid balance, the increase in blood pressure is required as a last resort to maintain salt and water balance. In fact, the systems analysis of Guyton and co-workers (13) suggest that a longterm change in blood pressure as occurs in hypertension, is always the result of a change in the relationship between arterial pressure and renal fluid excretion. In all experimental forms of hypertension (generally by manipulation of the kidneys, or salt and volume loading) a change in this relationship causes the hypertension (128). However, it has not yet been determined whether a similar change is the primary mechanism causing essential hypertension.

3.6 LOCAL CONTROL MECHANISMS

A final group of control mechanisms include several factors acting locally at the level of the different vascular beds. These include mainly the local autoregulatory mechanism and the fluid shift system at the capillary level affecting the distribution of extracellular fluid between the vascular and interstitial beds. (These two mechanisms have been reviewed in the previous chapter). Another of these local mechanisms is the stress-relaxation phenomenon (129). This relatively rapid mechanism serves to stabilize rises and falls in blood pressure. The pressure induced changes in vessel diameter changes the resistance to flow, hence enabling the pressure to rise or fall towards its normal level. However, when the reflex regulations such as the baroreceptor reflex are functioning, the effect of local factors (e.g. the autoregulatory mechanism) will be masked (130).

Chapter 4

4.1 HAEMODYNAMIC MODELLING

In this study our concern will be with those variables which are lumped parameter properties of the haemodynamics of the cardiovascular system.

On the basis of the pressure/force-voltage electrical analogy, the criteria for lumping, based on simple electrical circuit analysis may be stated as follows: components in series can be lumped together when the same flow is passing through them and parallel components can be lumped when the same pressure gradient occurs across them (131). Under these conditions the minimun requirement of circulatory elements consists of pulmonary, bronchial and lumped systemic circuits.

The lumped systemic and pulmonary circuits consists of arteriolar compliance, afferent and efferent resistances separated by trançapillary circuits, venous compliance and output venous resistance. In this modelling procedure the parallel renal circulation with its afferent and efferent resistances and filtration/absorption processes will be considered separately. The bronchial circulation is considered of little consequence in this overall systems

analysis. Further division of the systemic circulation, in order to gain a deeper insight into the distribution of body fluids under various pathological conditions, could be incorporated in this simplified procedure.

The resultant windkessel model is most appropriate for studying the reservoir properties of the circulatory system (132). This model has also been successfully employed in the past as an appropriate system for studying pressure/flow relationships (132).

Implicit in such a model approach is the understanding that only gross behaviour of the circulation is being investigated. The amount of detail of other cardiovascular components, to be included in the resultant lumped parameter model, is dependent on the issue of study, and on the context in which a solution is sought.

The overall model is nonlinear as nonlinearities are introduced into the system by the action of various controllers (e.g. autoregulation, baroreceptor and other reflexes) on the systemic resistance and compliance properties and the cardiac flow source.

In 1959 Grodins (133) published a mathematical analysis of the control of blood pressure . Guyton and colleagues (13)

subsequently published several mathematical models which described both the short term and long term components of blood pressure control. These latter models have focused extensively on the role of renal salt and water excretion in pressure control, and on autoregulation as a possible vasoconstrictive mechanism in hypertensive disorders.

Guyton (13) has used evidence accumulated over the years to put together a mathematical model in an attempt to better analyze the interrelationships between the different components of the blood pressure control system. The merits of this approach have been the quantification of the various haemodynamic parameter changes in various blood pressure abnormalities, the interrelationships of these parameters as well as distinguishing between mechanisms responsible for acute and chronic regulation of blood pressure. Distinctions have been made between the mechanisms that raise the blood pressure and those mechanisms which determine the level to which the arterial pressure will rise.

Guyton's model realistically regulates blood pressure, cardiac output and sodium balance through a series of feedback loops. However, certain limitations are explicit in the model. There is no attempt to adapt the model for individual to individual variation of system parameters.

This however, will be necessary in any system to be used for model predictions for diagnosis or for therapeutic purposes.

Luetscher (38,134) has presented another model of the circulation regulated by the autonomic nervous system, blood volume and the renin-angiotensin system. This model allows the classification of essential hypertensives into two groups:

(i) with increased autonomic activity or circulating catecholamines, high plasma renin activity, low to normal plasma volume and high to normal cardiac output.

(ii) with increased exchangeable sodium, high to normal plasma volume, subnormal plasma renin activity and often evidences of impaired function of the autonomic system.

The model studies so far have been used to assist in the understanding of the mechanisms of blood pressure control and to guide in experimentation. It appears however, that they might also prove to be useful in epidemiological as well as clinical studies of hypertension. Models, if properly formulated, might provide parameters which can be easily monitored during the intervention period and through the dynamics of their changes allow an assessment of the intervention on an ongoing basis. Such modelling procedures would represent a major enhancement of present epidemiological methods which rely primarily on morbidity and mortality data (135).

Ghista (136) has published a model describing functional mechanisms of the controlled left ventricle in interaction with the circulatory system, and regulated by the central nervous system. From this model an attempt has been made to derive parameters of diagnostic value.

While the physiology of blood pressure control is quite a complicated network of nonlinear feedback controls, the use of mathematical models allows the lumping of many of these control functions into blocks, and thus simplifies the system while maintaining enough richness to yield more than trivial linear control functions.

Several other attempts at applying haemodynamic modelling of the circulation to hypertension have been published (137,138,139). However, as Coleman (128) has pointed out, an uncertain number of models such as those used by the NASA remain relatively uncirculated and unknown to most of the scientific community.

4.2 CIRCULATORY PARAMETER ESTIMATION

Apart from the modelling of the circulation and its control aspects, of equal importance in reaching the final goal of patient classification is the identification and estimation of individual parameters (16,140,141,142).

Many circulatory parameters of considerable diagnostic and therapeutic value are not directly assessable. In these cases, values of parameters are estimated on the basis of relationships obtained, between measured variables and parameters, by applying physical laws to the model system. As an example, the resistance parameter is found by the application of Ohm's Law to the lumped parameter model of the circulation, obtained by the use of the pressure/force-voltage electrical analogy (section 4.1). Parameters obtained by this method accurately express the state of the cardiovascular system as describe in the model; the only assumptions being made in the formulation of the model.

Parameter estimates obtained from regression relationships between the experimentally measured variables are only parameters of regression, and may not be indicators of a biological property. However, such parameters may be useful as indicators of changes in the state of a system, and for comparing and classifying the states of different systems.

Parameter estimation procedures have had their greatest success in the analysis of linear systems. However, the cardiovascular system displays a wide range of intrinsic nonlinearities, in the presence of which parameter estimation procedures may not behave as expected. Several procedures are found in the literature for the estimation of many parameters employed in various models of the circulation. However, these procedures are specific to the model, and no general procedure exists (142).

In this study, parameter and state variable (steady state values) estimates are obtained from four different methods:

(i) Literature, e.g. PRA- right atrial pressure ~0 mm Hg.

(ii) Data, including the use of model relationships to generate more values (Appendices 1 & 2).

(iii) From an assumed relation, e.g. CV=100xCA.

(iv) Parameter estimation during simulation runs, e.g. time constants and controller gains (Chapter 5).

Noninvasive methods have proven to be of great diagnostic importance for the evaluation of cardiovascular function. These methods have included the ECG, the echocardiogram, carotid pulse recordings and systolic and diastolic blood pressures recorded by sphygmomanometry. The estimation of cardiovascular steady-state parameters using non-invasively

recorded data, obtained from the procedures indicated above, forms the basis of the thesis proposed here. In assessing the dynamic aspects of the cardiovascular system, the assigning of values to the various control parameters will be required (Chapter 5).

Using the noninvasive procedures mentioned above, the following measurements were made: left ventricular volumes and stroke volume were obtained from echocardiographic measurements of left ventricular dimensions. The estimate of stroke volume together with heart rate obtained from the ECG recording permitted the calculation of cardic output. Estimates of mean arterial pressure, and of the various components of the systemic arterial blood pressure, were estimated based on shygmomanometric measurements of systolic and diastolic pressures and from the carotid pulse recording. The systemic parameters of arterial compliance, peripheral resistance and degree of arterial filling can then be estimated based on the steady-state model relationships (Appendix 2).

As may be noticed above, mathematical models form an integral part of the application of noninvasive methods for the analysis of cardiovascular function. This results from the fact that several critical parameters and variables cannot be directly assessed (e.g. arterial compliances and

'volumes'). The use of mathematical models of the circulation, expressing the physical laws relating the measured variables and parameters, allows these critical parameters to be tracked and monitored.

The requirement of adapting the model to the variation of parameter values between individuals, excludes many of the approaches to cardiovascular systems modelling based on transmission properties (131,143), and on the complex multicomponent system of Guyton (13). A complete specification of an individual's parameter values, in a model as detailed as that of Guyton's, would require an inordinate amount of data. Hence, the need to specify the parameter values for each subject restricts the complexity of the model.

Finally, before the classification can be fully assessed, an analysis must be made of the sensitivity (144,145,146) of the model parameters (Appendix 3).

Chapter 5

5.1 CLINICAL STUDIES FOR VALIDATION OF PROFILING PROCEDURE

In this chapter, four studies, carried out in order to validate the steady-state model procedure for obtaining haemodynamic profiles, are presented.

First, we compared the values of mean systolic, end systolic and mean arterial blood pressures obtained by measurements made on the carotid pulse curve, to those obtained by modelling the arterial pressure curve (Appendix 1). The use of the modelling procedure for obtaining components of the arterial pressure eliminates the need for carotid pulse recordings as a necessary part of our profiling procedure.

Systolic and diastolic pressures measured by sphygmomanometry have been shown to correlate well with values obtained by direct intraarterial recordings. Mean arterial pressure has often been estimated by the equation:
MEAN ARTERIAL PRESSURE=DIASTOLIC PRESSURE + k(PULSE PRESSURE)
where k=1/3.

This method is not always accurate due to wide variations in the morphology of the intraarterial pressure wave, for which k has been shown to vary in the dog (range .[illegible] to .6) even at the same pressure in the same artery (147).

Given the striking resemblance between the intraarterial pressure and noninvasive externally recorded carotid pressure pulse, changes in morphology have been accounted for by obtaining mean arterial pressures by integration of the carotid pulse curve.

In our second study (section 5:3), we assessed the repeatability of the haemodynamic measurements and derived haemodynamic profiles. The profiling procedure was then applied to a cross-section of treated hypertensives (section 5:4), in an effort to determine whether the procedure is capable of detecting haemodynamic differences between responders and non-responders to anti-hypertensive therapy.

Finally (section 5:5), we applied the procedure to a longtitudinal study of a group of male hypertensives, in order to assess the capability of the procedure to detect pre- and post-therapy haemodynamic differences between diuretic and beta-blocker treated subjects, who responded or did not respond to the therapy.

Due to the relatively small number of hypertensive subjects studied, it was necessary to ascertain whether major differences in anti-hypertensive responses in the subjects studied would have been due to large differences in the level of drug intervention, or (for the cross-section study)

major differences in the therapeutic regimen. Hence, a code for the various hypertensive drugs and combination of drugs was drawn up (Table 5:1:1), and used to assess differences in therapeutic regimen between the different subject groupings, e.g., between hypertensives with controlled and uncontrolled blood pressures.

Four major anti-hypertensive drug groups were considered in this study, namely: diuretics, beta-blockers, vasodilators, and alpha-methyldopa/other drugs. Using the literature on within- and between-group drug potency (152-158), an empirical scale for the therapeutic dosage providing equivalent blood pressure lowering effects was derived. The scale was drawn up by setting 50mg hydrochlorothiazide = 80mg propanolol = 1 unit of therapeutic vigor (Table 5:1:2). Therapeutic vigor was considered additive within and between drug groups, e.g. the drug preparation DYAZIDE, a combination of two different diuretics. For a stepped-care approach to therapy, the number of different drug groups in a patients therapeutic regimen provides another scale for assessment of the degree of drug intervention.

Table 5:1:1. Code for hypertensive drug groups and drug combinations.

DRUG THERAPY	THERAPY CODE
No Medication	Ø
Diuretic only	1
Beta-blocker only	2
Diuretic+Beta-blocker	3
Diuretic+Alpha-methyldopa	4
Diuretic+Vasodilator	5
Beta-blocker+Vasodilator	6
Diuretic+Beta-blocker+vasodilator	7
Diuretic+Beta-blocker+Alpha-methyldopa +Vasodilator	8

Table 5:1:2. Equivalent daily dosage of various anti-hypertensive drugs corresponding to one unit of therapeutic vigor.

GENERIC DRUG NAME	DOSAGE/DAY
Diuretics	
Amiloride	10mg
Furosemide	80mg
Hydrochlorothiazide	50mg
Metolazone	5mg
Spironolactone	100mg
Triamterene	100mg
Beta-blockers	
Metoprolol	100mg
Oxprenolol	160mg
Pindolol	15mg
Propanolol	80mg
Timolol	10mg
Vasodilators	
Hydralazine	50mg
Prazosin	5mg
Other Drugs	
Alpha-methyldopa	500mg
Captopril	150mg
Clonidine	0.6mg
Guanethidine	25mg

Statistical Analysis

Means, standard errors of the mean, and correlation coefficients were calculated according to standard statistical methods (159). Regression analysis was performed using the least-squares method. Both paired and unpaired differences in means were assessed using the Student's t test. When comparisons of three groups were made, the validity of the statistical analysis was confirmed by analysis of variance. A p value of < 0.05 was accepted as being statistically significant. The statistical analyses were carried out using the MINITAB program package.

5.2 STUDY I - ARTERIAL PRESSURE

Method

Simultaneous EKG and carotid pulse tracings (Fig 5:2:1), suitable for planimetry, were obtained in our laboratory on 27 patients in our study group (DATA SOURCE 1). Recordings were made with the subjects in the supine position at which time blood pressure was obtained by standard sphygmomanometry.

Equations derived for calculating mean arterial pressure, end-systolic and mean systolic pressures, were compared to values measured and planimetered on carotid/brachial pulse curves (Fig 5:2:2-5:2:8), using both data recorded in our laboratory, and from (DATA SOURCE 2) data published by Shaver et al (148).

The derived equations were calculated by fitting a sinusoid to the ejecting phase of the arterial pressure curve, and an exponential decay to the diastolic phase (Appendix 1). The required data items were: systolic and diastolic pressures, heart rate (HR) averaged over a minimum of 10 consecutive beats of the EKG recording, measured at the most stable phase of the carotid pule tracing, and left ventricular ejection time (TS). The ejection time was measured from the initial rapid upstroke of the carotid pulse to the incisura

of the dicrotic notch, and an average value over a minimum of 5 consecutive pulse recordings was used.

End-systolic pressure (PS) was measured from the level of the diastolic pressure to the dicrotic notch. This measurement was scaled by the pulse pressure measured from the level of the diastolic pressure to the peak of the pressure pulse recording, the scale being set by the pulse pressure (SYSTOLIC minus DIASTOLIC) obtained by sphymomanometry. Mean systolic pressure was obtained by planimetry over the ejecting phase of the carotid pulse tracings, the measurements being scaled by the pulse pressure. An average value for a minimum of 5 consecutive carotid pulse tracings was obtained for both end-systolic and mean systolic pressures.

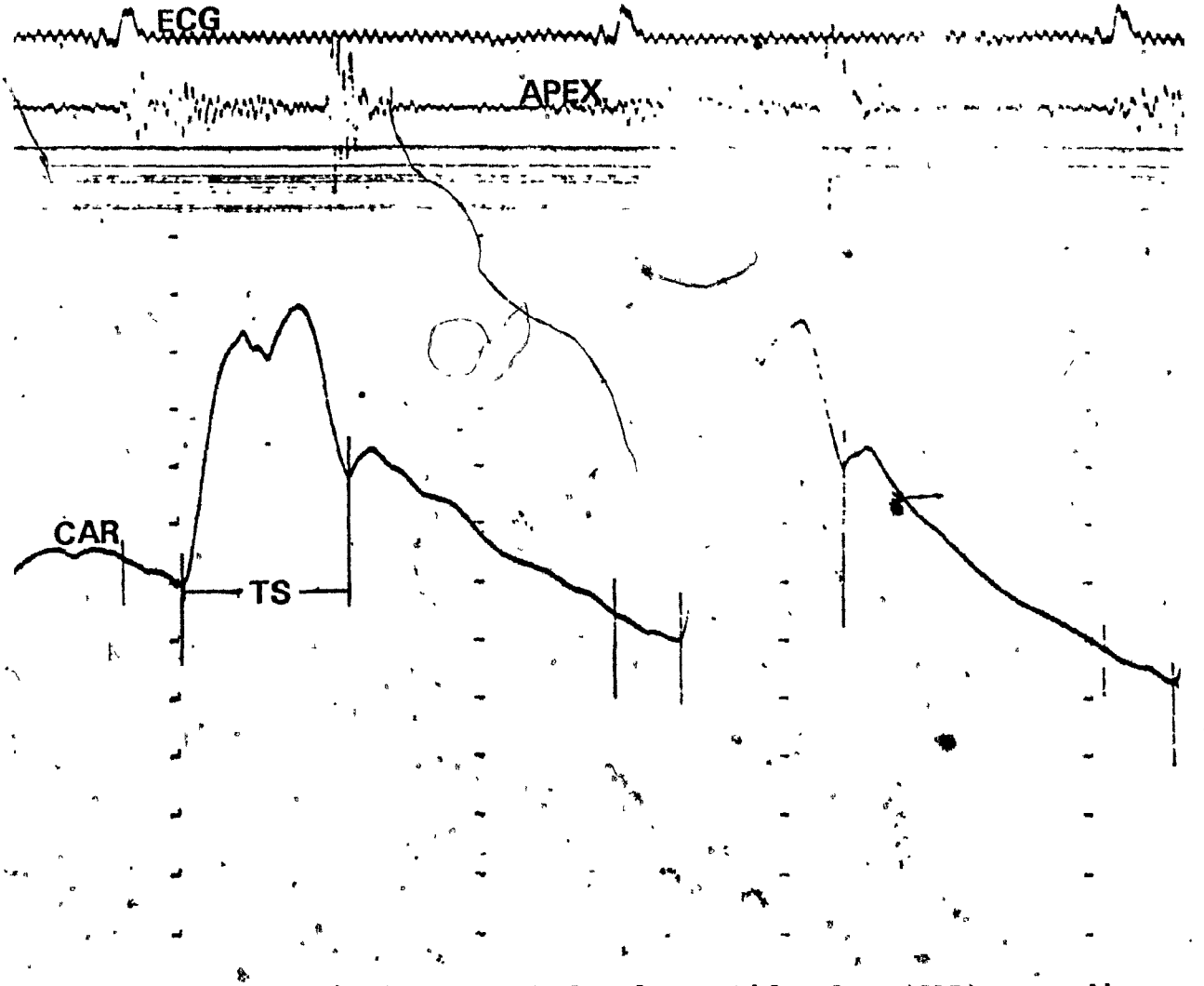


Figure 5:2:1. Simultaneous EKG and carotid pulse (CAR) recordings. (APEX - apexcardiogram).

Results

Figures 5:2:2-5:2:8 show that the derived model equations for calculating the components of systemic arterial blood pressure compares well with measured values. The calculated mean systolic arterial pressure (PSA) underestimates the value obtained by planimetry (Table 5:2:1). This is consistent with the observation that planimetry overestimates the directly recorded pressure (160). The calculated mean systemic arterial blood pressure consistenly overestimates the measured pressure, and the pressure value estimated using the equation:PA = PD + k*(PSP-PD), where k=1/3.

In assessing the variability of the parameter k (147), calculations were made using the relation k=(PA-PD)/(PSP-PD). Using measured mean arterial pressure values (DATA SOURCE 2), a mean value of k=0.37±0.07 (MEAN±SEM) was obtained with range (0.25,0.52). With the use of mean arterial pressure values calculated from model relations, k values were less variable. This indicates that variations in the shape of the arterial pressure curve was not completely realised by inclusion of heart rate and ejection time changes. The parameter k was observed to be positive correlated with blood pressure.

Table 5:2:1. Comparison of measured and calculated components of systemic arterial blood pressure.

	MEASURED	CALCULATED	ESTIMATED
PS mmHg	120±4.3	120±4.4	
PSA mmHg	127±4.7*	126±4.7	
PSA' mmHg	129±3.0	127±2.9	
PA mmHg		110±4.1	104±3.9*
PA' mmHg	105±2.8*	110±2.7	103±2.5*

(' Data derived from Shaver et al. J Clin Invest 1967.)

Values are MEAN ± SEM.

Significance level * $p < .001$ compared to calculated values.

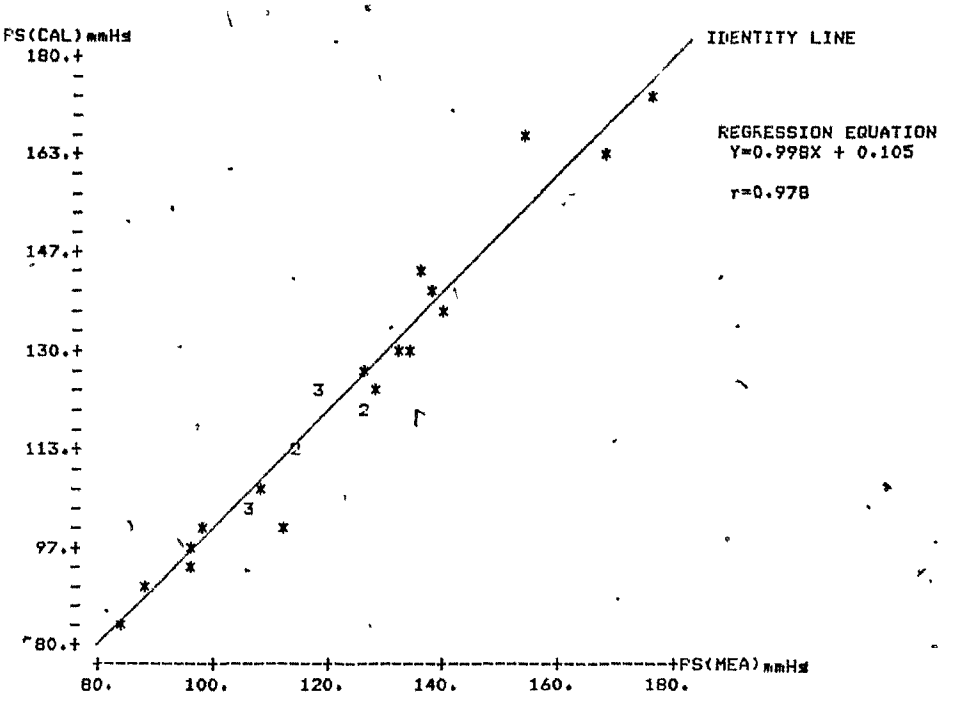


Figure 5:2:2. End-systolic arterial pressure, calculated versus measured.

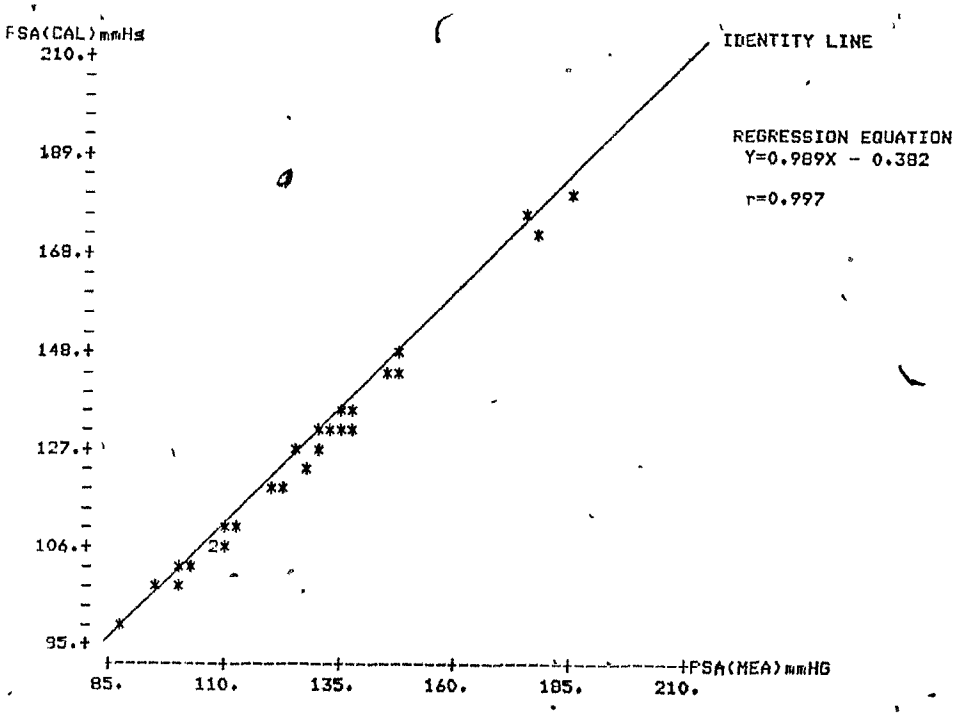


Figure 5:2:3. Mean arterial systolic pressure, calculated versus measured.

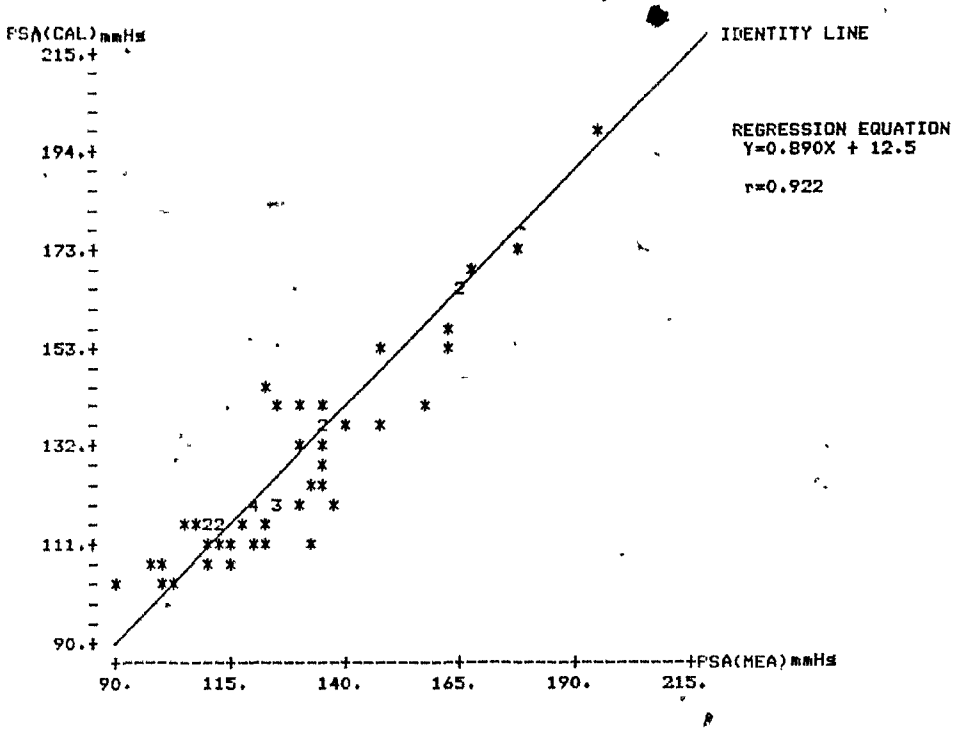


Figure 5:2:4. Mean arterial systolic pressure, calculated versus measured. (Data from Shaver et al., J Clin Invest 1967).

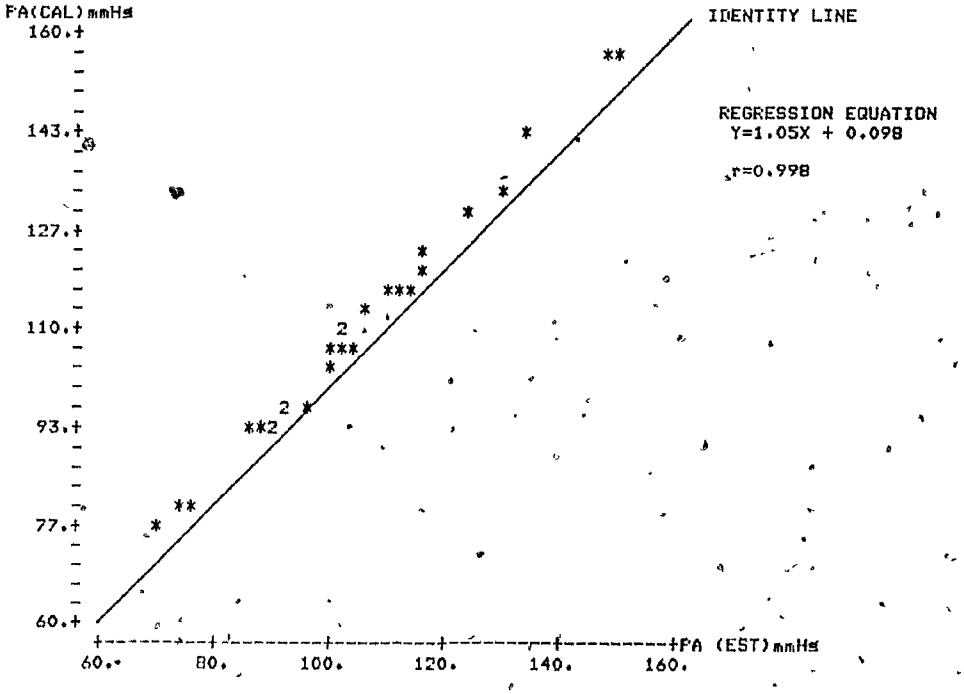


Figure 5:2:5. Mean arterial blood pressure, calculated versus value estimated from the relation: PA=diastolic + 1/3pulse pressure.

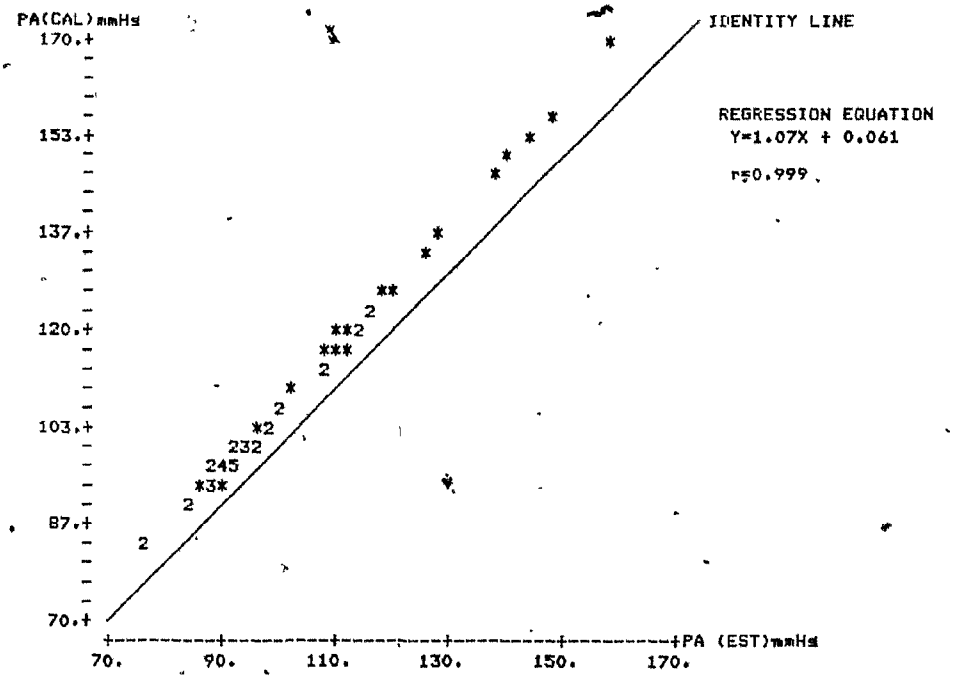


Figure 5:2:6. Mean arterial blood pressure, calculated versus value estimated from the relation:
PA=diastolic + 1/3pulse pressure.
(Data from Shaver et al., J Clin Invest, 1967).

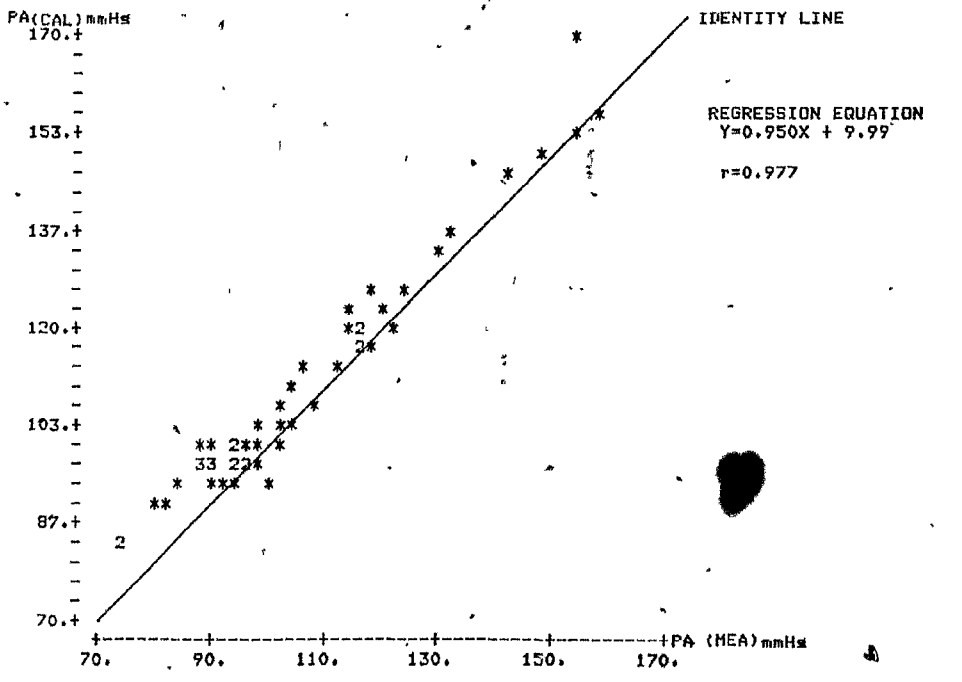


Figure 5:2:7. Mean arterial blood pressure, calculated versus measured. (Data from Shaver et al., J Clin Invest 1967).

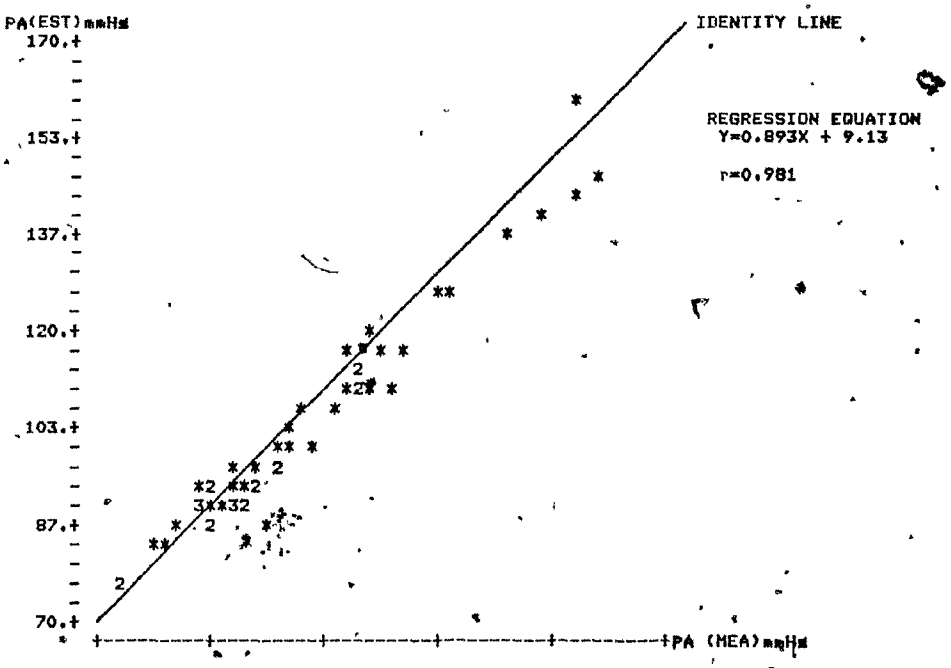


Figure 5:2:8. Mean arterial blood pressure, value estimated from the relation: PA=diastolic + 1/3pulse pressure versus measured value. (Data from Shaver et al., J Clin Invest, 1967).

5.3 STUDY II - REPEATABILITY OF MEASUREMENTS

Method

At the same time as the carotid pulse recording, a M-mode echocardiographic study was performed, either in the supine or left lateral decubitus position (whichever was required for optimal visualization of the cardiac structures in question). Standard methods of M-mode echocardiographic study (149,150) were performed, using an ultrasonoscope (Smith-Kline Echoline 20) interfaced with a strip chart recorder (Honeywell 1856Å Visicorder). Ultrasonic emission characteristics were as follows: frequency of ultrasonic pulses 1000/sec, ultrasonic wave frequency 2.25MHz, and focal length 10cm.

From the echocardiograms (Fig 5:3:1-5:3:2), left ventricular end-systolic (LVES), end-diastolic (LVED) and left atrial (LAD) dimensions were measured by the leading edge method (149). Ventricular end-systolic (VLVS) and end-diastolic (VLVD) volumes were calculated using the correction formulas of Teichholz (151). Stroke volume (SV) was then calculated as:

$$SV = VLVD - VLVS.$$

Cardiac output (FCO) can then be calculated from stroke volume and heart rate:

$$FCO = SV \times HR.$$

From the windkessel model of circulation various cardiovascular parameters were derived (Appendix 2), and calculations were made using the above data as input. From the echocardiogram various indices of cardiac contractile function were also calculated namely: left ventricular ejection fraction (EF%)

$$EF\% = SV/VLVD*100,$$

percentage fractional shortening (%FS)

$$\%FS = (DLVD-DLVS)/DLVD*100,$$

and velocity of circumferential fiber shortening (SCF)

$$SCF = (DLVD-DLVS)/DLVD/TS.$$

The repeatability of the derived haemodynamic profile was assessed using subjects in our study group (DATA SOURCE 1). Subjects returned on the following day for repeat measurements. The time of day and position of subject and recording devices were standardized. All measurements were made in the morning 10am-noon, and after sufficient time was allowed for the subjects to adjust to the room conditions. Suitable repeat echocardiograms were obtained on 21 subjects of our study, 11 male (4 normotensive subjects, 7 hypertensive subjects on medication) and 10 female (3 normotensive subjects, 7 hypertensive subjects on medication). From these subjects an assessment was made of the repeatability of the derived profiles (Fig 5:3:3-5:3:19).

Using the equations derived for calculating cardiovascular parameters, a theoretical assessment was made of the sensitivity of the calculated parameters to variations in the input data (Appendix 3).

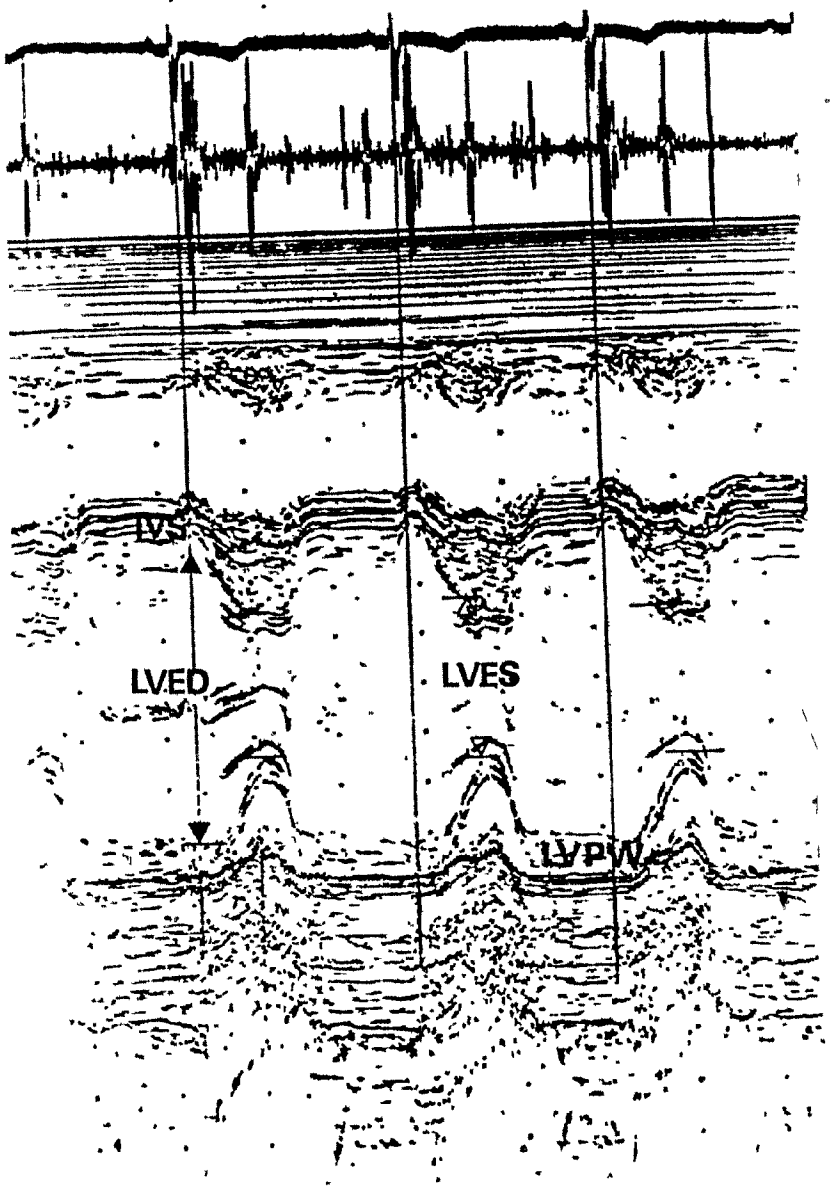


Figure 5:3:1. Echocardiographic recording of cardiac ventricules.

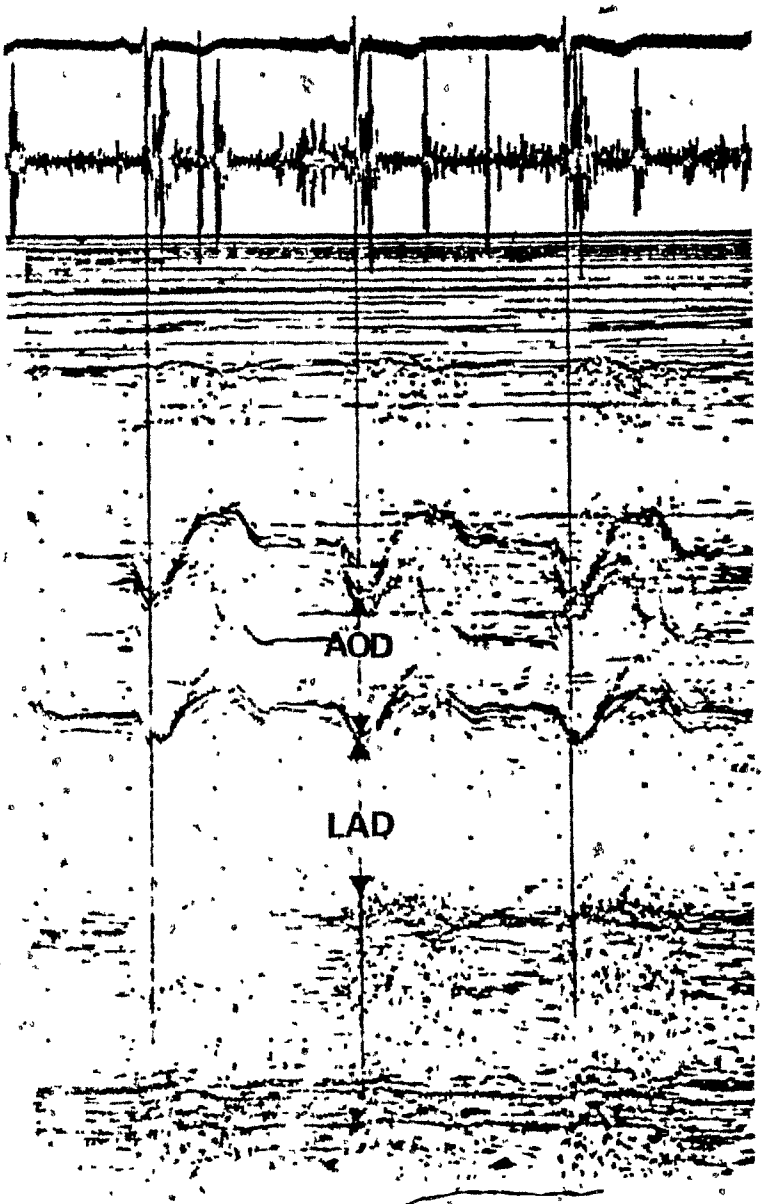


Figure 5:3:2. Echocardiographic recording made at the aortic root.

Results

As can be seen from Figures 5:3:3-5:3:19, the haemodynamic profiles obtained by our procedure provides for a reliable assessment of an individuals haemodynamic state. As may be noted from the data, there is a tendency for systemic blood pressures, heart rate, stroke volume, and cardiac output to be reduced on the repeat visit while peripheral resistance tends to increase. Arterial compliance and degree of arterial filling tend also to decrease (Table 5:3:1). This result is consistent with the interpretation of a decreasing level of anxiety (alarm reaction) on a repeat visit (161). This is borne out by a decrease in all three indices of cardiac contractile function: EF(-4.6 ± 1.9 $p<.03$), ELV(-0.043 ± 0.030 NS), SCF(-0.137 ± 0.05 $p<.014$). Also there is an inconsistency in day1-day2 correlations of cardiac contractile state. However, a high degree of correlation was maintained for all other measured and calculated variables.

A comparison of day1 and day2 measurements of left ventricular posterior wall (LVPW) and interventricular septal (IVS) thickness were indicative of reproducibility in our echocardiographic recording procedures. Repeated measurements were in the 1mm accuracy range of echocardiographic recordings (Fig 5:3:18-5:3:19).

Table 5:3:1. Haemodynamic parameters derived from measurements made on consecutive days.

	DAY 1 (N=21)	DAY 2 (N=21)	CORRELATION COEFFICIENT
PSP mmHg	145±5.9	142±5.9	0.937
PD mmHg	88±2.9	85±3.6	0.891
PA mmHg	113±3.9	110±4.3	0.923
HR bts/min	59±2.2	58±2.1	0.849
TS msec	323±8.8	331±6.7	0.807
LVED mm	49±1.2	49±1.3	0.954
LVES mm	31±1.1	33±1.0	0.776
SV ml	74±3.6	69±4.1*	0.869
FCO L/min	4.39±0.29	4.07±0.31*	0.895
RTP dyn.cm.sec-5	2211±135	2357±160	0.799
CA ml/mmHg	1.43±0.12	1.32±0.10	0.892
VAE ml	157±11	142±11*	0,840
ELV mmHg/ml	1.16±0.08	1.12±0.07	0.923
EF%	65±1.6	61±1.5	0.225 NS
SCF circs/sec	1.13±0.06	1.00±0.04	0.312 NS

Values are MEAN ± SEM. (NS- not significant, * $p < .05$).

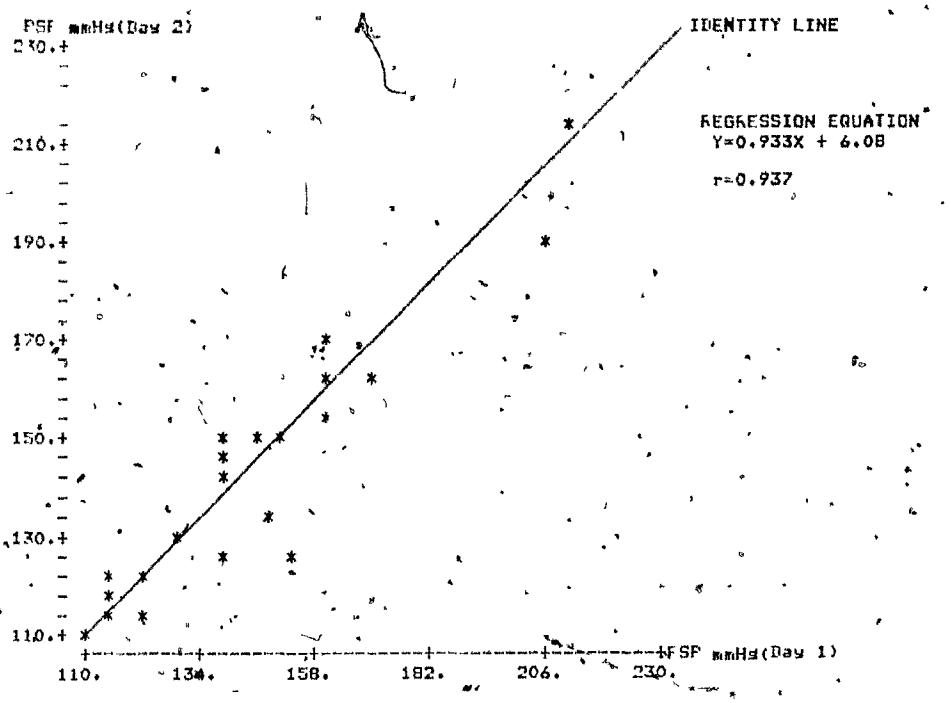


Figure 5:3:3. Comparison of systolic blood pressure measurements made on consecutive days.

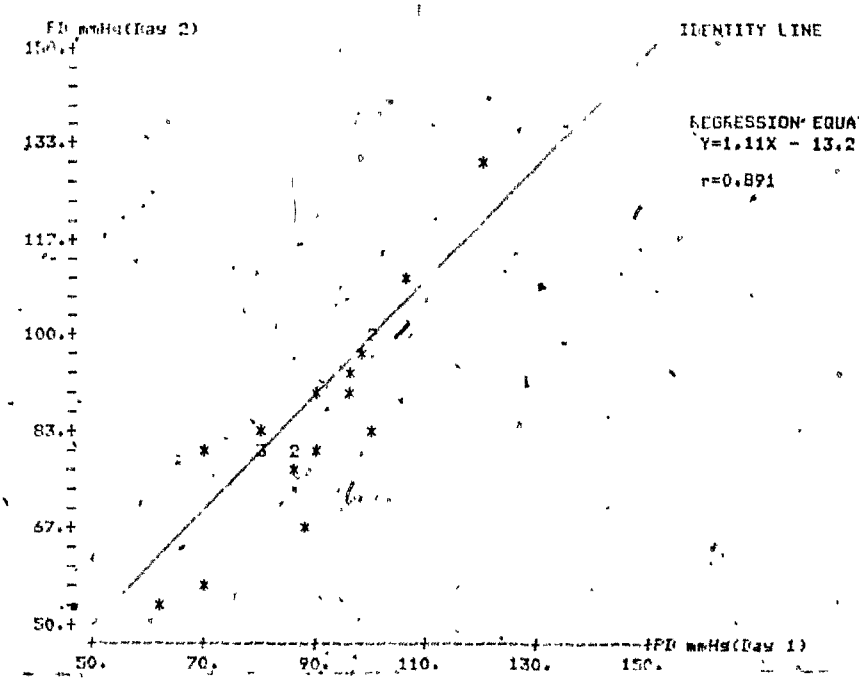


Figure 5:3:4. Comparison of diastolic blood pressure measurements made on consecutive days.

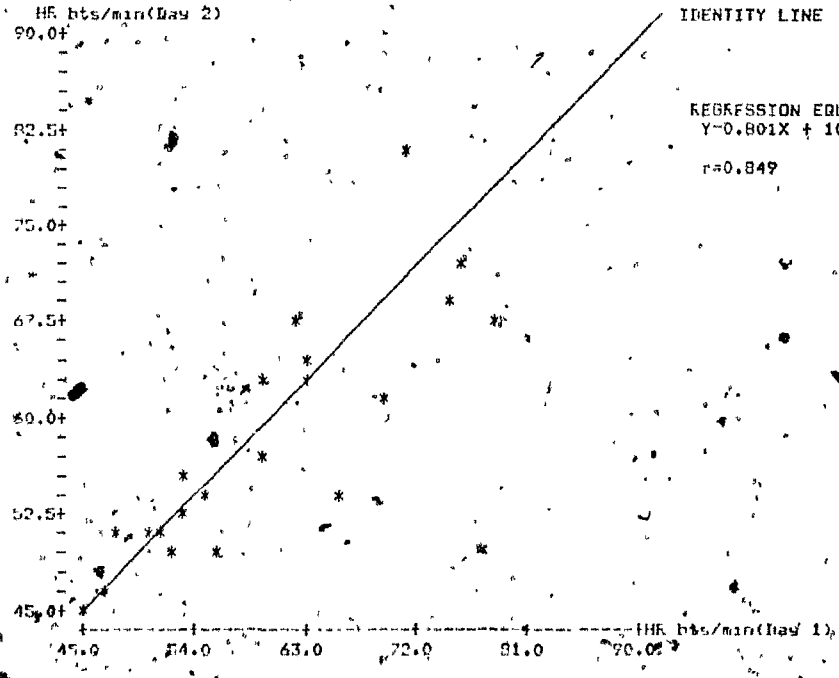


Figure 5:3:5. Comparison of heart rate measurements made on consecutive days.

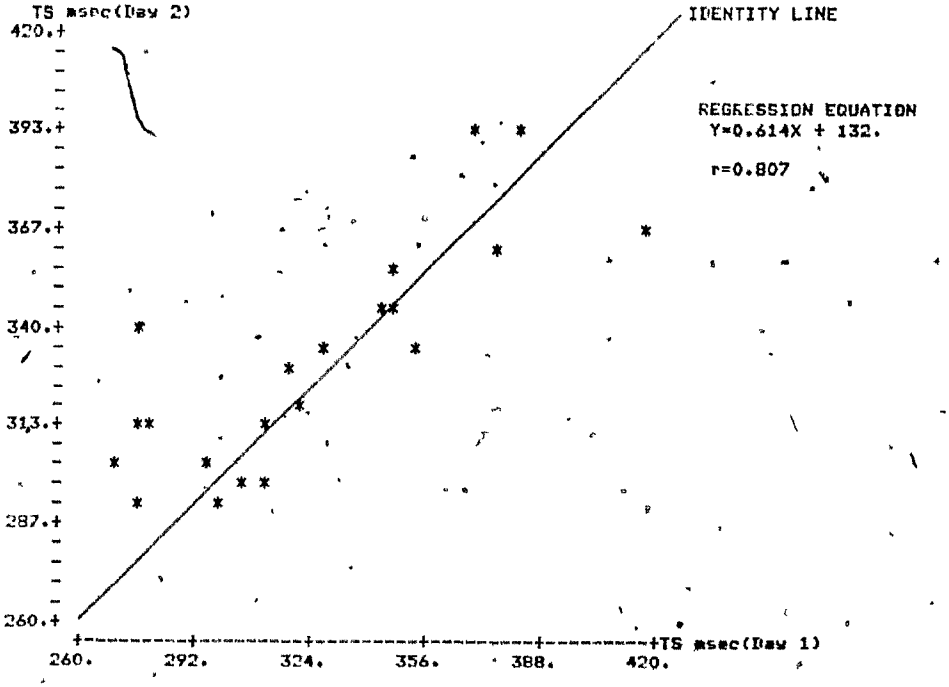


Figure 5:3:6. Comparison of left ventricular ejection time measurements made on consecutive days.

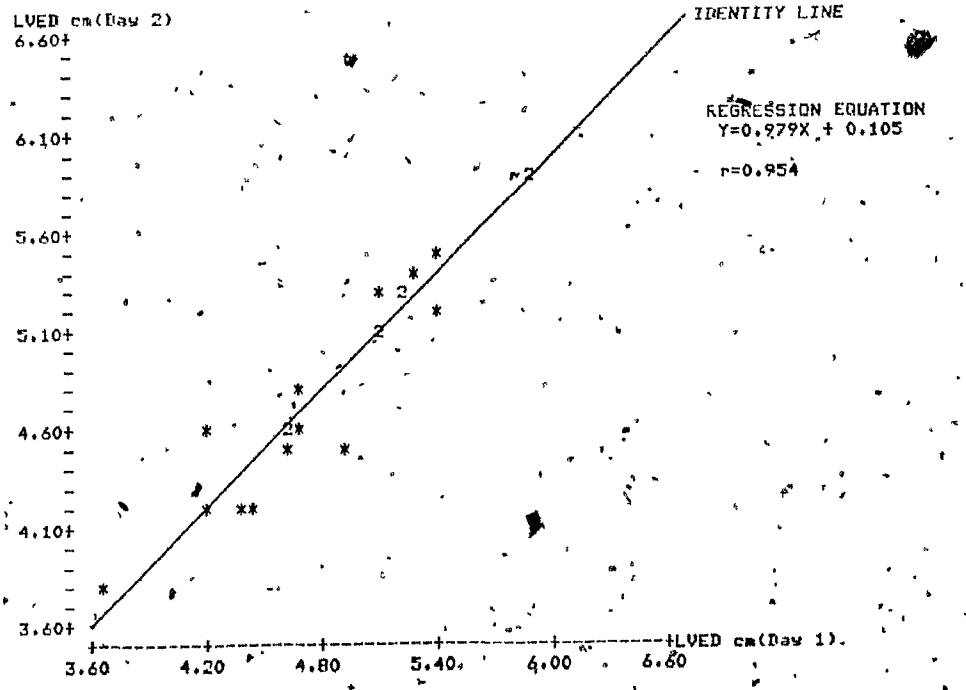


Figure 5:3:7. Comparison of measurements of left ventricular diastolic dimension made on consecutive days.

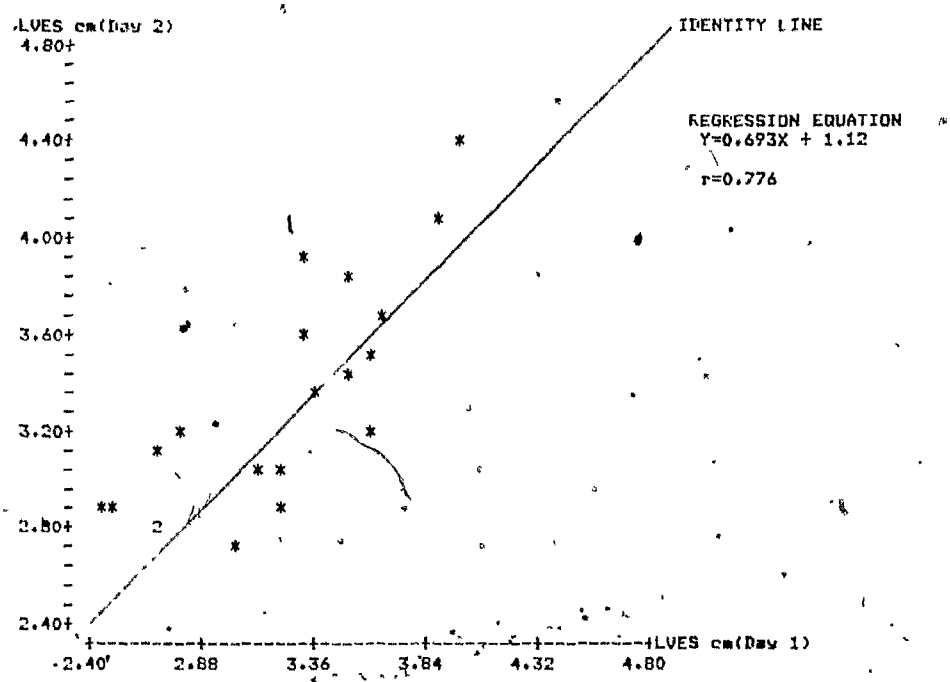


Figure 5:3:8. Comparison of measurements of left ventricular systolic dimension made on consecutive days.

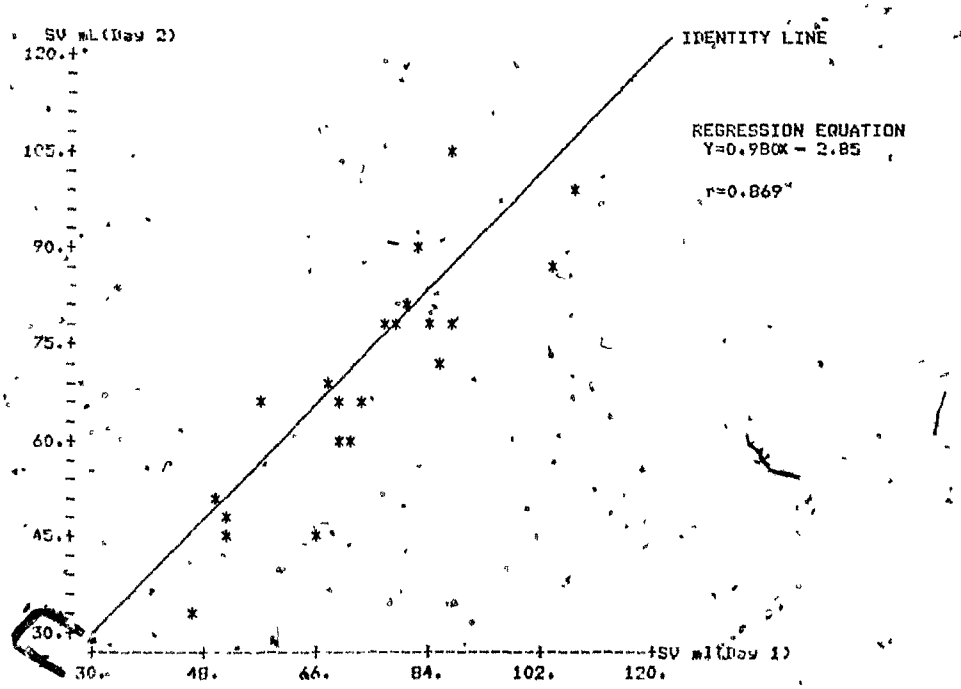


Figure 5:3:9. Comparison of values of stroke volume calculated from measurements made on consecutive days.

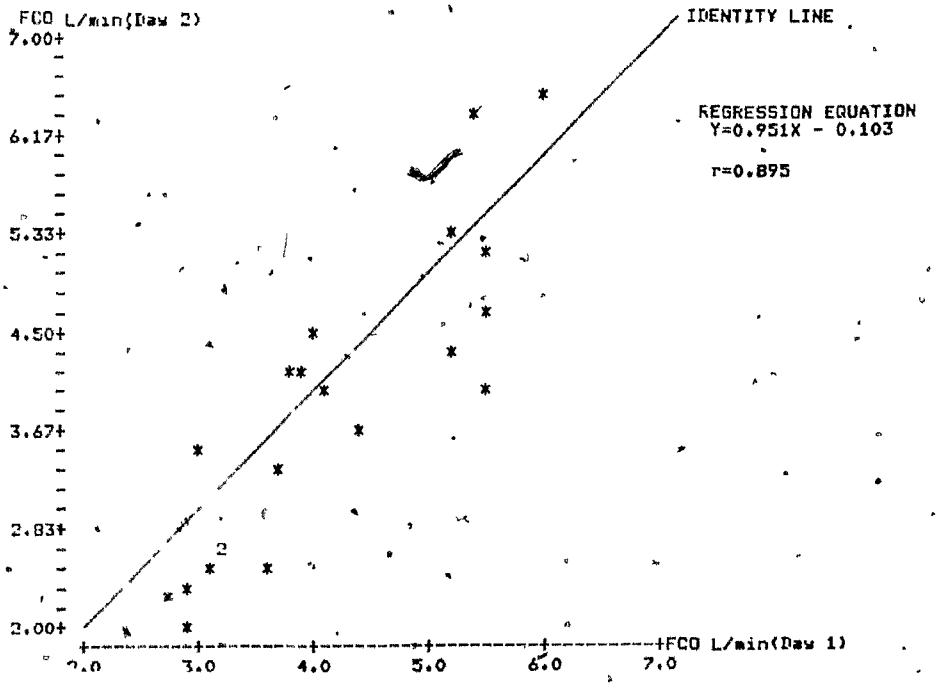


Figure 5:3:10. Comparison of values of cardiac output calculated from measurements made on consecutive days.

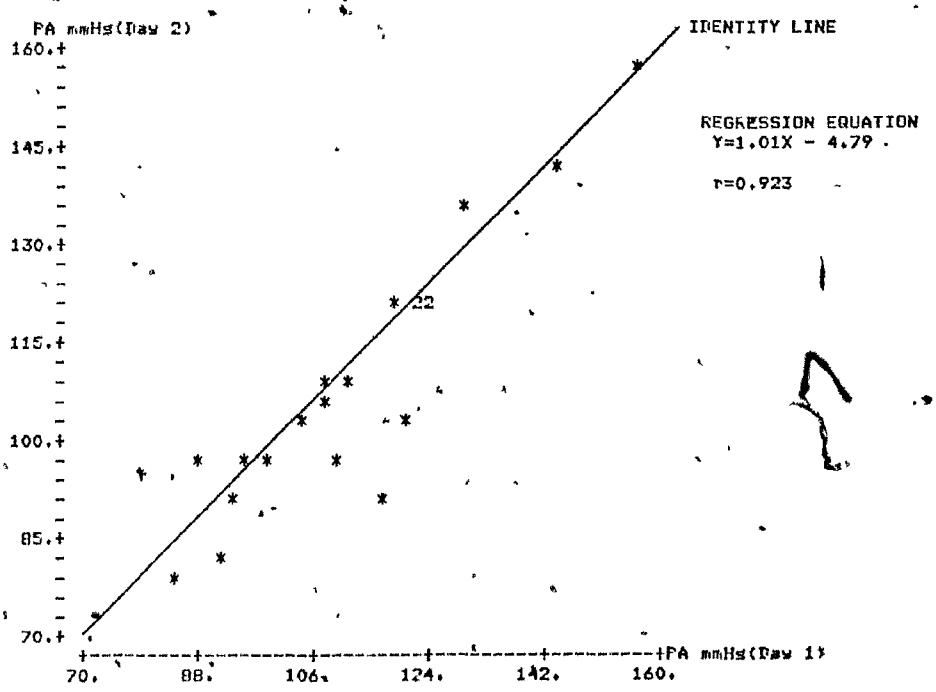


Figure 5:3:11. Comparison of values of mean arterial blood pressure calculated from measurements made on consecutive days.

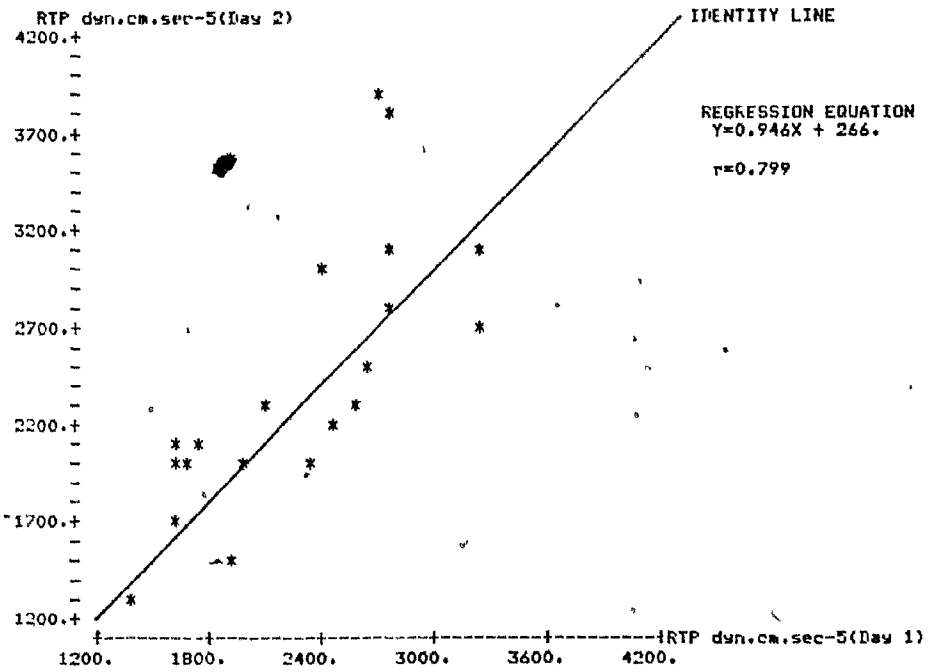


Figure 5:3:12. Comparison of values of total peripheral resistance calculated from measurements made on consecutive days.

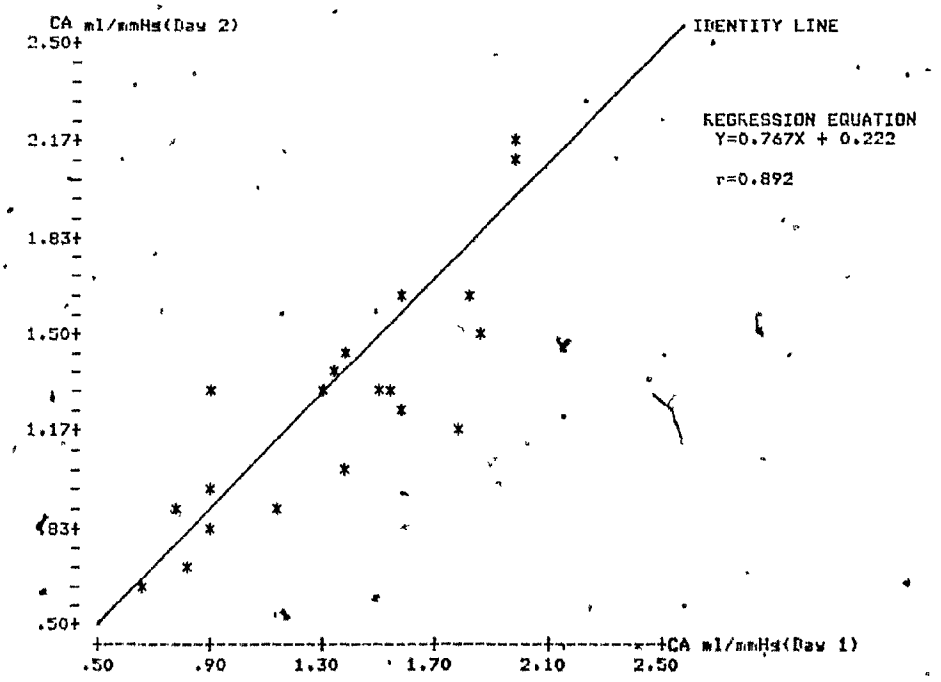


Figure 5:3:13. Comparison of values of arterial compliance calculated from measurements made on consecutive days.

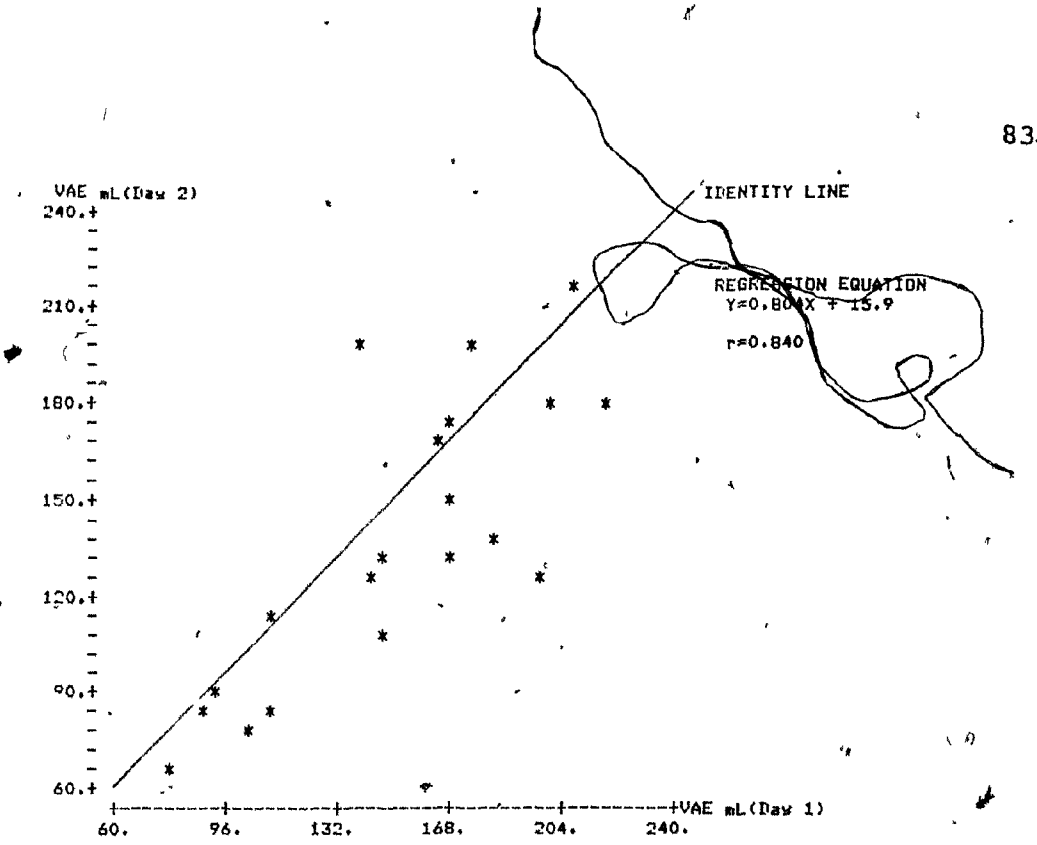


Figure 5:3:14. Comparison of values of arterial volume excess calculated from measurements made on consecutive days.

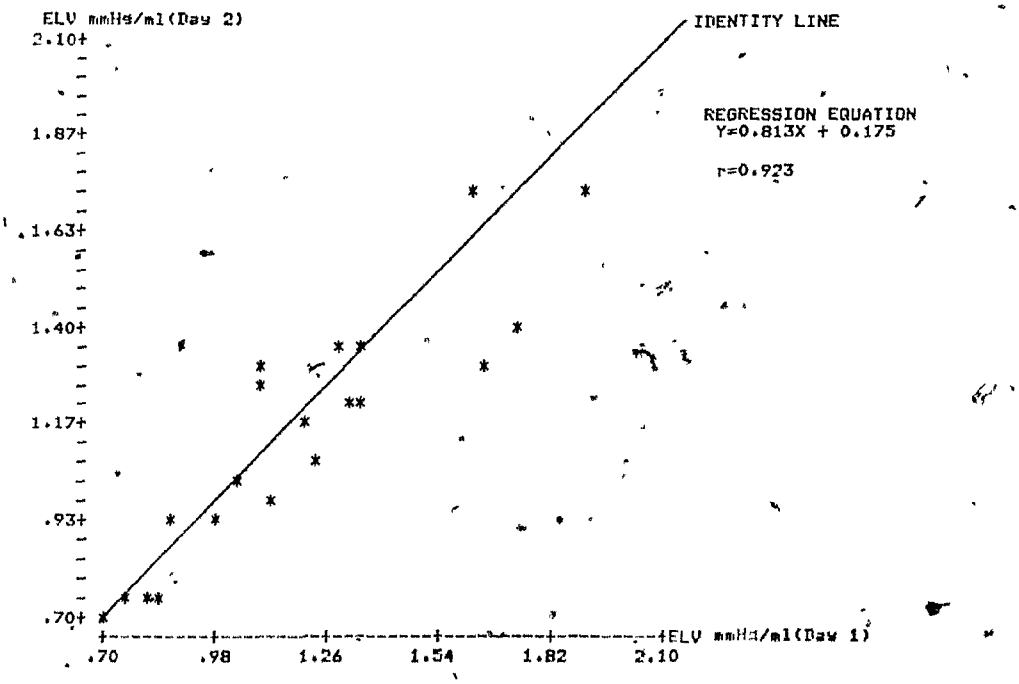


Figure 5:3:15. Comparison of values of left ventricular elastance calculated from measurements made on consecutive days.

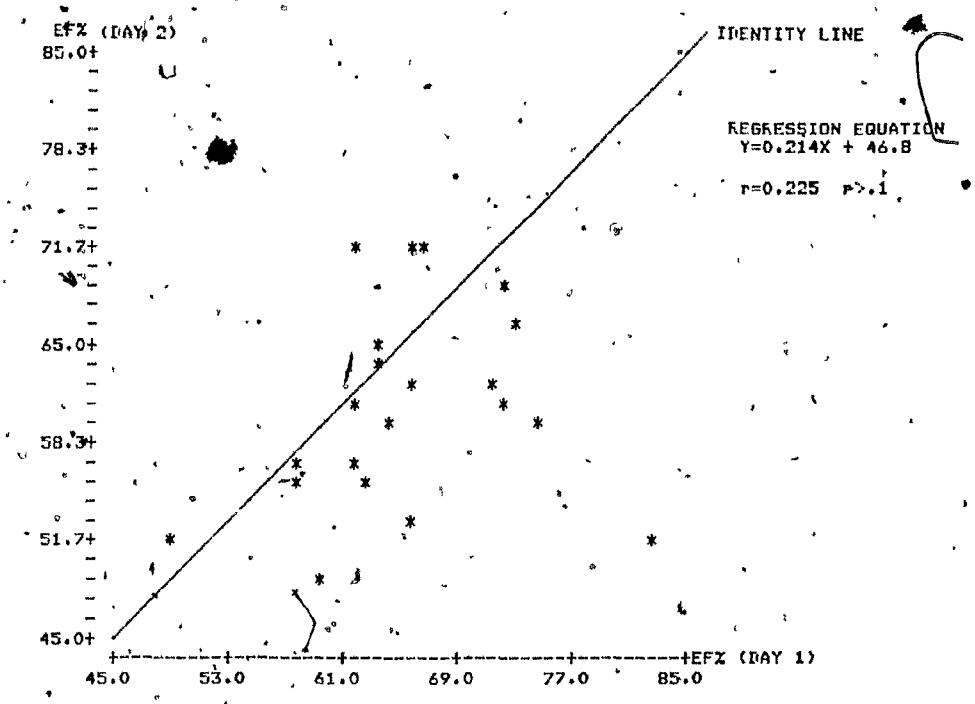


Figure 5:3:16. Comparison of values of left ventricular ejection fraction calculated from measurements made on consecutive days.

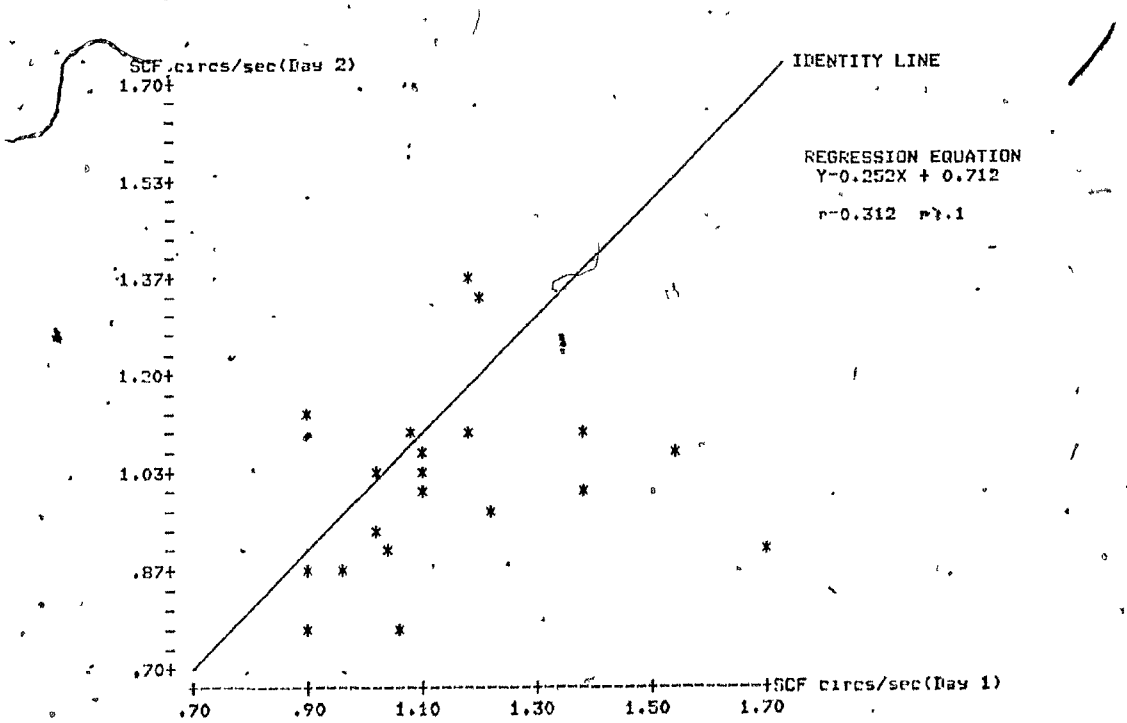


Figure 5:3:17. Comparison of values of circumferential fiber shortening calculated from measurements made on consecutive days.

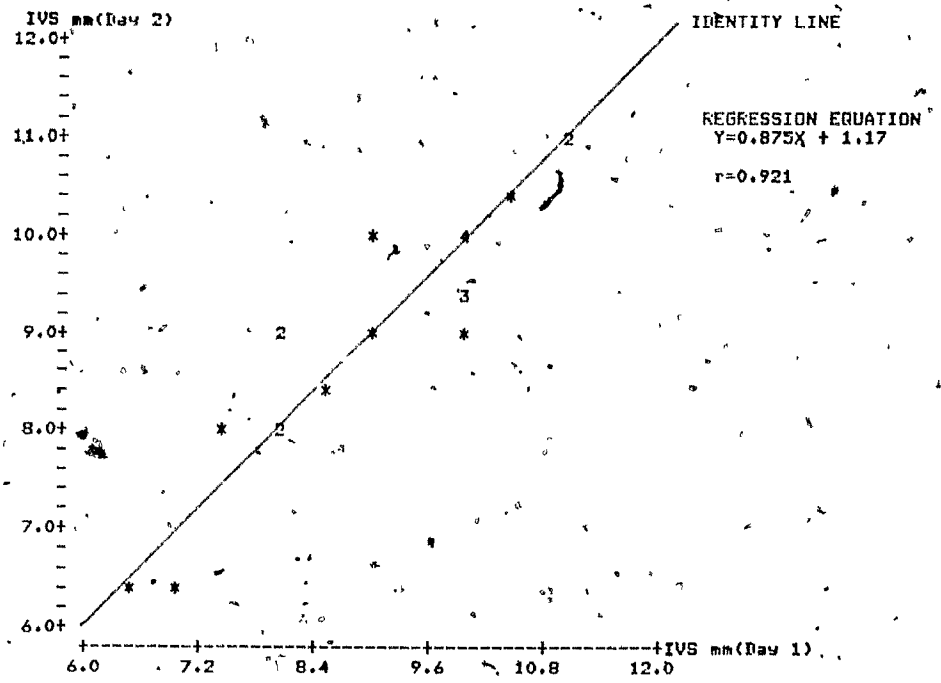


Figure 5:3:18. Comparison of measurements of interventricular septal thickness made on consecutive days.

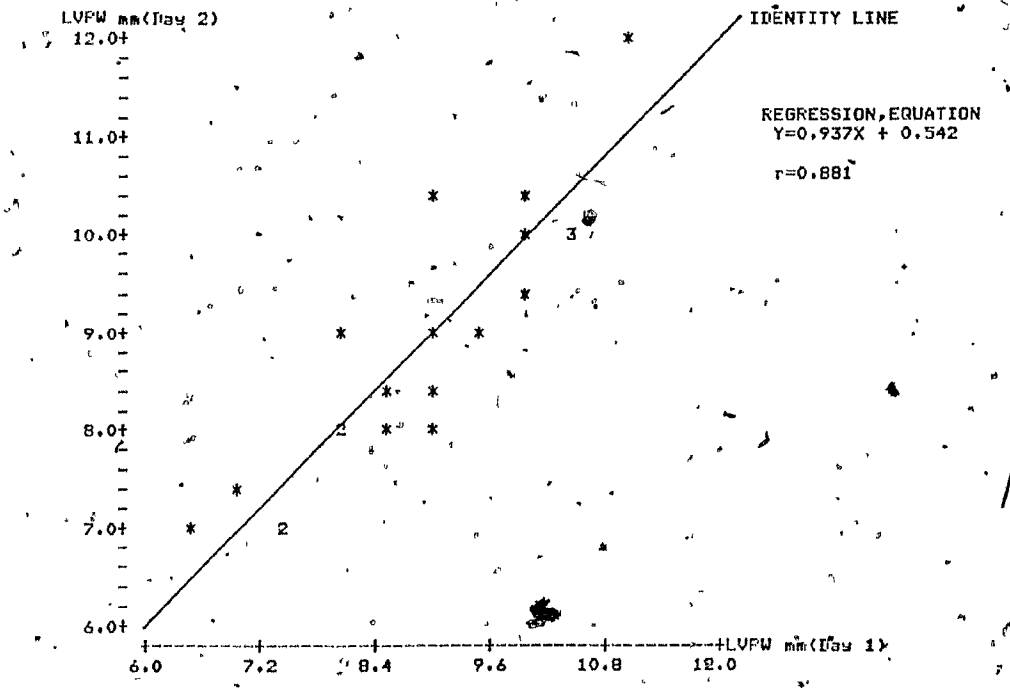


Figure 5:3:19. Comparison of measurements of left ventricular posterior wall thickness made on consecutive days.

5.4 STUDY III - COMPARISON OF RESPONDERS AND NON-RESPONDERS

Method

From our study group of subjects (DATA SOURCE 1), haemodynamic profiles were obtained for 36 of these subjects. The echocardiograms of 3 subjects were unsuitable for measurements due to large chest sizes. Subjects were divided into three groups: normotensives, responders (hypertensives on medication with diastolic pressure < 95 mmHg, systolic pressure < 150 mmHg), and non-responders (hypertensives on medication with diastolic pressure $\geq$ 95 mmHg, systolic pressure $\geq$ 150 mmHg). Clinical characteristics of this subject group are indicated in Table 5:4:1.

Analysis was then made to determine haemodynamic differences between responders and nonresponders to anti-hypertensive medication (Table 5:4:2).

TABLE 5:4:1. Clinical Characteristics

	Control Subjects	Responders	Non-responders
MEN			
NUMBER	8	9	5
AGE (years)	38±4.9	49±3.6	47±6.3
WEIGHT (kg)	77±4.0	90±5.4	74±4.6
HEIGHT (cm)	175±3.4	177±1.4	178±2.1
BSA (sq m)	1.92±0.05	2.06±0.06	1.91±0.06
WOMEN			
NUMBER	3	3	8
AGE (years)	37±5.8	46±6.9	52±3.8
WEIGHT (kg)	56±4.0	62±3.5	70±4.3
HEIGHT (cm)	160±5.4	164±4.7	166±1.3
BSA (sq m)	1.58±0.09	1.68±0.07	1.77±0.04
ALL SUBJECTS			
NUMBER	11	12	13
AGE (years)	37±3.8	48±3.1	50±3.3
WEIGHT (kg)	71±4.2	82±5.5	72±3.1
HEIGHT (cm)	171±3.4	173±2.3	171±2.2
BSA (sq m)	1.83±0.06	1.96±0.07	1.84±0.04

Values are MEAN ± SEM.

Results

The data here show that our profiling procedure provides the capability of distinguishing between different groups of hypertensives (Table 5:4:2). The data show that despite being treated at a higher level of anti-hypertensive intervention, non-responders had higher peripheral resistances compared to responders and to controls. Non-responders also had reduced arterial compliance, stroke volume and cardiac output. However, no reduction in cardiac contractile function was observed in either of the three indices tested. In fact, left ventricular elastance (ELV) was increased, with a slightly, though not significantly higher heart rate. Non-responders also had an increased interventricular septal thickness, compared to responders and control subjects.

TABLE 5:4:2. Haemodynamic Characteristics.

MEN

		Control Subjects	Responders	Non-responders
Number		8	9	5
PSP	mmHg	124±4.8	136±4.2	166±9.9*****+++
PD	mmHg	77±3.5	85±2.0	104±5.2*****++
PA	mmHg	97±3.3	107±3.3	131±7.1*****++
HR	beats/min	58±3.5	59±3.0	63±5.8
TS	msec	322±7.6	319±13.6	305±24.3
LVED	cm	5.22±0.25	5.21±0.24	4.92±0.23
IVS	cm	0.90±0.04	0.97±0.04	1.03±0.03*
SV	ml	79±8.4	82±7.9	71±7.5
FCO	L/min	4.68±0.68	4.79±0.43	4.35±0.47
RTP	dyn.cm.sec-5	1894±249	1950±256	2496±250
CA	ml/mmHg	1.89±0.32	1.62±0.12	1.17±0.23+
VAE	ml	183±31	173±14	150±15
ELV	mmHg/ml	2.20±0.30	2.62±0.37	3.41±0.43
EF%		59±2.1	62±2.2	61±2.8
SCF	circs/sec	1.00±0.05	1.08±0.09	1.09±0.03
NO.DRUGS		-----	1.56±0.24	2.00±0.32
DRUG CODE units		-----	2.78±0.62	4.40±0.93
VIG.THER. units		-----	2.33±0.53	3.00±0.63

Values are MEAN±SEM.

* p < .05, ** p < .01, *** p < .001 compared to controls.

+ p < .05, ++ p < .01, +++ p < .001 compared to responders.

TABLE 5:4:2 (continued).

ALL SUBJECTS

NUMBER		11	12	13
PSP	mmHg	120±4.2	133±3.4**	164±3.6***+++
PD	mmHg	74±3.1	82±2.9	100±2.3***+++
PA	mmHg	94±3.2	104±2.9*	128±3.3***+++
HR	beats/min	59±2.7	58±2.8	59±2.9
TS	msec	322±6.1	332±13.1	331±12.1
LVED	cm	4.95±0.23	5.07±0.20	4.79±0.12
IVS	cm	0.86±0.04	0.95±0.04	0.99±0.03*
SV	ml	72±6.9	78±6.6	68±3.7
FCO	L/min	4.34±0.52	4.51±0.38	3.97±0.27
RTP	dyn.cm.sec-5	1935±185	2030±211	2707±171**+
CA	ml/mmHg	1.71±0.24	1.55±0.11	1.14±0.11*+
VAE	ml	163±24	163±13	144±12
ELV	mmHg/ml	2.66±0.34	2.73±0.29	3.81±0.31*+
EF%		62±2.1	63±1.7	63±2.2
SCF	circs/sec	1.04±0.05	1.05±0.07	1.05±0.05
NO.DRUGS		-----	1.75±0.28	2.08±0.18
DRUG CODE	units	-----	3.25±0.70	4.38±0.54
VIG.THER.	units	-----	2.58±0.64	3.92±0.83

5:5 STUDY IV - COMPARISON OF DIURETIC AND BETA-BLOCKER TREATED SUBJECTS.

Method

Using data from a prospective trial to assess the effects of anti-hypertensive therapy with diuretics and beta-blockers (Appendix 4), haemodynamic profiles were obtained. This subject group (DATA SOURCE 3), consisted of males between the ages 42-65 years, who at the beginning of this study were not on medication, or who had their anti-hypertensive medication discontinued at least four weeks prior to the beginning of the study. Simultaneous EKG and echocardiograms were obtained, together with sytolic and diastolic blood pressure by ramdom-zero sphymomanometry.

Of the 50 subjects initially in this study, suitable initial echocardiograms were obtained on 31 of the 36 subjects on whom echo-recordings were made prior to the commencement of anti-hypertensive therapy. Blood pressure and pulse rate were obtained two months after the 50 subjects were randomized into either a diuretic or beta-blocker treatment group. Four patients were lost to further study. After 20 months of stepped care therapy, (according to the protocol Appendix 4), M-mode echocardiograms were again recorded on 39 subjects, of which 32 suitable recordings were obtained, and for whom haemodynamic profiles were again calculated.

Eighteen of these latter subjects had had initial profiles and for this group a comparison between pretherapy and posttherapy data was carried out, using each subject as their own control (Table 5:5:1-5:5:2).

Results

From the analysis of the pre-therapy, 2 month and 24 month data on pulse rate, systolic and diastolic blood pressures, subjects on longterm beta-blocker therapy showed a recovery of heart rate towards the pre-therapy state after an initial decrease (Fig. 5:5:1). Blood pressure, however, remained decreased (Fig 5:5:2-5:5:3). No significant changes in heart rate were observed in the diuretic treated group (Fig 5:5:4). However, blood pressure was significantly reduced on both shortterm and longterm therapy (Fig 5:5:5-5:5:6).

All subjects had their blood pressure controlled (diastolic pressure <95mmHg). Subgrouping of subjects into monotherapy and poly-drug therapy for both diuretic and beta-blocker treatment groups, showed that a higher percentage of diuretic treated subjects had their blood pressures controlled with a single drug than for the beta-blocker treatment group (83% vs. 53%). This result is almost identical to that obtained in studies published by the Veterans Administration Study Group (157,158), for the comparison of hydrochlorothiazide and propanolol as initial drugs in the treatment of hypertension.

The pre-therapy analysis on 18 subjects showed no overall differences between the diuretic and beta-blocker treatment groups. However, subjects on beta-blocker mono-therapy had

higher initial cardiac output and lower peripheral resistances than other beta-blocker treated subjects (Table 5:5:1). Diuretic treated subjects showed increases in cardiac contractile function post-therapy, while there was no change for beta-blocker treated patients (Table 5:5:2). Subjects on beta-blocker alone had higher post-therapy ventricular septal thickness than diuretic treated patients (Table 5:5:2).

The data in Tables 5:5:3-5:5:4 show that normally observed correlation between blood pressure, age, body size and various cardiovascular parameters on subjects without cardiovascular intervention, are not preserved for subjects on anti-hypertensive drug therapy. Notably, the correlation between body surface area and the various cardiac function are weakly positive pre-therapy, while been significantly negative post-therapy; also there was a change in the sign of the correlation between cardiac function (ELV) and systolic blood pressure.

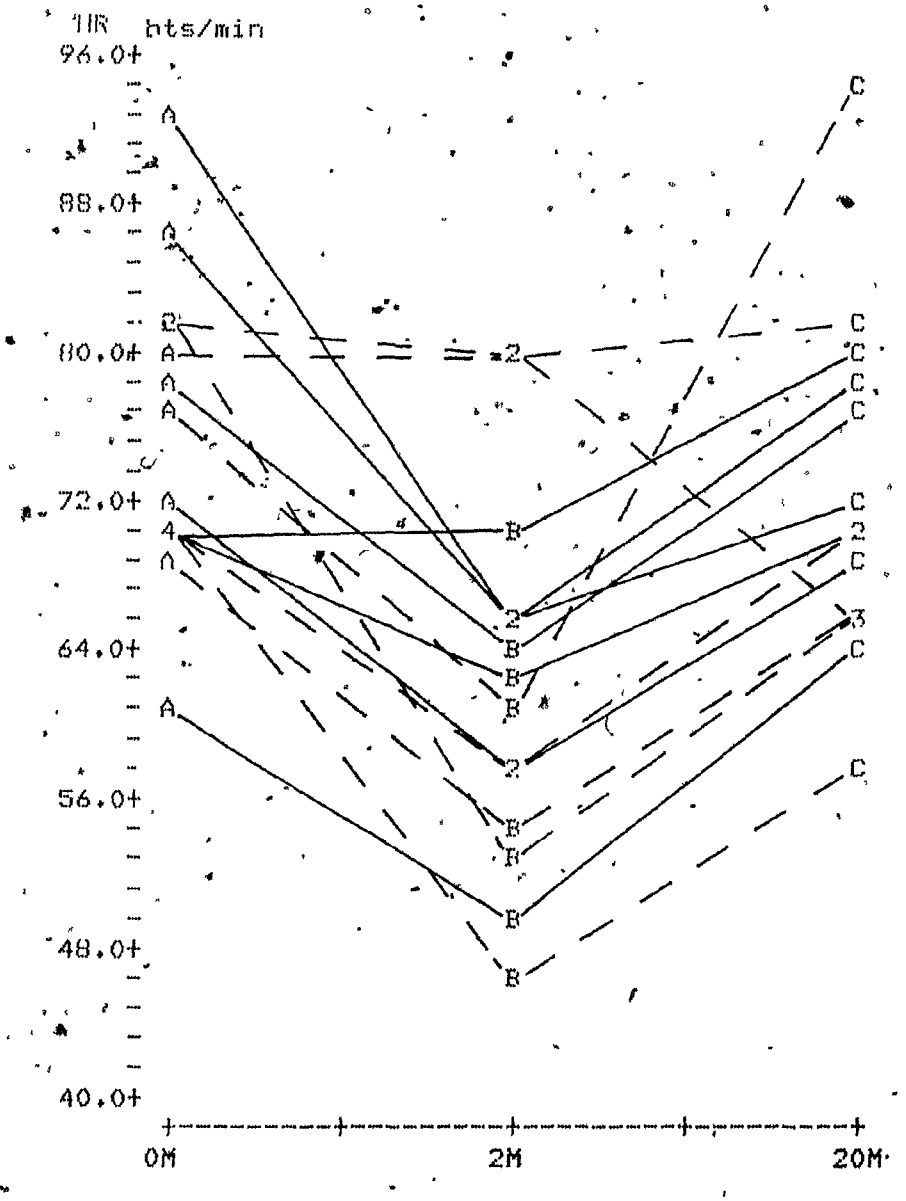
The initial overall pre-therapy correlations indicate that the increased blood pressure in this subject group was not due to excessive blood flow, but to increased vascular resistance. As may be expected, there was a positive relation between blood pressure and ventricular septal thickness.

The data also show that the level of blood pressure was not a primary determinant for the required vigor of antihypertensive drug therapy. Therapeutic vigor correlates significantly with ventricular septal thickness and left atrial size, especially in the latter case for the diuretic patient group, for which, given left atrial size as an index of volume load, we speculate that there was a greater diuretic requirement to overcome this volume load. Increased septal thickness is an indicator of longstanding hypertension and hence of a possible resetting of the cardiovascular system to the higher pressure state, hence requiring a higher degree of drug intervention to change the cardiovascular state.

There are several post-therapy correlations of significant interest namely: cardiac function (SCF) was negatively correlated with subject age for diuretic treated subjects, positive for metoprolol treated and pre-therapy subjects; cardiac function (ELV) was weakly negatively correlated with systolic blood pressure for diuretic treated subjects, significantly positive for metoprolol treated and pre-therapy subjects; a surprisingly negative correlation between peripheral resistance and blood pressure for the diuretic monotherapy group; the positive correlation between systolic blood pressure and interventricular septal thickness was more pronounced for subjects on multiple drug therapy.

LEGEND Figures 5:5:1-5:5:6

0M	pretherapy(A)
2M	after 2 months on antihypertensives(B)
20M	after 20 months on antihypertensives(C)
———	subject taking a single drug (monotherapy)
-----	subject taking more than one drug



Fisure 5:5:1. Changes in pulse rate for subjects on beta-adrenersic blockins drus therapy.

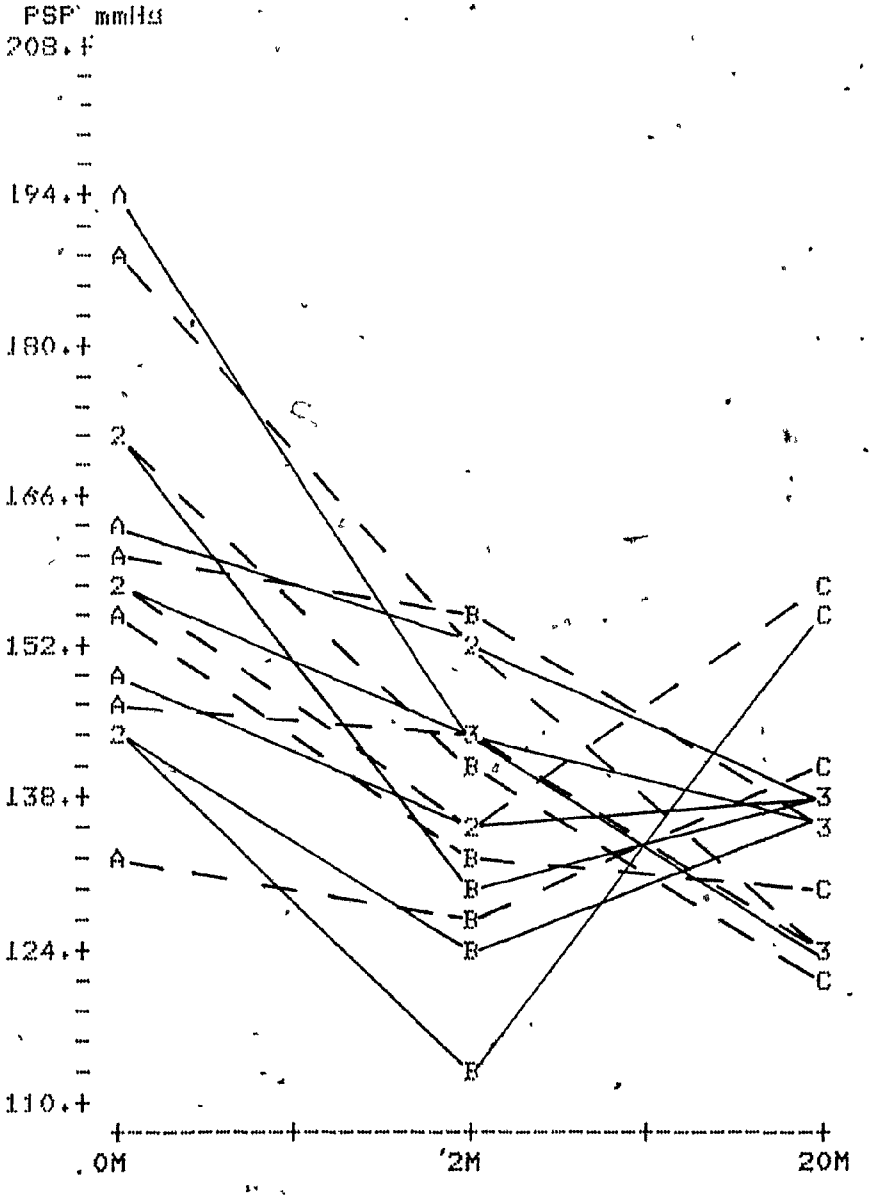


Figure 5:5:2. Changes in systolic blood pressure for subjects on beta-adrenergic blocking drug therapy.

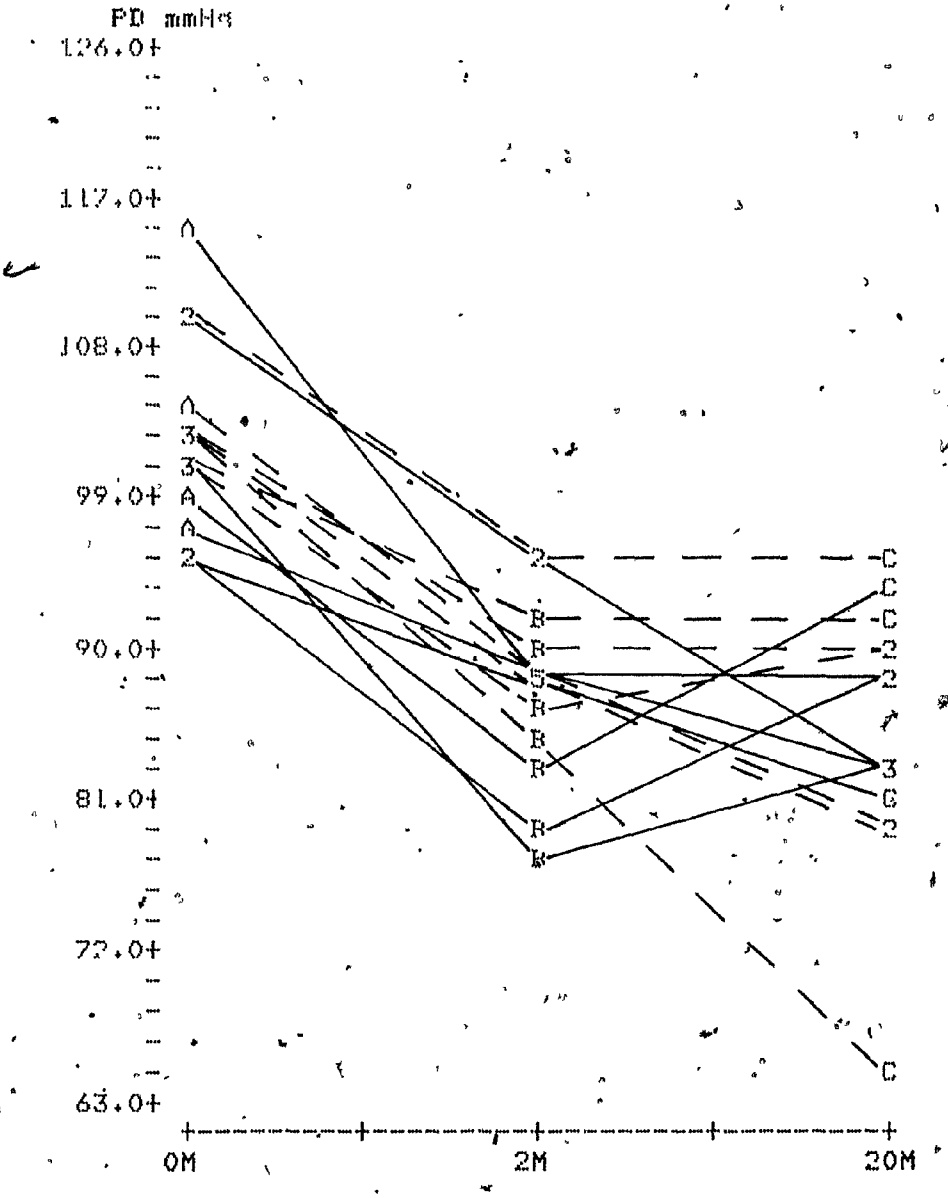


Figure 5:5:3. Changes in diastolic blood pressure for subjects on beta-adrenergic blocking drug therapy.

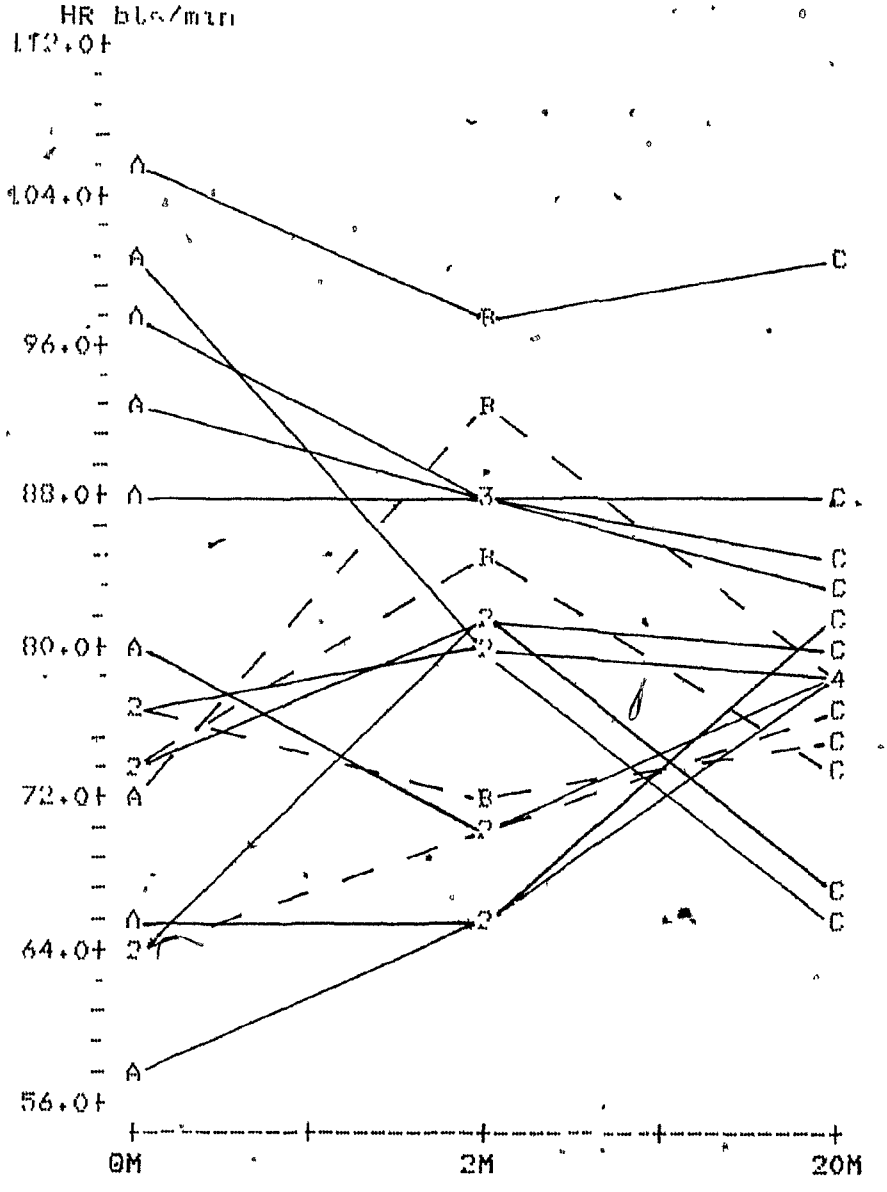


Figure 5:5:4. Changes in pulse rate for subjects on diuretic drug therapy.

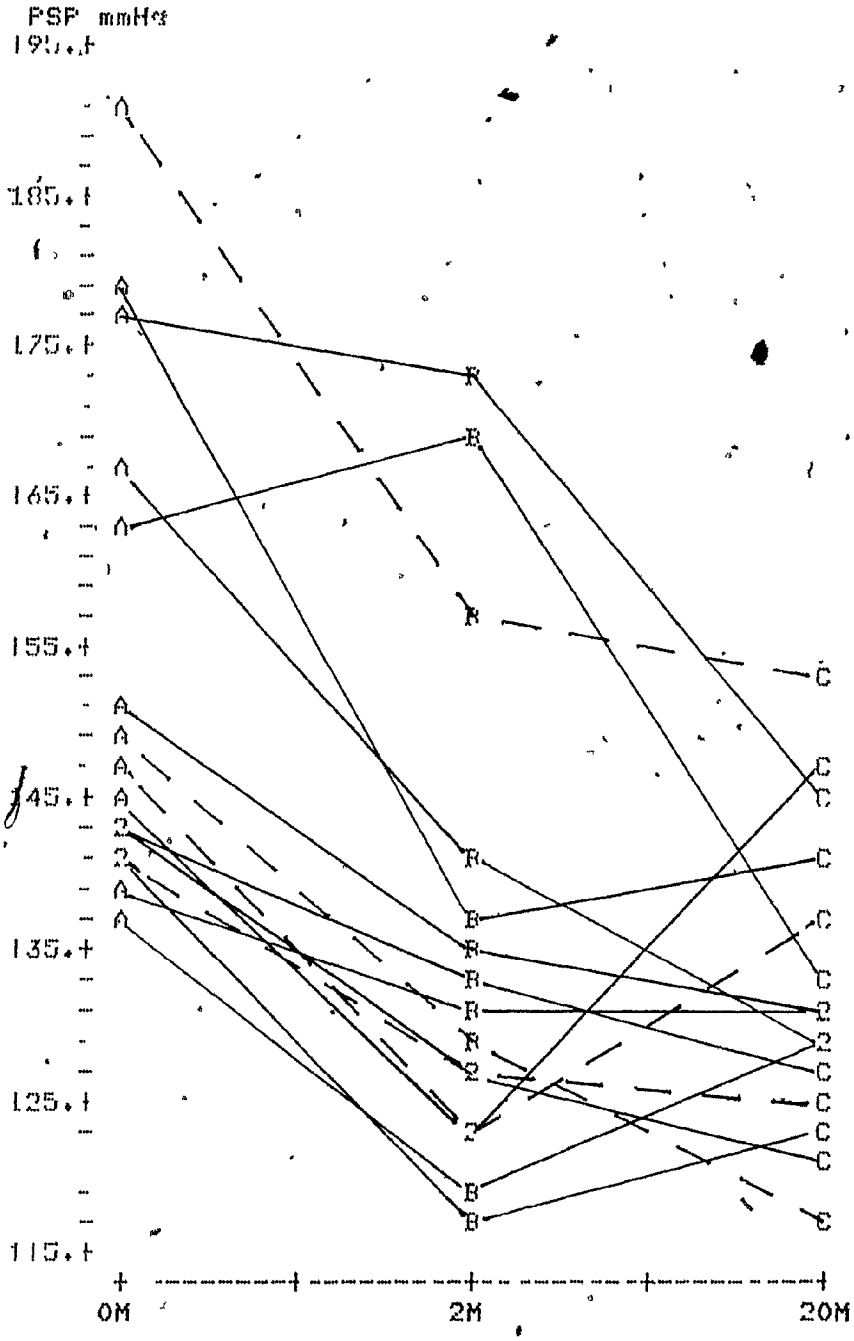


Figure 5:5:5. Changes in systolic blood pressure for subjects on diuretic drug therapy.

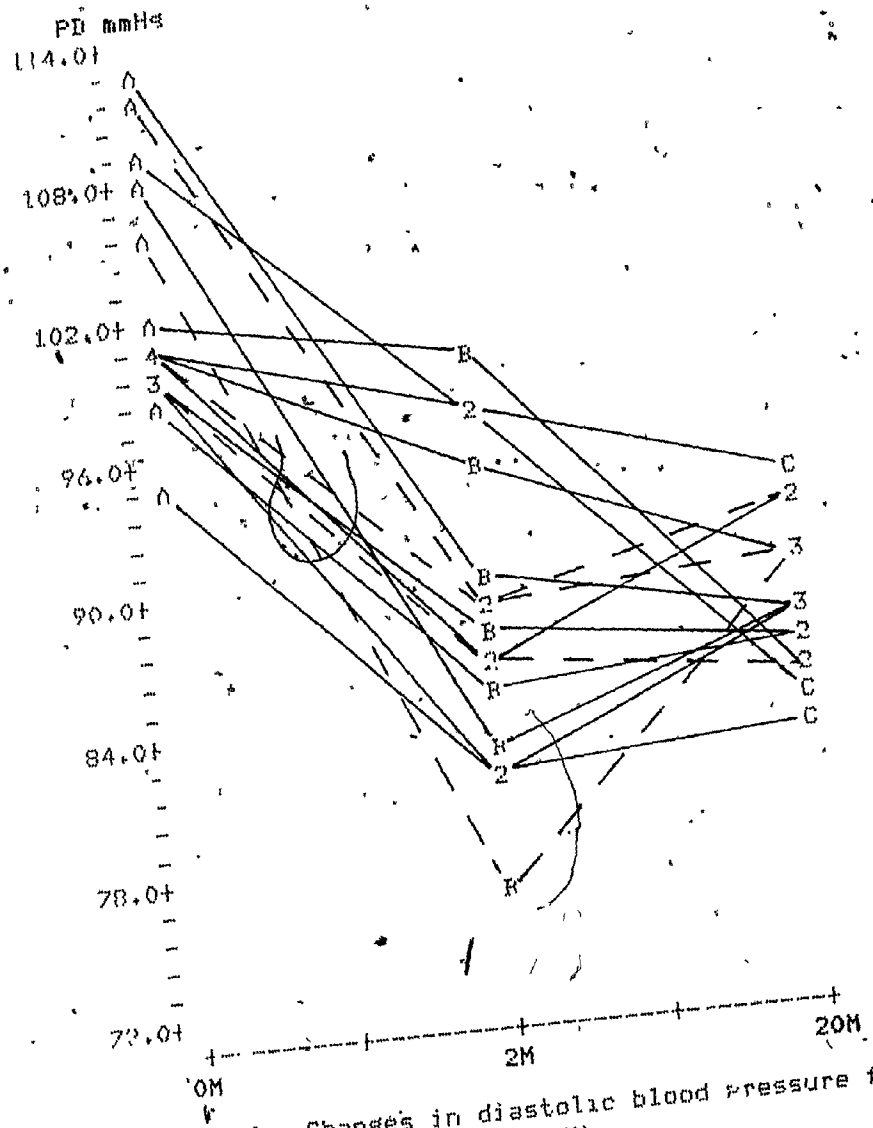


Figure 5:5:6. Changes in diastolic blood pressure for subjects on diuretic drug therapy.

TABLE 5:5:1. Pre-therapy characteristics of diuretic and beta-blocker subject groups, both monotherapy and polytherapy.

		DIURETIC GROUP		BETA-BLOCKER GROUP	
		Mono Therapy	Poly Therapy	Mono Therapy	Poly Therapy
Number		9	3	3	3
AGE	years	50±2.2	48±2.1	46±3.5	49±2.6
VIG.THER.	units	1.61±.20**	3.33±.60	1.17±.44	3.23±1.4
BSA	sq m	1.96±.05	1.96±.03	2.07±.05	2.00±.07
PSP	mmHg	152±5.5	161±15.	149±2.9	145±6.2
PD	mmHg	103±1.6	105±3.5	103±4.2	105±2.0
HR	bts/min	70±2.4	64±2.1	74±2.6	73±14.
LVED	cm	5.28±.23	5.57±.13	5.47±.27	4.80±.29
LVES	cm	3.56±.27	3.77±.19	3.47±.38	3.33±.43
IVS	cm	1.20±.05	1.20±.30	1.17±.03	1.23±.23
LAD	cm	3.56±.15	4.07±.47	3.83±.50	3.27±.15
SV	ml	80±9.3	91±1.8	94±4.8**	61±1.4+++
FCO	l/min	5.63±.67	5.81±.30	7.02±.25*	4.40±.77
RTP	dyn.cm.s-5	1995±254	1781±46.	1405±12.	2369±414
CA	ml/mmHg	1.75±.25	1.80±.33	2.07±.17	1.62±.17
VAE	ml	214±29	227±29.	256±30.	198±17.
ELV	mmHg/ml	3.01±.48	2.32±.22	2.88±.66	3.25±.89
EF%		60±5.0	60±2.7	66±5.5	58±7.2
SCF	circs/sec	1.13±.11	1.04±.07	1.30±.14	1.11±.27

TABLE 5:5:2. Post-therapy charateristics of diuretic and beta-blocker subject groups, both monotherapy and polytherapy.

		DIURETIC GROUP		BETA-BLOCKER GROUP	
		Mono Therapy	Poly Therapy	Mono Therapy	Poly Therapy
Number		9	3	3	3
BSA	sq m	1.95±.06	1.97±.04	2.00±.10	2.01±.08
PSP	mmHg	133±3.4##	133±9.4	136±1.2#	132±5.1
PD	mmHg	89±0.9###	88±1.4#	90±1.7	88±4.7#
HR	bts/min	73±3.5	77±2.8	68±5.1	64±2.6+
LVED	cm	4.84±.31	5.40±.31	5.47±.41	5.23±.15
LVES	cm	2.92±.28#	3.53±.24	3.10±.06	3.47±.28
IVS	cm	1.09±.04	1.30±.25	1.57±.30+	1.13±.07
LAD	cm	3.80±.17	3.87±.27	3.37±.79	3.73±.29
SV	ml	78±9.9	90±11.	110±23.	81±17.
FCO	l/min	5.69±.76	7.00±1.1	7.19±.99	5.12±.93
RTP	dn.cm.s-5	1804±293	1310±256	1279±200	1764±251
CA	ml/mmHg	1.87±.23	2.18±.57	2.37±.46	2.06±.74
VAE	ml	202±25.	230±55.	260±48.	223±83.
ELV	mmHg/ml	4.75±1.1	2.30±.37	3.14±.15	2.49±.57
EF%		70±3.7	63±2.5	73±3.5	60±8.8
SCF	circs/sec	1.46±.11	1.26±.07#	1.46±.07	1.13±.21

* significance level mono- vs poly-therapy.

\+ significance level diuretic vs beta-blocker treatment group.

\# significance level pre- versus post-therapy.

\- $p < .05$, -- $p < .01$, --- $p < .001$.

Table 5:5:3. Pre-therapy correlations between various clinical, therapeutic and haemodynamic parameters. (N=31).

		AGE	BSA	PSP	VIG.THER
HR	bts/min		.403*		
LVED	mm		.429*		
IVS	mm			.434*	.409*
LAD	mm				.370*
SV	ml	-.422*	.456**		
FCO	L/min	-.460**	.626***		
RTP	dyn.cm.s-5	.522**	-.634***		
CA	ml/mmHg	-.507**	.366*	-.677***	
VAE	ml	-.533**	.394*	-.575***	
ELV	mmHg/ml			.426*	

Table 5:5:4. Post-therapy correlations between various clinical, therapeutic and haemodynamic parameters. (N=32).

	AGE	BSA	PSP	PD
HR				
LVED		.478**		
IVS				
LAD		.398*		
SV				
FCO				
RTP				
CA		.364*	-.417*	
VAE		.376*		
ELV				

Significance levels * $p < .05$, ** $p < .01$, *** $p < .001$.

5.6 DISCUSSION CHAPTER 5

As expressed in the introduction, a primary objective of this thesis has been to obtain a simple procedure for the calculation of haemodynamic parameters from noninvasively recorded data, with possible application towards differentiating between hypertensive patient groups, and as an aid in the prior selection of antihypertensive drug therapy.

The data above provide evidence that this objective has been met, and indeed pre-therapy selection of appropriate medication may indeed be possible, providing us with a more rational approach to antihypertensive drug therapy (hypothesis H2). Table 5:5:1 reveals a subgroup of hypertensive subjects with high cardiac output and normal peripheral resistance, who respond to mono-therapy with the beta-blocker metoprolol.

The data also provides evidence that hypertensives form a heterogeneous mix of individuals with respect to their haemodynamics (hypothesis H1). Published studies indicating heterogeneity of the haemodynamics of hypertension was reviewed in chapter 2.

The measurement most critical to the accuracy of our procedure is that of ventricular chamber dimensions and the subsequent estimation of ventricular volumes and stroke volume. However, the procedure is not restricted to the measurement techniques used in the above studies. As improved noninvasive measurement techniques occur (perhaps from M-Mode to 2D echos), similar improvements will occur in the sensitivity and accuracy of the procedure.

Echocardiology is today one the primary investigative tools in cardiology, and the echocardiogram has been shown to be sufficiently precise and reliable for cardiovascular assessment of the effects of drug therapy (162).

Mathematical relations for estimating arterial compliance, based on the first order Windkessel model of the arterial system, have previously been validated on normotensive and hypertensive subjects (163). However, the present procedure eliminates the need for catetherization, as is required in the referenced study. Catetherization remains however, the standard against which our procedure will have to be compared. The 'tool' has been presented here and its capabilities shown. There remains however, the process of establishing relationships between data obtained by our procedure and that obtained by catheterization.

Chapter 6

6.1 SIMULATION MODEL

In an attempt to assess, theoretically, the possible cardiovascular responses to a given cardiovascular intervention, a simulation study was carried out, the hope being that such a study may aid in delineating the haemodynamic control aspects determining response and non-response of blood pressure to the intervention.

Two simulation studies were carried out. The first study, a simulation of shortterm (~30 minutes) cardiovascular dynamics, was carried out to determine whether the cardiovascular control systems included in the model, (Figure 6:1:1), were sufficient to adequately simulate the clinically observed shortterm dynamics of various cardiovascular interventions.

In the second study, we looked at the possible longterm cardiovascular responses to drug interventions with diuretics, vasodilators and beta-blockers. In this simulation study, we examined the role adaptation plays in non-response to cardiovascular drug interventions, as indicated by the heart rate adaptation to beat-blocker therapy (Figure 5:5:1).

A regulated cardiovascular system model is presented here involving the dynamics and interactions of the heart and the circulation, and their regulation by the autonomic nervous system (baroreceptors and cardiopulmonary receptor mechanisms), autoregulation, and renal control functions.

Model responses to simulated interventions help to delineate various possible responses to therapeutic interventions in hypertensive patients. External interventions are provided through imposed drug input levels and imposed heart function stresses (e.g. simulated cardiac pacing). The model is intended to be used for predictive/diagnostic purposes, as it permits the study of cardiovascular responses to physiological stresses and various hypotensive drug interventions.

The circulation is modelled on the basis of the Windkessel system. The model includes the arterial, capillary (including the microcirculatory interstitial fluid system), and venous systems. The circuit is completed via the coupling of the central venous pressure with the cardiac stroke output via the Frank-Starling mechanism. The kidneys are also included for the output of renal fluid volume (Fig 6:1:1).

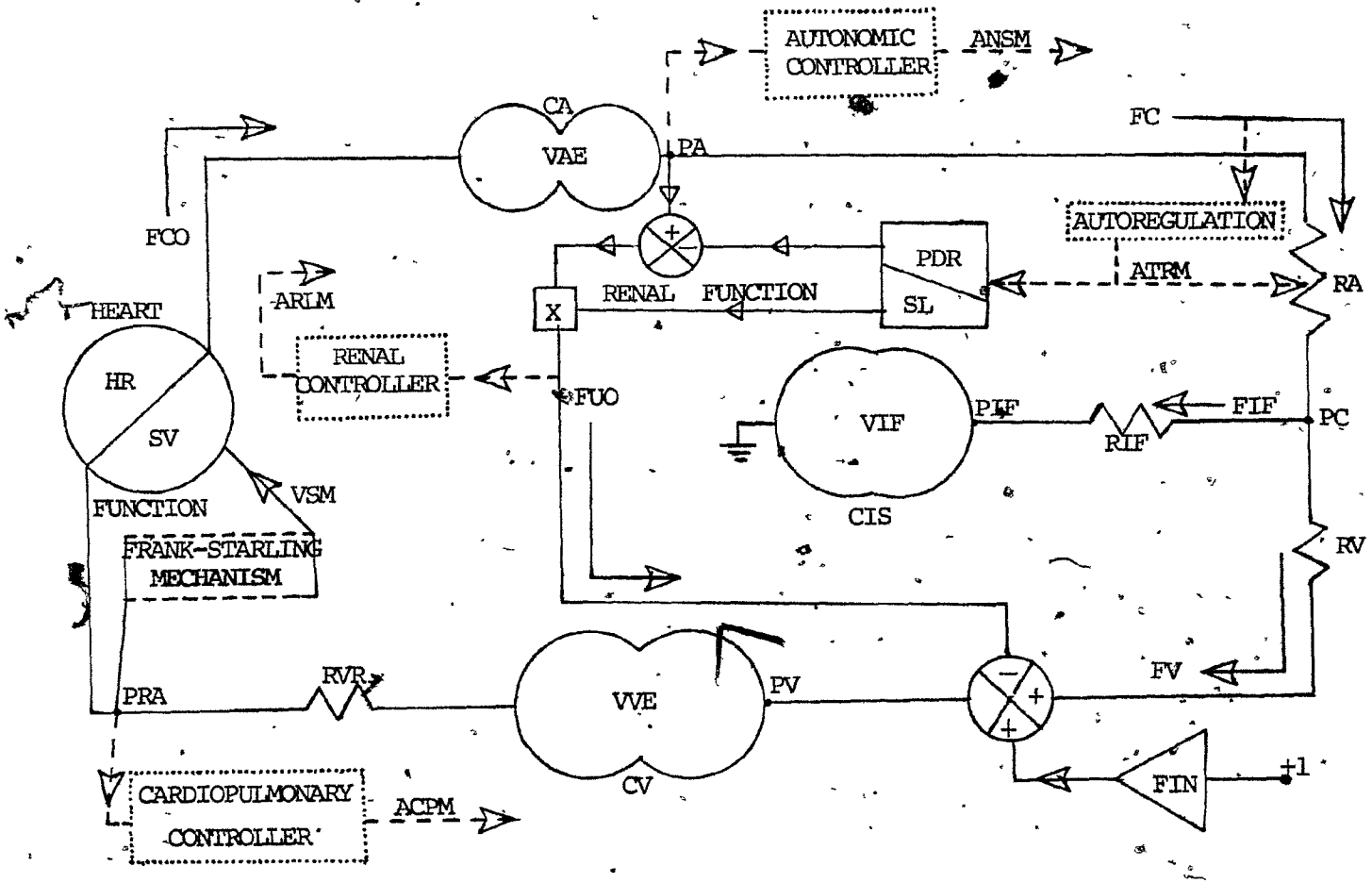


Figure 6:1:1. Schematic diagram of the model of the cardiovascular system used in simulation studies of cardiovascular interventions.

The governing equations of the model relate the cardiac, circulatory, and renal variables with the controlling systems namely; the baroreceptors, cardiopulmonary receptors, autoregulatory, and renal renin-angiotensin systems. Other vasoactive substances will be incorporated within these basic controls. For example, prostraglandin mechanisms will be assumed to function through the autoregulatory mechanism, while circulating catecholamines will be related to level of autonomic activity.

The control relationships are expressed in terms of certain parameters of the controlled system model listed in the nomenclature. The cardiovascular controllers as represented in the model are expressed as multipliers with normal values of unity. For example, the autonomic output due to arterial baroreceptors with mean arterial pressure input, is represented by the variable ANSM for which;

ANSM > 1 represents increased sympathetic output,
and ANSM < 1 represents decreased sympathetic or
increased parasympathetic activity.

The two arms of the autonomic nervous system (sympathetic and parasympathetic) are here represented as a single system in the model. This was done since the sympathetic and parasympathetic activities with regards to arterial baroreceptors act reciprocally (90), with algebraic

summation of their effects (90). However, due to the different reflex properties for cardiopulmonary low pressure receptors, this segment of the autonomic input was kept separate from the arterial baroreceptor autonomic input, hence its distinctive effects may be separately and clearly represented. The cardiopulmonary control function is represented by the varible ACPM for which,

ACPM > 1 represents autonomic inhibition, while

ACPM < 1 represents autonomic stimulation.

The two other control functions ARLM and ATRM which responds to the level of fluid volume load presented to the kidneys and to the level of peripheral blood flow, respectively, are similarly constituted.

Each control function affects several of the system variables external to region of origin of the controller, except for the autoregulatory control which is here defined as 'local', affecting only vascular arteriolar resistance, representing a resetting of the basic local resistance. This may be represented by the equation,

$$RAB = RAZ*(ar*ATRM + 1-ar).$$

The effect of central volume load on cardic function via the Frank-Starling mechanism is here represented by the multiplier SVM with normal value 1, and its contribution to changes in stroke volume expressed as:

SVB=SVZ*(av*SVM + 1-av).

The total effect on the variables of the system due to the contributions of the various controllers are represented by the linear coupling of the controlling variables, with coupling constants representative of the relative magnitudes of the various controller gains with respect to the variable at hand.

e.g.

RA = RAB*(ka*ACPM + kb*ANSM + kc*ARLM + kd)

where

ka + kb + kc + kd = 1.

In the control system presented so far, control is obtained through the parameters of the system, hence the system is highly nonlinear, despite its relatively simple conceptual form.

As mentioned previously, adaptation of the controllers to the prevailing levels of the 'sensed' system variable is paramount to this systems analysis. Receptor systems tend to adapt to the prevailing level of input with varying time constants of adaptation. For example, arterial (91) and cardiopulmonary (164) baroreceptors adapt to the level of arterial blood pressure. The adaptation of the arterial baroreceptors may be expressed diagramatically as:

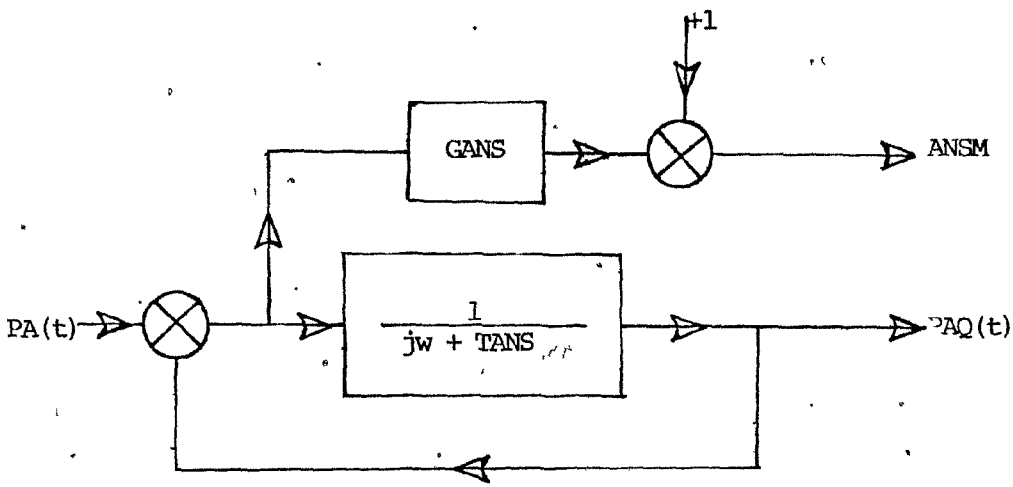


Figure 6:1:2. Baroreceptor-Autonomic function controller.

Hence we may write for controller adaptation,

$$dPAQ/dt = TANS*(PA-PAQ),$$

and the central autonamic output as,

$$ANSM = 1.-GANS*(PA-PAQ).$$

Similarly, we may write for the other controllers:

$$dFUOQ/dt = TARL*(FUO-FUOQ)$$

$$dFCQ/dt = TATR*(FC-FCQ)$$

$$dPVQ/dt = TACP*(PV-PVQ)$$

and,

$$ARLM = 1.-GARL*(FUO-FUOQ)$$

$$ATRM = 1.+GATR*(FC-FCQ)$$

$$ACPL = 1.+GACP*(PV-PVQ).$$

As can readily be seen from the diagram above, the dynamics of the system is based on closed loop control. This provides the system with more rapid damping of perturbations and allows for the control of equilibria which is relatively independent of the operating accuracy of the systems components.

Therapeutic interventions into the system is included for the primary effects of various drugs on system parameters. For example, the effect of triple drug therapy on vascular arterial resistance may be represented as:

$$RAX = RAZ*(da*XBLM + db*XHHM + dc*XVLM + dd)$$

where

$$da + db + dc + dd = 1.$$

The drug effects are represented as multipliers with normal value 1. The adaptation of the system to the level of drug input is also incorporated in the model. This adaptation may be expressed in the following equations:

$$dXBLQ/dt = TXBL*(XBL-XBLQ)$$

$$dXHHQ/dt = TXHH*(XHH-XHHQ)$$

$$dXVLQ/dt = TXVL*(XVL-XVLQ).$$

6.2 SIMULATION STUDY PROCEDURES

Shortterm simulation

This study was carried out in order to examine the haemodynamic range of operation of the model, to test the ability of the model's control systems to simulate the haemodynamic events of various interventions, and to 'fine-tune' the various parameters of the control systems. A computer listing of the model equations is given in Appendix 5.

The model was tested on the data of Shaver et al. (148). Data on five subjects from that study were selected (Table 6:2:1). They were the subjects whose protocol consisted of recordings made in the control (pre-intervention) state, controlled right atrial pacing, methoxamine infusion with continued right atrial pacing and continued methoxamine infusion without pacing. Methoxamine, a pressor amine of predominantly vasoconstrictive activity, but lacking significant inotropic effect, was administered intravenously resulting in an average increase in mean arterial pressure of 27mmHg. Heart rate was held constant by high right atrial pacing.

Right atrial pacing was simulated in this study by setting the heart rate (HR) to the heart rate level during the

pacing period as given by the data i.e. HR=HRP. At the end of the atrial pacing period (20 minutes), heart rate was returned to the 'basic' level with a slight time delay, as given by the equation,

$$HRB = HRN + (HRP-HRN)*\exp(15*(1-T/20),$$

where HRN is the pre-intervention heart rate.

The coupling constants, relating the relative effects of the controllers on the system parameters, were selected on a physiological basis. Minor adjustments were made based on our experience with the model.

Heart rate and cardiac contractility respond positively to increased sympathetic activity (108,165), and to increased right atrial filling (109,166,167), contractile function exhibiting minimal response to atrial filling (167,168). Weak positive inotropic and chronotropic responses to angiotensin have been demonstrated in isolated cardiac preparations (169). In vivo these effects are overridden by baroreceptor reflexes so that the hypertension of angiotensin II infusion is accompanied by bradycardia (169). The reflex effects of the controllers on heart rate and stroke volume have been represented as follows:

$$HR = HRB*(0.5*ANSM + 0.05*ARLM + 0.35*ACPM + 0.1)$$

$$SV = SVB*(0.2*ANSM + 0.05*ARLM + 0.05*ACPM + 0.7).$$

Renal function is known to be decreased by increased sympathetic stimulation (114). Stimulation of cardiopulmonary receptors results in diuresis with decreasing levels of antidiuretic hormone (102,167), and a decreased renal resistance (107,109). Cardiopulmonary reflexes have been found to exert an equivalent or even a slightly greater effect on the renal vasculature than the arterial baroreceptor reflexes (107,109). The renal circulation is also under autoregulatory control. One study has indicated that as much as 30% of the increase in renal artery resistance due to the infusion of norepinephrine was due to autoregulation (170). The renal circulation is also affected by negative feedback effects of the renin-angiotensin system (169). The reflex effects of the controllers on renal function have been represented as follows:

$$PDRB = PDRZ*(0.3*ATRM + 0.7)$$

$$PDR = PDRB*(0.3*ANSM + 0.3*ARLM - 0.6*ACPM + 1.0)$$

$$SL = SLB*(-0.2*ANSM - 0.5*ARLM + 0.3*ACPM + 1.4).$$

Increased sympathetic efferent activity leads to peripheral circulatory vasoconstriction (68,107,170), systemic arterial resistance being the major area of response (68). Arterial resistance is also under autoregulatory control. However, autoregulatory effects can sometimes be masked by the more powerful baroreflexes (130,171). The vasodilatory effect of

increased right atrial pressure (107,109) can also be completely masked when the arterial baroreceptors are maximally activated (109).

Stimulation of the renin-angiotensin system has been shown to result in increased vascular resistance (169), while blocking of the system leads to decreased peripheral resistance and right atrial and pulmonary pressure (172), with a more significant effect on the pulmonary venous than on the pulmonary arterial resistance (172). The effect of the controllers on the peripheral circulation has been represented as follows:

```
CA = CAB*(-0.3*ANSM - 0.3*ARLM + 0.05*ACPM + 1.55)
CV = CVB*(-0.2*ANSM - 0.3*ARLM + 0.05*ACPM + 1.45)
RAB = RAZ*(0.2*ATRM + 0.8)
RA = RAB*( 0.3*ANSM + 0.5*ARLM - 0.05*ACPM + 0.25)
RV = RVB*( 0.2*ANSM + 0.6*ARLM - 0.05*ACPM + 0.25)
```

Methoxamine infusion was simulated by first setting the vasodilator input level, in this case XVLI=-10 (negative sign indicating vasoconstriction). This drug infusion began after ten minutes of high right atrial pacing. The active drug level was calculated, with appropiate time delay for drug accumulation, by the relation:

```
XVL = XVLI*(1-exp(10*(1-T/10))).
```

The drug effect XVLM was then calculated as:

XVLM = 1 + GXVL*(XVL-XVLQ),

where initially XVLQ=Ø, and

dXVLQ/dt = TXVL*(XVL-XVLQ).

In this simulation drug elimination was incorporated in the adaptive process via the time constant of drug adaptation TXVL, and XVLM was restricted to the range (Ø,3).

The cardiovascular effects of methoxamine infusion was restricted to the resistance and compliance components of the circulation, namely:

CAB = CAX*(Ø.25*XVLM + Ø.75)

CVB = CVX*(Ø.25*XVLM + Ø.75)

PDRZ = PDRX*(-Ø.25*XVLM + 1.25)

RAZ = RAX*(-Ø.75*XVLM + 1.75)

RVB = RVX*(-Ø.25*XVLM + 1.25).

Simulation was carried out using the FORSIM simulation package (173,174), with fixed simulation time steps being the only option appropriate for our purposes. For economy of computer time, the Euler method was used for solving the differntial equations. The Euler method was compared to the Runge-Kutta method, and no loss of accuracy was encountered. The FORSIM selected time step for simulation was Ø.ØØ1 minutes. Output was generated every 5ØØ iterations i.e. every Ø.5 minutes, and comparison with the data made every 1Ø minutes.

Initially, the FORSIM optimization option was used for modifying the time constant and gain parameters in the model, in order to obtain better correspondence with the data. However, this procedure was later abandoned due to lack of sufficient data for meaningful optimization. Five variables at three intervention stages gave only 15 data points for optimization usage.

Since controller outputs are determined by the state parameters, and in turn affect the state parameters, we have relationships of the form $x=f(y)$, $y=g(x)$. These algebraic relations were solved iteratively using the FORSIM supplied subroutine IMPL.

Table 6:2:1. Clinical data on 5 subjects from data of Shaver et al., used in simulation studies.

Subject	EW	TH	GB	MB	RH
BSA sq m	2.ØØ	2.4Ø	2.4Ī	1.8Ø	1.74
AGE years	17	2Ø	24	18	29

(Data from Shaver et al. J Clin Invest 1967).

Longterm simulation

In simulating the longterm model of the circulation, several changes were made to the original shortterm simulation model. However, no changes were made to the coupling constants or controller gains. Considering the requirement for simulation over a time period of up to one year, efforts were made to increase the time step of each iteration of the model. Considering the equation dVAE/dt=FCO-FC, with VAE=250 ml and FCO=FC=5000 ml/minute, a 1% increase in FCO (5050 ml/min) due to increased cardiac function say, will require a cautious selection of the appropriate time step, as indicated below:

Time Step(min)	VAE(ml)	% VAE
.001	.05	.02
.01	.5	.2
.05	2.5	1.0
.1	5.0	2.0
1.0	50.0	20.0
10.0	500.0	200.0
100.0	5000.0	2000.0

Hence a time step greater than 0.05 minutes would give possible unrealistic results.

For the longterm simulation, we therefore eliminated the systemic arterial bed as a separate component of the simulation model. Arterial pressure was then calculated from

the steady state pressure/flow relation, PA=FCO*RTP, with capillary blood flow equal to cardiac output i.e. FC=FCO. The system was considered to move from one quasi-steady state to another from time step to time step, since under conditions of stable functioning of the control systems, the cardiovascular system can be considered stationary over short periods of time, 5 to 15 minutes (175).

Drug input ports for beta-adrenergic blockers, diuretics and vasodilators were included in the model. Drug input levels were set e.g. XBLI=XHHI=XVLI=5.Ø. Active drug levels were represented by sinusoids, with maximun values at mid-intake periods, and encorporating an inital time delay for drug accumulation. This can be represented by the equation:

XBL= XBLI*(1 + ABS(Sin(KXBL*TANG)))*(1/(1 + Exp(-T/12Ø))-.5)

where TANS=Π*T/144Ø, and KXBL is the number of times per day the beta-adrenergic blocker is to be taken. Most of the simulation runs, however, were carried out with the circulating drug rising to a constant level XBLI, with a time constant of two hours.

The drug effect parameter was then calculated as:

$$XBLM = 1 + GXBL*(XBL-XBLQ)$$

where initially XBLQ=Ø and dXBLQ/dt=TXBL(XBL-XBLQ). TXBL is the time constant of cardiovascular adaptation to the active beta-adrenergic blocking drug level.

Similarly, we may write for the other drugs:

XHH = XHHI*(1 + ABS(Sin(KXHH*TANG)))*ZDLY

XVL = XVLI*(1 + ABS(Sin(KXVL*TANG)))*ZDLY

where ZDLY = 1/(1 + Exp(-T/120))- 0.5;

XHHM = 1 + GXHH*(XHH-XHHQ),

and XVLM = 1 + GXVL*(XVL-XVLQ).

The effect of the drugs were represented as follows:

beta-adrenergic (beta-1) blockers e.g. metoprolol,

HRB = HRX*(-0.25*XBLM + 1.25)

SVZ = SVX*(-0.25*XBLM + 1.25)

GARLZ = GARL*(-0.25*XBLM + 1.25)

affecting cardiac function and the operating gain of the renal system function (176,177); beta-adrenergic receptor mediated sympathetic activity being one of the factors controlling renin secretion (114).

diuretics e.g. hydrodiuril,

SLB = SLX*(0.5*XHHM + 0.5)

producing diuresis only (178,179);

vasodilators e.g. hydralazine,

CVB = CVX*(0.05*XVLM + 0.95)

PDRZ = PDRX*(-0.25*XVLM + 1.25)

RAZ = RAX*(-0.5*XVLM + 1.5)

RVB = RVX*(-0.10*XVLM + 1.10)

affecting systemic and renal arterial resistive properties, with minimal effects on venous properties (180).

The relative effects of different beta-blockers, diuretics, or vasodilators may be specified from knowledge of their cardiovascular properties, e.g. the vasodilator effects of nitroglycerine infusion would be represented with a greater effect on venous resistance and compliance properties (180).

The system was simulated using the Euler method for solving the differential equations. A time step of 10 minutes was found to be most economical in computer time without loss of accuracy.

6.3 RESULTS CHAPTER 6

Shortterm simulation

The results of our shortterm simulation (Table 6:3:1), indicate that our model contains the requisite controls to account for the haemodynamic effects of various cardiovascular interventions. The pattern of changes occuring under clinical conditions are clearly represented in our simulation results. Excellent correlations are obtained between the clinical data and simulated values of the various cardiovascular parameters, ranging from a correlation coefficient of Ø.772 for compliance, to Ø.949 for the resistance parameter. The arterial pressure, stroke volume and cardiac output were simulated within a 5% maximun error of the clinical data values, for each of the cardiovascular interventions. Other parameters simulated were within 7% of their clinical data value, for each intervention.

The clinical effects of intervention on mean arterial pressure changes were followed closely by the simulation, and the post pacing decrease in heart rate was accurately represented. The constancy of stroke volume and cardiac output under conditions of increasing blood pressure by methoxamine infusion, with reflex bradycardia blocked by right atrial pacing, was clearly represented in the simulation results.

The simulation results indicated a slight degree of vasodilation with the initial intervention of atrial pacing, while the clinical data indicated some vasoconstriction. This vasoconstriction could be indicative of psychological/emotional effects, which are not accounted for in the model. However, both clinical data and simulation show a degree of vasoconstriction when right atrial pacing was stopped.

The data for all 5 subject and for all intervention states were pooled, and regression equation equation for the simulated values on clinical data values, for each of the haemodynamic parameters. The slope of regression lines varied from 0.80 to 1.07 (Table 6:3:1).

Table 6:3:1. Comparison of simulation (S) and data (M) values for simulation study of 5 subjects.

	CONTROL STATE	CONTROL PACING	METHOX. PACING	METHOX. NO PACE	REGRESS. CORREL.
PA(M)		96±2.8	116±2.8	104±3.3	-5.2,1.07
mmHg	90±3.4				
PA(S)		92±3.3	122±5.2	107±3.6	.820
HR(M)		80±6.0	80±6.0	60±5.7	3.9,0.95
/min	74±5.5				
HR(S)		80±6.0	80±6.0	61±4.4	.987
SV(M)		106±13.	109±14.	117±10.	15.6,0.88
ml	114±11.				
SV(S)		109±11.	109±12.	120±12.	.930
FCO(M)		8.5±1.1	8.7±1.3	7.1±1.0	1.2,0.87
L/min	8.4±1.1				
FCO(S)		8.7±1.1	8.7±1.1	7.4±1.0	.955
RTP(M)		955±104	1148±139	1278±180	188,0.80
d.cm.s-5	904±92.				
RTP(S)		893±89.	1165±116	1206±124	.949
CA(M)		1.76±0.17	1.62±0.2	1.67±0.15	.34,0.81
ml/mmHg	1.84±.17				
CA(S)		1.87±0.13	1.65±0.2	1.60±0.16	.772
VAE(M)		169±16.	186±20.	173±12.	3.2,1.01
ml	168±20.				
VAE(S)		174±21.	203±25.	174±21.	.781

METHOX., study during methoxamine infusion;

REGRESS., regression coefficients; CORREL., correlation coefficients; haemodynamic values are expressed as MEAN±SEM. (M) (S) measured/calculated, simulated values respectively.

Longterm simulation.

The results of the longterm simulation of antihypertensive drug therapy (Table 6:3:2), show haemodynamic patterns which have been obtained from various clinical studies.

Beta-adrenergic blockage

The simulation results show that the initial fall in blood pressure was associated with decreased heart rate and cardiac output (176,181). There was also a slight early increase in stroke volume and total peripheral resistance (181). There was a slight delay in the initial fall in blood pressure, due to reflex vasoconstriction (181,182); the haemodynamic effect of therapy being greatest after about one week (182). After one month of therapy, resistance and stroke volume returned towards normal, with decreased blood pressure maintained by decreased cardiac output (176,181). The pressure drop across the renal artery decreased (from 60 to 52 mmHg in the simulation), with an insignificant decrease in urine flow rate (177). Blood volume and interstitial fluid volume increased after a slight initial decrease (12,177). After 1 year of therapy the same haemodynamic pattern was observed, albeit with less significant changes, except for maintained fluid retention in the intravascular system.

Diuretics

Decreased blood pressure occured slowly after diuretic therapy (74). After 3 days of therapy the decrease in blood pressure was associated with decreased stroke volume, cardiac output, blood volume and interstitial fluid volume. However, there was an initial reflex increase in heart rate and peripheral resistance (74,179). After 1 month of therapy the haemodynamic effects were more significant, except for heart rate which had fallen slightly, and peripheral resistance which returned towards normal. This haemodynamic pattern was maintained after 1 year of therapy, though with less significant changes (74,179), except for a decreasing intravascular fluid volume.

Vasodilators

Vasodilator therapy was associated with an initial rapid decrease in blood pressure due to decreased peripheral resistance, with reflex tachycardia, increased stroke volume, cardiac ouput, blood and interstitial fluid volumes (180,183). This haemodynamic pattern persisted throughout therapy, though heart rate decreased towards the pre-therapy state, and intravascular fluid volume continued to increase.

The effects on cardiovascular adaptation on the effectiveness of antihypertensive drug therapy was studied via simulation runs with and without cardiovascular

regulator and drug adaptations (Tables 6:3:2-6:3:5). The results of these simulations indicate that drug adaptation may play a more critical role than the adaptation of cardiovascular regulators in patients who fail to respond to antihypertensive drug therapy.

For the drug therapies simulated, blood pressure was controlled in all studies with adaptation of cardiovascular regulators but without drug adaptations (Table 6:3:2). Some control was also obtained even in the absense of cardiovascular regulator adaptations (Table 6:3:3). However, no longterm blood pressure control was obtained in the presence of drug adaptations (Tables 6:3:4-6:3:5).

It should be noted that in these simulations, cardiovascular drug input increased to its peak level with a time constant of two hours, and was maintained at this level. However, in more practical situations, the average circulatory drug level may increase with continuing therapy over a period of several days. Hence, maximum cardiovascular effects may not be observed during the first weeks of therapy.

For studies carried out with varying cardiovascular drug levels, e.g.,

```
XBL=XBLI*(1 + ABS(SIN(KXBL*TANG)))/2,
```

diuretics showed the minimun daily variation in haemodynamic variables; vasodilators showed the largest swings for all variables.

Table 6:3:2. Simulation of cardiovascular effects of anti-hypertensive drug therapy: With adaptation of cardiovascular controls but without drug adaptation.

	PA	RTP	HR	SV	FCO	VVE	V1F
BETA-BLOCKER THERAPY							
Pre-Therapy	126	2015	60	83	4995	1181	3543
1 Day	114	2080	52	82	4250	1410	3500
7 Days	112	1992	49	88	4322	1600	3583
30 Days	112	1992	49	88	4309	1668	3637
90 Days	112	1992	49	87	4276	1819	3771
180 Days	112	1992	49	86	4220	2043	3967
360 Days	113	1992	49	85	4133	2464	4340
DIURETIC THERAPY							
Pre-Therapy	126	2015	60	83	4995	1181	3543
1 Day	118	2064	62	74	4599	1030	3286
7 Days	109	2040	59	72	4263	1036	3086
30 Days	108	2024	58	73	4257	1034	3064
90 Days	108	2024	58	73	4270	988	3023
180 Days	108	2024	58	73	4284	920	2961
360 Days	107	2024	58	74	4317	789	2844
VASODILATOR THERAPY							
Pre-Therapy	126	2015	60	83	4995	1181	3543
1 Day	101	1312	70	89	6281	1151	4069
7 Days	101	1176	64	109	6991	1572	4416
30 Days	102	1168	64	109	7009	1627	4472
90 Days	102	1168	64	109	6960	1748	4566
180 Days	102	1168	64	108	6889	1925	4704
360 Days	103	1168	64	106	6759	2261	4967

Table 6:3:3. Simulation of cardiovascular effects of anti-hypertensive drug therapy: Without cardiovascular controls or drug adaptations.

	PA	RTP	HR	SV	FCO	VVE	VIF
BETA-BLOCKER THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	116	2104	53	82	4319	1366	3536
7 Days	119	2072	52	86	4471	1455	3642
30 Days	119	2072	52	86	4472	1455	3643
90 Days	119	2072	52	86	4472	1455	3643
180 Days	119	2072	52	86	4472	1455	3643
360 Days	119	2072	52	86	4472	1455	3643
DIURETIC THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	120	2080	63	74	4618	1015	3299
7 Days	116	2136	64	68	4373	920	3161
30 Days	116	2136	64	68	4373	920	3161
90 Days	116	2136	64	68	4373	920	3161
180 Days	116	2136	64	68	4373	920	3161
360 Days	116	2136	64	68	4373	920	3161
VASODILATOR THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	107	1368	74	87	6405	1063	4159
7 Days	115	1296	70	104	7292	1353	4598
30 Days	115	1288	70	104	7314	1361	4609
90 Days	115	1288	70	104	7314	1361	4609
180 Days	115	1288	70	104	7314	1361	4609
360 Days	115	1288	70	104	7314	1361	4609

Table 6:3:4. Simulation of cardiovascular effects of anti-hypertensive drug therapy: With cardiovascular controls and drug adaptations.

	PA	RTP	HR	SV	FCO	VVE	VIF
BETA-BLOCKER THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	114	2080	52	82	4256	1409	3500
7 Days	112	1992	50	88	4364	1579	3583
30 Days	115	1992	51	87	4465	1565	3622
90 Days	119	2000	54	86	4645	1530	3694
180 Days	123	2008	57	84	4784	1505	3753
360 Days	125	2016	59	83	4888	1481	3790
DIURETIC THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	119	2064	62	74	4601	1031	3287
7 Days	109	2032	59	73	4283	1041	3099
30 Days	110	2024	58	74	4355	1055	3127
90 Days	115	2016	59	77	4544	1051	3209
180 Days	119	2016	59	80	4748	1050	3301
360 Days	124	2016	60	83	4942	1056	3394
VASODILATOR THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	101	1307	70	90	6297	1169	4077
7 Days	103	1210	64	108	6588	1556	4359
30 Days	107	1331	63	102	6451	1523	4220
90 Days	114	1571	62	94	5778	1464	3991
180 Days	120	1783	61	88	5331	1424	3846
360 Days	124	1952	60	84	5038	1393	3751

Table 6:3:5. Simulation of cardiovascular effects of anti-hypertensive drug therapy: Without adaptation of cardiovascular controls but with drug adaptation.

	PA	RTP	HR	SV	FCO	VVE	VIF
BETA-BLOCKER THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	117	2104	53	82	4324	1364	3537
7 Days	119	2072	53	86	4506	1440	3640
30 Days	121	2056	54	85	4594	1394	3622
90 Days	123	2040	56	85	4748	1311	3590
180 Days	124	2032	58	84	4872	1245	3566
360 Days	125	2016	59	84	4962	1198	3549
DIURETIC THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	120	2080	63	74	4620	1061	3300
7 Days	117	2128	64	69	4391	927	3173
30 Days	118	2120	63	70	4461	954	3215
90 Days	120	2088	62	74	4612	1016	3309
180 Days	123	2056	61	78	4775	1085	3409
360 Days	125	2024	60	82	4931	1152	3504
VASODILATOR THERAPY							
Pre-therapy	126	2015	60	83	4995	1181	3543
1 Day	107	1368	74	87	6395	1066	4154
7 Days	116	1328	70	102	7136	1348	4524
30 Days	118	1440	68	98	6660	1314	4302
90 Days	121	1648	65	91	5917	1253	3958
180 Days	123	1824	62	87	5423	1214	3733
360 Days	125	1968	61	84	5103	1189	3591

LEGEND Figures 6:3:1-6:3:3

Simulation of cardiovascular effects of antihypertensive drug therapy:

Ⓐ with adaptation of cardiovascular controls but without drug adaptation.

Ⓑ without cardiovascular controls or drug adaptations.

Ⓒ with cardiovascular controls and drug adaptations.

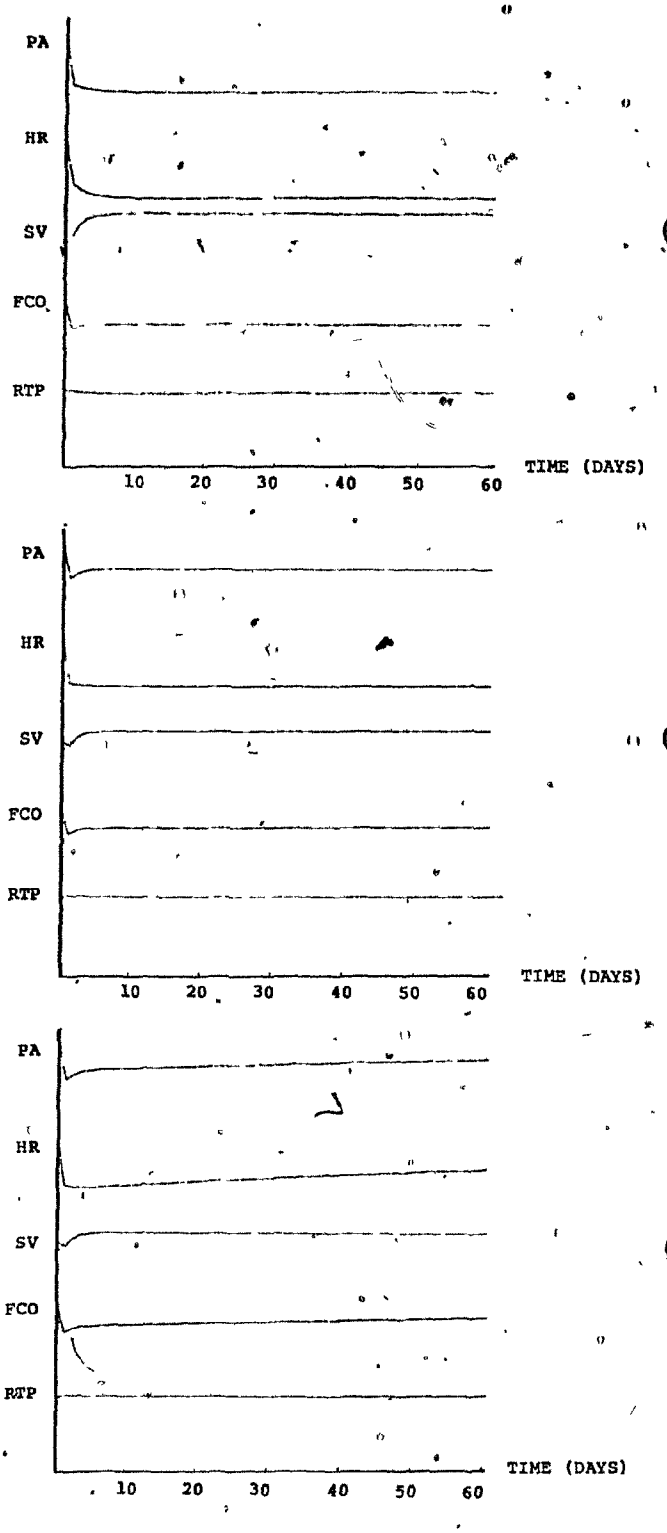


Figure 6:3:1. Haemodynamic effects of beta-blocker therapy.

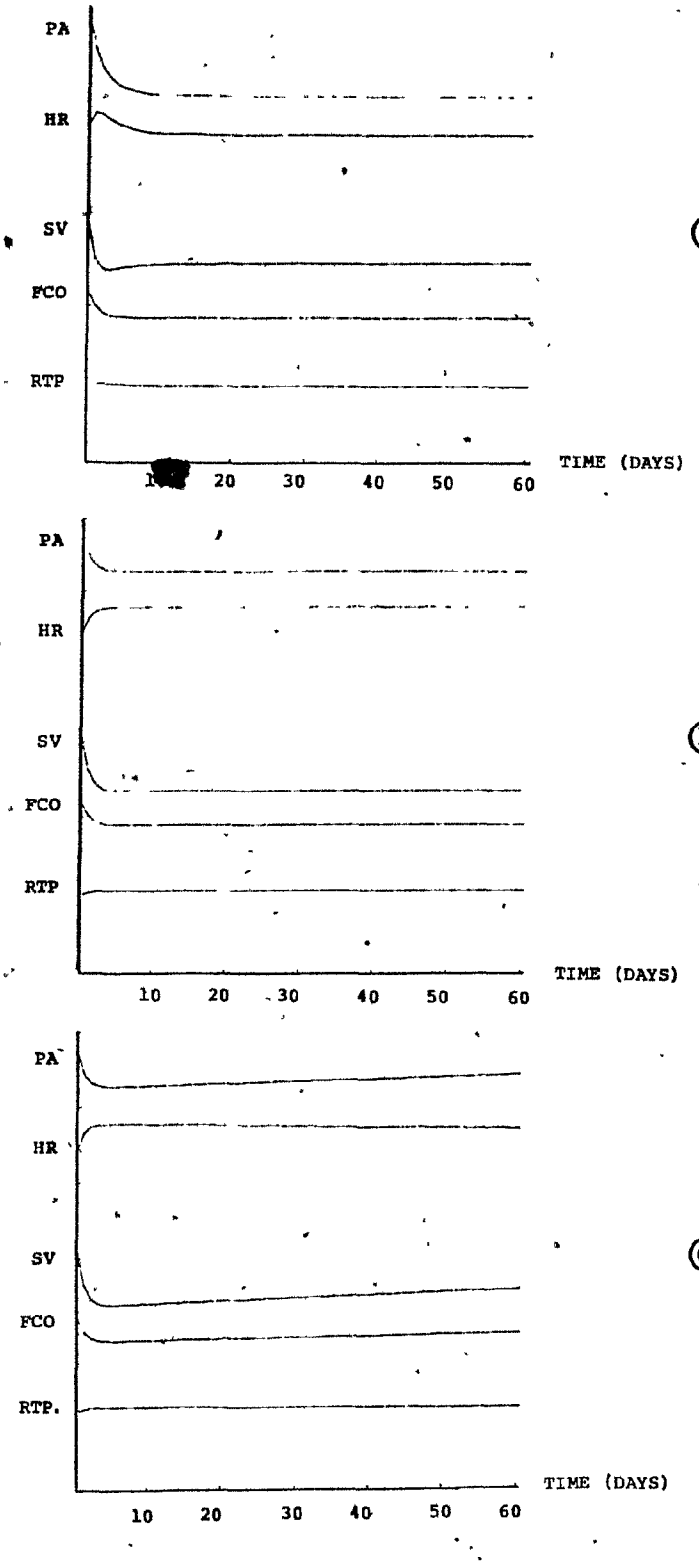


Figure 6:3:2. Haemodynamic effects of diuretic therapy.

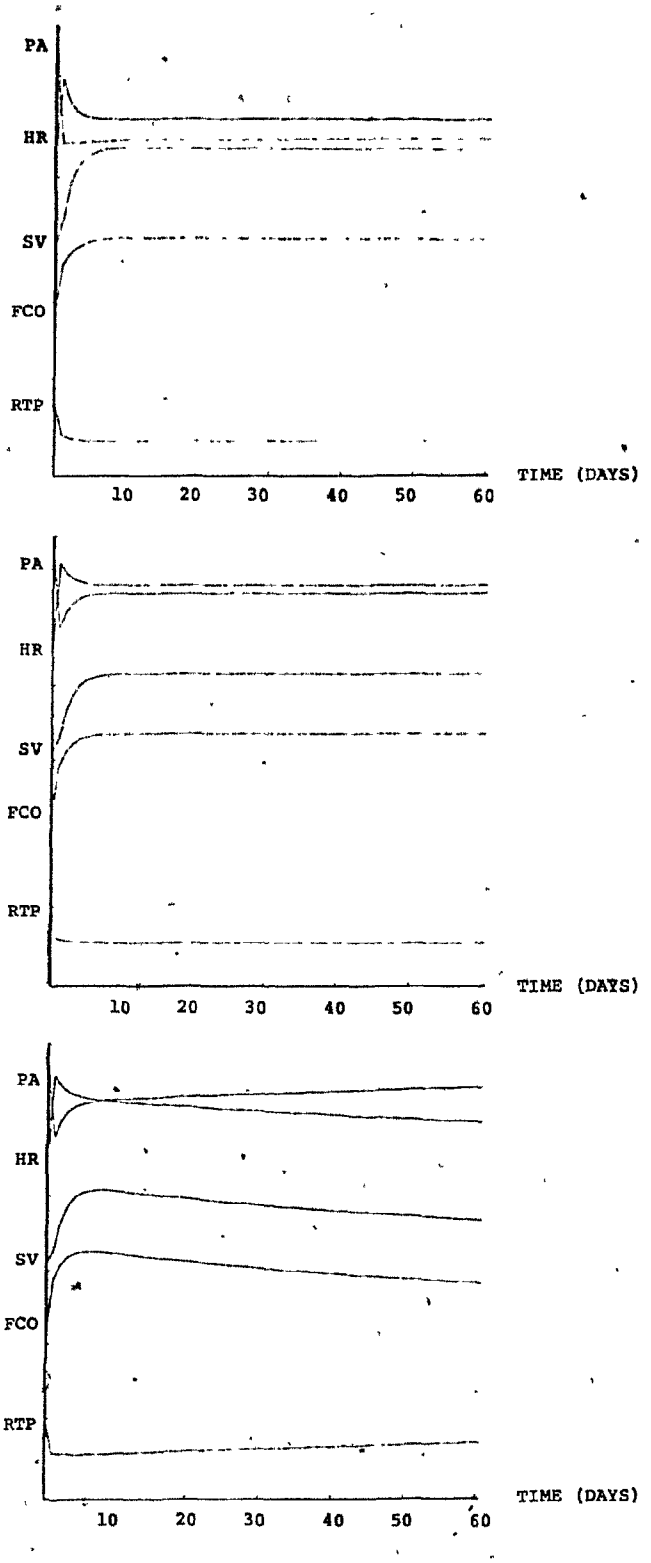


Figure 6:3:3. Haemodynamic effects of vasodilator therapy.

6.4 DISCUSSION CHAPTER 6

As stated in the introduction, the second of our two major objectives was to simulate the haemodynamics of the circulation in an effort to provide assistance in the understanding of the interrelationships of the various cardiovascular control systems. The simulation of the dynamics of shortterm intervention shows that the model has met this objective.

The accuracy of the simulation results depended on several factors which will be outlined here. First, the reflex effects of the various controllers (baroreceptors, cardiopulmonary receptors, autoregulation and renal control function) on the various system parameters was specified on the basis of literature studies (chapter 3). Estimates of the sign and magnitude of the various coupling constants were based on this literature review of the physiology. The accuracy of the simulation relates to the reliability of this transformation of clinical and experimentally observed phenomena into numbers (section 6:2).

Secondly, for comparison with the clinical data, a simulation real time of ten minutes was used for each intervention stage, though this was not explicitely specified in the clinical study (148). A time period of at

least 5 minutes was stated in the study for the initial intervention of high right atrial pacing, and other measurement after intervention when the system reached steady state.

Thirdly, the haemodynamic effects of psychological or emotional disturbances, due to the interventions, would vary from person to person and are not accounted for in the model. Also the accuracy of the simulation results depends heavily on the accuracy of the initial pre-intervention data, as this error will be propagated in the simulation results when comparison is made with the clinical measurements.

Despite these possible sources of error, the simulation model presented has shown itself to be a capable representer of cardiovascular dynamics and its control systems.

As part of our second major objective, we were interested in the use of the simulation model to study possible responses to therapeutic interventions. The model has shown itself capable of meeting this objective, as the various cardiovascular reflex effects of drug intervention have been demonstrated in the simulations. These include the tachycardia and fluid retention of vasodilator therapy (180,183); resistance pattern of beta-blocker therapy (181);

and the heart rate, resistance reflex changes of diuretic therapy (74).

The modelling approach to hypertensive study has been shown here to be capable of providing answers to some questions relating to the haemodynamics of hypertension. However, the full extent of this capability can only be exploited elsewhere.

We have attempted to examine the role of adaptation in the cardiovascular response to drug therapy (from hypothesis H3). Cardiovascular adaptation to the effects of beta-blocking drugs has been indicated (184). Our simulation indicates that this drug adaptation may be a most significant factor in the non-response to antihypertensive therapy. We may speculate that differences in response to therapy in different genetic groups may be due to differences in genetic factors controling this adaptation.

Finally, the use of this model as a teaching aid in the cardiovascular laboratory is another possibility to be exploited. The effects of various drug and non-drug interventions could be studied with relative ease, subject only to the constraint of computer central processing time.

Chapter 7

7.1 SUMMARY

Given the demonstrated capabilities of our modelling approach to the study of hypertension, we may here speculate on the future directions of our procedure.

Each submodel of the cardiovascular models may be improved with the increasing information on cardiovascular physiology. We have used the Windkessel approach for its simplicity, but more complex and detailed models of the haemodynamics may be applied in order to give a better representation of the mechanical response of the walls of the arteries to the stresses of maintained elevations of blood pressure.

Our study procedure can also be improved with the expansion of echocardiographic technology, leading to improved accuracy in the measurement of cardiac chamber dimensions. The automation of echocardiographic measurements makes feasible a larger number of simple measurements, and an improvement in sample accuracy. It also allows for the complete automation of the procedure for estimating cardiovascular parameters.

With respect to the modelling of the adaptation process, increasing knowledge on the physiology of receptor mechanisms makes for the expansion of this area of the model to incorporate this information. Further aspects of the adapative process that may be assessed include: the organization of the cardiovascular control systems (open versus closed loops); the possibility of opening and closing cardiovascular control loops via drug therapy, and the resultant effects on blood pressure stability; and to test the hypothesis that antihypertensive therapy should be directed towards the elimination (equivalent to the surgical removal of renal sympathetics) or reclosure of open blood pressure control loops. The theoretical investigation of such questions may serve as guides in the future design of antihypertensive drugs and in the selection of therapy schemes.

The wide variations in the time constants of the cardiovascular processes (from rapid blood flows into small arterial spaces to very slow overall volume changes), leads to a system of stiff differential equations. Solving such stiff systems of equations requires relatively large amounts of computer time. Hence, for greater efficiency in simulating such systems alternate solution algorithms, or alternative modelling approaches are required. The possibility of parallel computation will be an added

advantage, not only with respect to this problem, but also aid in reducing the time required in the solving the iterative system of algebraic equations for the effects of the controller variables.

APPENDIX 1

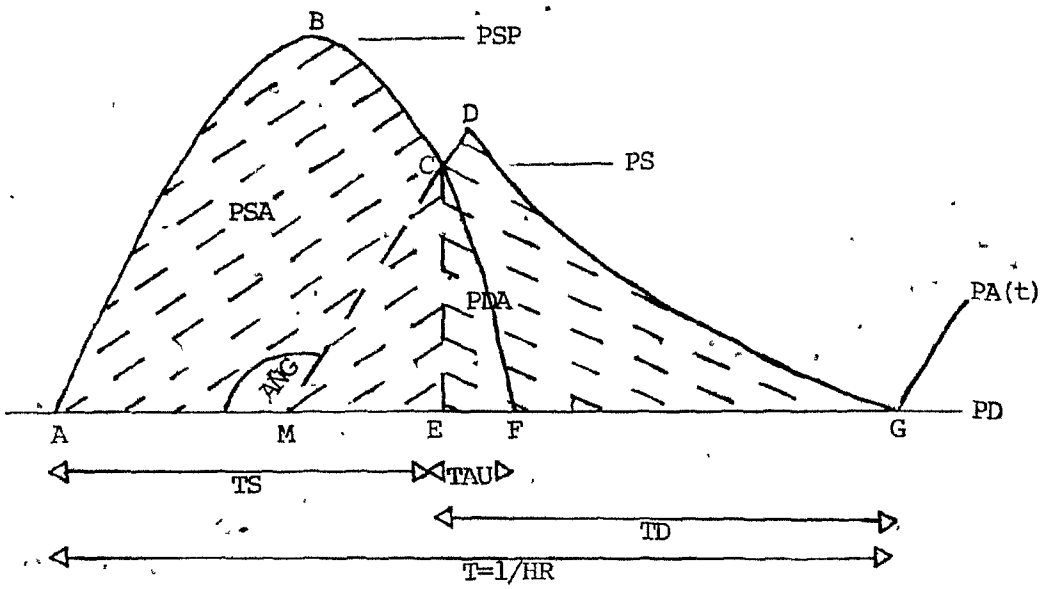


FIGURE A1.1. Arterial Pressure Curve PA(t).

The peak and trough of the arterial pressure curve PA(t) are equated with the measured systolic (PSP) and diastolic (PD) blood pressures.

The arc ABC of Figure A1.1 is extended to F to complete the sinusoidal ejection curve, with peak at B and half period TS + TAU and AM = AF/2.

An empirical relation for TAU is given by:

$$TAU = k*TS*TD/(T*ANG)$$

(where K is a regression constant).

Now, $ANG = \Pi*TS/(TS+TAU)$,

hence, for k=1 we have:

TAU = TS*TD*HR/(Π-TD*HR).

Now, PA(t) = PD + (PSP-PD)*Sin(Π*t/(TS+TAU)),

hence, for t=TS we have:

PS = PD + (PSP-PD)*Sin(ANG).

Taking an average pressure over time period Ø,TS we have:

PSA = PD + (PSP-PD)*B

where B = (1-Cos(ANG))/ANG, and hence B < Ø.725.

For the mean arterial pressure we have:

$$PA = 1/T\int_{\emptyset}^{T} PA(t)\ dt = 1/T\int_{\emptyset}^{TS} PA(t)\ dt + 1/T\int_{TS}^{TS+TD} PA(t)\ dt$$

$$= TS/T*PSA + TD/T*PDA$$

$$= HR*(TS*PSA + TD*PDA),$$

where PDA is given by:

PDA = (PS-PD)/Ln((PS-PRA)/PD-PRA)) + PRA

as derived in Appendix 2.

APPENDIX 2

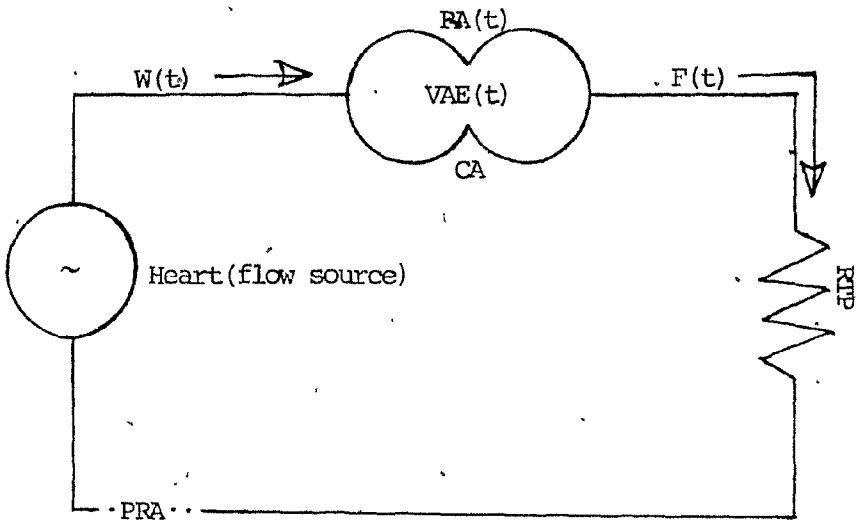


FIGURE A2.1. Arterial Circulation Model.

The above diagram gives a simple Windkessel representation of the arterial circulation. The dynamical flow equation may be expressed as:

$$dVA(t)/dt = W(t) - F(t).$$

Hence for the diastolic period we may write:

$$dVA(t)/dt = -F(t) = -(PA(t) - PRA)/RTP ,$$

for $TS < t < TS+TD$.

Hence,

$$dPA(t)/dt = 1/CA*dVA(t)/dt$$
$$= -1/TRC*(PA(t) - PRA) ,$$

where $TRC = RTP*CA$.

Therefore,

$$PA(t) = (PS - PRA)*Exp(-(t-TS)/TRC) + PRA.$$

Integrating PA(t) from TS to TS+TD we get:

PDA = (PS - PD)*TRC/TD + PRA.

Substituting for t = TS+TD in the original equation we get:

PD = (PS - PRA)*Exp(-TD/TRC) + PRA ,

hence,

TRC = TD/Ln((PS-PRA)/(PD-PRA)) ,

and therefore,

PDA = (PS - PD)/Ln((PS-PRA)/(PD-PRA)) + PRA.

From echocardiographic data we obtain the left ventricular volumes VLVD, VLVS and stroke volume SV(=VLVD-VLVS).

From these cardiac output:

FCO = HR*SV,

total peripheral resistance:

RTP = (PA-PRA)/FCO,

arterial compliance:

CA = TRC/RTP,

arterial filling volume

VAE = PA*CA,

and an estimate of left ventricular elastance

ELV = PS/VLVS

are obtained.

APPENDIX 3

Given the equations for which the parameters are calculated, their sensitivity to variations in the input data can be readily assessed, for example:

$$FCO = SV*HR$$

$$\Delta FCO = \partial FCO/\partial SV * \Delta SV + \partial FCO/\partial HR * \Delta HR ,$$

hence

$$\Delta FCO/FCO = \Delta SV/SV + \Delta HR/HR.$$

Similarly for $PA = HR*(TS*PSM + TD*PDM)$ we have,

$$\Delta PA/PA = \Delta HR/HR + TS/T*(PSA/PA)*(\Delta TS/TS + \Delta PSA/PSA) + TD/T*(PDA/PA)*(\Delta TD/TD + \Delta PDA/PDA).$$

Errors arise from two main sources:

(i) errors in the input data,

(ii) errors in the model relationships.

If errors in the input data cause proportionately larger changes in the estimated parameters then there can be little confidence in the model's diagnostic/predictive capabilities. However, if the changes are negligible, then the sensitivity of the model may not be sufficient to provide for the separation of various haemodynamic states. In the above two examples, none of the above considerations apply.

APPENDIX 4 - Excerpt from Manual of Operations
European Canadian Hypertension Trial

SCHEMATIC REPRESENTATION OF SUBJECT SELECTION

STEP	CRITERION FOR ADVANCING TO NEXT STEP
Enumeration	Male, 40-64 years old
Home Screen	Diastolic >99 mmHg
Clinic Visit I ≥2 weeks	DBP_{11}/DBP_{12}
Clinic Visit II	$400 \leq DBP_{11} + DBP_{12} + DBP_{21} + DBP_{22} \leq 520$
Trial Entry	No history of: - myocardial infarction, angina pectoris, stroke - secondary or malignant hypertension - malignant disease, cirrhosis of liver, alcoholism, other serious diseases No contraindication to treatment with betablockers or diuretics.

3.4 Treatment

Once a participant has been randomized, his medication has to follow the step care plan of Figure 3.4. Each of the two treatment groups is started with either the saluretic diuretic or the Metoprolol. These base drugs will be administered in one of two dosage levels and are to be distributed free of charge to the participants by the Regional Centre. If the blood pressure can not be lowered to below target level of 95 mm Hg by either dose 1 or dose 2 of the base drugs, combination treatment may be started in accordance with the plan in Figure 3.4. Any of the additional drugs may only be prescribed by the participant's family physician and the participant has to obtain them from a pharmacist bearing the costs himself.

If the blood pressure is still high after exhausting the step-care plan of Figure 3.4, another drug (free choice) is to be added until pressure is below 95 mmHg. However, the free choice drug may not be a β-blocker if the participant is randomized into the diuretic group or vice versa.

FIGURE 3.4 - Treatment combinations which are invoked in steps until the diastolic blood pressure is controlled below 95 mmHg.

	β-BLOCKER GROUP		DIURETICS GROUP	
Step 1	Metoprolol	100 mg bid	Hydrochlorothiazide	25 mg bid
Step 2	Metoprolol	200 mg bid	Hydrochlorothiazide	50 mg bid
Step 3	Metoprolol	200 mg bid	Hydrochlorothiazide	50 mg bid
	+ Hydralazine	25 mg tid	+ Hydralazine	25 mg tid
Step 4	Metoprolol	200 mg bid	Hydrochlorothiazide	50 mg bid
	+ Hydralazine	50 mg tid	+ Hydralazine	50 mg tid
Step 5	Metoprolol	200 mg bid	Hydrochlorothiazide	50 mg bid
	+ Hydralazine	50 mg tid	+ Hydralazine	50 mg tid
	+ Spironolactone	25 mg tid	+ Spironolactone	25 mg tid
Step 6	Metoprolol	200 mg bid	Hydrochlorothiazide	50 mg bid
	+ Hydralazine	50 mg tid	+ Hydralazine	50 mg tid
	+ Spironolactone	50 mg tid	+ Spironolactone	50 mg tid

Patients whose diastolic blood pressure is repeatedly above 110 mmHg, in spite of treatment, are to be excluded from the study.

Patients whose diastolic blood pressure is repeatedly between 95 and 110, despite treatment, may remain in the trial if their physician considers further reduction of the blood pressure not possible or desirable.

3.41 Drug Titration

The individualized treatment plan is determined by step-care approach after the randomization has been received from the Coordinating Centre and the physical examination has not revealed any contraindications or exclusion criteria.

The appropriate drug of step 1 dosage is distributed to the participant and an appointment for BP determination is made for 2 to 3 weeks after start of treatment. If on the next visit the participant's pressure is still above 100 mmHg, the dosage is to be increased to step 2 and another 2 week appointment is made.

If, however, the pressure is between 95 and 100, no change in dosage is made but instead another 2 week visit is scheduled and the dosage is increased to step 2 only if at that visit the pressure is still above target of 95 mmHg. Patients whose blood pressure was controlled prior to enrolment with a single medication may not be titrated beyond step 2. If their BP can not be brought under control with step 2 medication, they have to be discontinued and returned to their original drug regimen.

The titration visits should not be spaced closer than 2 weeks to allow the medication to become fully active. Increase to the next step treatment should only take place if the BP on titration visit is above 100 mmHg or if BP was between 95 and 100 on 2 consecutive visits.

3.42 Exception to Treatment Plan

i) If hypotensive symptoms occur at the first dosage level with the diuretic or β-blocker, the dose may be halved.

ii) If blood pressure can not be controlled by either step 1 or step 2 and there is no significant difference between step 1 and step 2 and the participant complains about the large number of tablets prescribed, a modification of step 3 can be adopted combining the dosage of step 1 rather than step 2 with hydralazine.

iii) The lowest treatment step at which BP control (diastolic BP 95 mmHg) has been achieved during titration is to be maintained throughout the trial unless the participant complains about hypotensive symptoms.

iv) If there is reasonable evidence that a participant is not taking medication as prescribed, a required step-up in treatment is delayed until improved compliance has been achieved. (see Section 10, Compliance Aids).

v) If contraindications to one of the adjunct drugs exist, such as hyperkalemia ($K > 5$ mEq/L) this prevents the use of Spironolactone. These situations will be rare and difficult to predict. No generally applicable remedies are therefore listed here and it is left to the judgement of the family physician what form of substitution drug is used in each case.

APPENDIX 5

```
SUBROUTINE UPDATE     73/730  OPT=0 TRACE                    FTN 4.8+577

      1          SUBROUTINE UPDATE
                 C THIS SUBROUTINE IS CALLED FROM THE FORSIM MAIN PROGRAM AND
                 C SIMULATES THE HAEMODYNAMICS EFFECTS OF CARDIAC PACING AND
                 C OF VASOACTIVE DRUG INFUSION.
      5          C*************************************************************
                 C*      SECTION 1 - STORAGE                                  *
                 C*************************************************************
                        COMMON/INTEGT/FCQ,FUOQ,PAQ,PVQ,XVLQ,VAE,VIF,VVE
                        COMMON/DERIVT/FCQT,FUOQT,PAQT,PVQT,XVLQT,VAET,VIFT,VVET
     10                 COMMON/RESERV/T,DT,DTOUT,EMAX,TFIN,METHOD
                        COMMON/CNTROL/INOUT
                        COMMON/DATA/YD(20),YC(20)
                        COMMON/PES/TATR,TANS,TACP,TARL,TXVL,GATR,GANS,GACP,GARL,GASV
                        COMMON/OPTVAL/ACC,DMAX,H,IPRINT,MAXFUN
     15                 COMMON/OPTIM/OPT,PRNT,VAR
                        COMMON/EFS/F(20)
                       LOGICAL OPT,PRNT
                       REAL F2(20)
                       DATA DTOUT/10./
     20                DATA EMAX/.00001/,TFIN/50./,METHOD/3/
                       DATA PI/3.1415927/
                 C*************************************************************
                 C*       SECTION 2 - INITIALIZATION                          *
                 C*************************************************************
     25             10 IF (INOUT .NE. -1) GO TO 15
                 C SET OPTIMIZATION PARAMETER TO TRUE
                 C TURN OFF THE PRINTING PRODUCED BY THE FINISH ROUTINE
                        OPT=.TRUE.
                        PRNT= .FALSE.
     30         C SET PARAMETERS USED BY THE OPTIMIZER
                        H=.001
                        DMAX=5.
                        ACC=.05
                       MAXFUN=50
     35                IPRINT=5
                 C INITIALIZE GAINS USED IN SIMULATION **********************G
                        GATR=0.0001
                       GANS=0.025
                        GACP=0.1
     40                 GARL=0.1
                        GASV=0.3
                        GXVL=0.2
                 C INITIALIZE CONTROLLER TIME CONSTANTS **********************T
                       TATR=0.0005
     45                TANS=0.0005
                        TACP=0.000005
                        TARL=0.000005
                        TXVL=0.01
                 C INITIALIZE VARIANCE AND COUNTER USED IN OPTIM. STORAGE ***I
     50               M=1
                      VAR=0.0
                 C*************************************************************
                 C*CALCULATE AND STORE DATA FOR OPTIMIZATION INTO ARRAY YD( )*
                 C*************************************************************
     55                 J=1
                        DO  5 I=1,3
                        READ (7,*) TS,HR,SV,PSP,PD,PRA
```

```
      CALL HAEVAL(TS,HR,SV,PSP,PD,PRA,FCO,PA,RTP,CA,VAE)
      YD(J)=PA
      YD(J+1)=RTP
      YD(J+2)=CA
      YD(J+3)=HR
      YD(J+4)=SV
    5 J=J+5
C END DATA STORAGE ******************************************
      PRINT*,(YD(I),I=1,15)
C READ PRE-INTERVENTION HAEMODYNAMIC DATA
      READ (7,*) TSO,HRO,HRPO,SVO,PSPO,PDO,PRAO
   15 IF (T .NE. 0.0) GO TO 20
      IF ( INOUT .EQ. 0 .OR. INOUT .EQ. 1 ) GO TO 20
C CHECK NON-NEGATIVITY OF OPTIMIZER SELECTED PARAMETER VALUES
C IF NEGATIVE ASSIGN LARGE PENALTY AND RESTART OPTIMIZER
      IF ( TXVL .LT. 0. ) GO TO 17
      IF ( TATR .LT. 0. ) GO TO 17
      IF ( TANS .LT. 0. ) GO TO 17
      IF ( TACP .LT. 0. ) GO TO 17
      IF ( TARL .LT. 0. ) GO TO 17
      IF ( GXVL .LT. 0. ) GO TO 17
      IF ( GATR .LT. 0. ) GO TO 17
      IF ( GANS .LT. 0. ) GO TO 17
      IF ( GACP .LT. 0. ) GO TO 17
      IF ( GARL .LT. 0. ) GO TO 17
      IF ( GASV .LT. 0. ) GO TO 17
        GO TO 19
   17 DO 18 I=1,15
      F(I)=F2(I)*2.
   18 CONTINUE
      INOUT=2
     GO TO 300
   19 CONTINUE
C REASSIGN INITIAL VALUES FOR SUBSEQUENT OPTIMIZATION RUNS
      TS=TSO
      HR=HRO
      HRP=HRPO
      SV=SVO
      PSP=PSPO
      PD=PDO
      CALL HAEVAL(TS,HR,SV,PSP,PD,PRA,FCO,PA,RTP,CA,VAE)
C*PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP*
C*PRINT INITIAL DATA AND CALCULATED VALUES *
C*PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP*
     PRINT*,TS,TD,HR,SV,FCO
     PRINT*,PSP,PD,PRA,PA
     PRINT*,RTP,CA,VAE
C REINITIALIZE VARIAINCE FOR OPTIMIZATION
       VAR=0.0
C**********************************************************
C*                     SECTION 3                          *
C*THIS SECTION BEGINS THE SIMULATION OF THE DYNAMICS      *
C*          OF THE CARDIOVASCULAR SYSTEM                  *
C**********************************************************
     ANSM=ATRM=ACPM=ARLM=SVM=1.0
     ANSN=ATRN=ACPN=ARLN=SVN=1.0
     CAB=CAX=CA
```

```
      SUBROUTINE UPDATE     73/730  OPT=0 TRACE                    FTN 4.8+577
  115               CIS=CA*100.
                    CVB=CVX=CV=CA*100.0
                    FC=FCQ=FVI=FCO
                    FIF=0.
                    FIN=FUOQ=FUO=1.0
  120               HRN=HRX=HR
                    J=500
                    L1=L2=L3=L4=L5=0
                    PAQ=PA
                    PDRB=PDRX=PDRZ=PDR=60.0
  125               RFAC=25.0/PA*ZFAC
                    RIF=0.18
                    RVL=RTP*RFAC
                    RVR=RVL/3.
                    RVB=RVX=RV=RVL-RVR
  130               RAB=RAX=RAZ=RA=RTP-RVL
                    PIF=PC=(PRA+PA*RVL/RA)/(1.+RVL/RA)
                    PVQ=PV=PRA+(PC-PRA)*RVR/RVL
                    SLB=SLX=1./(PA-PDR)
                    SVB=SVX=SV
  135               TCP=SECOND(CP)
                    VIF=CIS*PIF
                    VVE=PV*CV
                    XVL=0.0
                    XVLQ=0.0
  140               XVLM=1.0
              C METHOXAMINE INPUT LEVEL
                       XVLI=-10.0
              C END DRUG INPUT
                 20 IF ( INOUT .EQ. 0 ) GO TO 50
                    IF ( INOUT .NE. 1 ) GO TO 300
  145         C ITERATIONS BEGIN HERE ************************************I
                 50 CONTINUE
              C*XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX*
              C*CARDIAC PACING AND METHOXAMINE INFUSION *
  150         C*XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX*
                 70 IF ( M .LT. 11) GO TO 80
                       XVL=XVLI*(1.-EXP(10.0*(1.-T/10.)))
                 80 IF ( M .LT. 16) GO TO 90
                       HRX=HRN+(HRP-HRN)*EXP(15.*(1.-T/20.))
  155            90 CONTINUE
              C END EXTERNAL INPUTS
              C CARDIOVASCULAR EFFECTS OF CIRCULATING METHOXAMINE *******XD
                       XVLM=1.+GXVL*(XVL-XVLQ)
                       IF ( XVLM .LT. 0.0 ) XVLM=0.0
  160            CAB=CAX*(0.25*XVLM+0.75)
                 CVB=CVX*(0.25*XVLM+0.75)
                 PDRZ=PDRX*(-0.25*XVLM+1.25)
                 RAZ=RAX*(-0.8*XVLM+1.8)
                 RVB=RVX*(-0.25*XVLM+1.25)
  165         C END CARDIOVASCULAR EFFECTS
              C*AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA*
              C*THIS SECTION BEGINS THE CONTROL ANALYSIS *
              C*AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA*
                100 CONTINUE
  170         C URINE OUTPUT FUNCTION ***********************************UO
                 PDRB=PDRZ*(0.3*ATRM+0.7)
```

```
SUBROUTINE UPDATE     73/730  OPT=0 TRACE                    FTN 4.8+577

                PDR=PDRB*(0.3*ANSM+0.3*ARLM-0.6*ACPM+1.0)
                SL=SLX*(-0.2*ANSM-0.5*ARLM+0.3*ACPM+1.4)
                FUO=(PA-PDR)*SL
175           C END RENAL FUNCTION
              C CARDIAC FUNCTION ***************************************CC
                SVB=SVX*(0.5*SVM+0.5)
                SV=SVB*(0.2*ANSM+0.05*ARLM+0.05*ACPM+0.7)
                HR=HRP
180              IF ( M .LT. 16 .AND. M .GT. 1) GO TO 110
                HR=HRX*(0.5*ANSM+0.05*ARLM+0.35*ACPM+0.1)
              110 FCO=HR*SV
              C END CARDIAC FUNCTION
              C THE CIRCULATION ****************************************C
185             RAB=RAZ*(0.20*ATRM+0.80)
                CA=CAB*(-0.3*ANSM-0.3*ARLM+0.05*ACPM+1.55)
                CV=CVB*(-0.2*ANSM-0.3*ARLM+0.05*ACPM+1.45)
                RA=RAB*(0.3*ANSM+0.5*ARLM-0.05*ACPM+0.25)
                RV=RVB*(0.2*ANSM+0.6*ARLM-0.05*ACPM+0.25)
190             RTP=RA+RV+RVR
                PA=VAE/CA
                PIF=VIF/CIS
                PV=VVE/CV
                PRA=PA-FC*RTP
195             PC=(PVI*A*RV/RA+PIF*RV/RIF)/(1.+RV/RA+RV/RIF)
                FIF=(PC-PIF)/RIF
                FC=(PA-PC)/RA
                FVI=FC-FIF
              C END CIRCULATION
200           C BARORECEPTOR CONTROL************************************B
                ANSN=1.-GANS*(PA-PAQ)
                ANSN=ALIM(ANSN,0.5,2.0)
              C END BARORECEPTOR
              C CARDIOPULMONARY CONTROL*********************************CP
205             ACPN=1.+GACP*(PV-PVQ)
                ACPN=ALIM(ACPN,0.5,2.0)
                SVN=1.+GASV*(PV-PVQ)
                SVN=ALIM(SVN,0.5,2.0)
              C END CARDIOPULMONARY
210           C AUTOREGULATION *****************************************A
                ATRN=1.+GATR*(FC-FCQ)
                ATRN=ALIM(ATRN,0.5,2.0)
              C END AUTOREGULATORY CONTROL FUNCTION
              C LOCAL RENAL CONTROL ************************************R
215             ARLN=1.-GARLZ*(FUO-FUOQ)
                ARLN=ALIM(ARLN,0.5,2.0)
              C END RENAL CONTROL
              C IMPLICIT FUNCTION CALLS ********************************IMPL
                   L1=L1+1
220             CALL IMPL( ATRM,ATRN,1,1.0E-3 ) , RETURNS (100)
                   L2=L2+1
                CALL IMPL( ARLM,ARLN,2,1.0E-3 ) , RETURNS (100)
                   L3=L3+1
                CALL IMPL( ACPM,ACPN,3,1.0E-3 ) , RETURNS (100)
225                L4=L4+1
                CALL IMPL( ANSM,ANSN,4,1.0E-3 ) , RETURNS (100)
                    L5=L5+1
                CALL IMPL(  SVM, SVN,5,1.0E-3 ) , RETURNS (100)
```

```
      C****************************************************************PP
      C*PRINTOUT OUT SIMULATION DATA AT 0.5 MINUTE INTERVALS ****PP
      C****************************************************************PP
               IF ( J .LT. 500 ) GO TO 150
            PRINT (8,125) T,PA,HR,SV,VAE,FCO,RTP,CA,PV,FUO,XVL
        125 FORMAT(1X,F7.2,4F9.1,F10.2,F10.6,4F9.3)
               PRINT*,T,PA,FUO,L1,L2,L3,L4,L5,TCP
               PRINT*,PRA,PV,PC,CA,RTP,HR,SV,FCO
               PRINT*,'  '
               J=L2=L3=L4=L5=0
        150 CONTINUE
            J=J+1
      C****************************************************************
      C*          DYNAMIC EQUATIONS                                   *
      C****************************************************************
      C SIMULATION EQUATIONS
            FCQT=TATR*(FC-FCQ)
            FUOQT=TARL*(FUO-FUOQ)
            PAQT=TANS*(PA-PAQ)
            PVQT=TACP*(PV-PVQ)
            XVLQT=TXVL*(XVL-XVLQ)
            VAET=FCO-FC
            VIFT=FIF
            VVET=FVI-FCO+FIN-FUO
      C END SYSTEMS ANALYSIS
        200 IF ( INOUT .NE. 1 ) GO TO 300
            IF  ( T .EQ. 0. )   GO TO 250
      C*SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS*
      C*STORE CALCULATED VALUES IN ARRAY YC( )     *
      C*CALCULATE PENALTY FUNCTION F( ) VARIANCE *
      C*SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS*
               YC(M-5)=PA
               F2(M-5)=F(M-5)=YC(M-5)/YD(M-5)-1.0
               VAR=VAR+F(M-5)**2.0
               YC(M-4)=RTP
               F2(M-4)=F(M-4)=YC(M-4)/YD(M-4)-1.0
               VAR=VAR+F(M-4)**2.0
               YC(M-3)=CA
               F2(M-3)=F(M-3)=YC(M-3)/YD(M-3)-1.0
               VAR=VAR+F(M-3)**2.0
               YC(M-2)=HR
               F2(M-2)=F(M-2)=YC(M-2)/YD(M-2)-1.0
               VAR=VAR+F(M-2)**2.0
               YC(M-1)=SV
               F2(M-1)=F(M-1)=YC(M-1)/YD(M-1)-1.0
               VAR=VAR+F(M-1)**2.0
      C****************************************************************
      C*       SECTION 4 - PRINTOUT SECTION                          *
      C****************************************************************
        250 CONTINUE
            PRINT*,T,PAQ,PVQ,FUOQ,FCQ,VAE,VVE,VIF
            PRINT*,FC,FVI,FIF,PIF,PDR,SL,HRX,VAR
            PRINT*,RV,RA,RAB,CV
            PRINT*,ATRM,ARLM,ACPM,ANSM,SVM,J,XVL,XVLQ,XVLM
            PRINT*,'  '
      C ADVANCE COUNTER FOR OPTIMIZATION STORAGE
            M=M+5
```

```
      SUBROUTINE UPDATE     73/730  OPT=0 TRACE                    FTN 4.8+577

                      IF ( M .LT. 17 ) GO TO 300
                      INOUT=2
                      PRINT*,'//    '
                  300 IF ( INOUT .NE. 2 ) GO TO 400
290                    M=1
                  400  TCP = SECOND(CP)
                C CHECK ON COMPUTER CENTRAL PROCESSING TIME USED
                      IF ( TCP .LT. 90. ) GO TO 500
                      INOUT=3
295                   PRINT*,'      '
                  500 CONTINUE
                      RETURN
                      END
      SUBROUTINE HAEVAL     73/730  OPT=0 TRACE                    FTN 4.8+577

 1                     SUBROUTINE HAEVAL(HR,TS,SV,PSP,PD,PRA,FCO,PA,RTP,CA,VAE)
                C*****************************************************************
                C*THIS SUBROUTINE CALCULATES THE VALUES OF SEVERAL              *
                C*PARAMETERS AND INITIAL VARIABLES FROM THE INPUT DATA          *
 5              C*****************************************************************
                C TIME INTERVALS
                      TS=TS/60000.
                      TD=1./HR-TS
                C CARDIAC OUTPUT CALCULATION
10                    FCO=SV*HR
                C HAEMODYNAMIC PRESSURES
                        PRA=0.
                C PRESSURE ESTIMATES
                      TAU=TS*TD*HR/(PI-TD*HR)
15                    ANG=PI*TS/(TS+TAU)
                      PS=PD+(PSP-PD)*SIN(ANG)
                      PSA=PD+(PSP-PD)*(1.-COS(ANG))/ANG
                      A=ALOG((PS-PRA)/(PD-PRA))
                      PDA=PRA+(PS-PD)/A
20                    PA=HR*(TS*PSA+TD*PDA)
                C ESTIMATION OF ARTERIAL COMPLIANCE TOTAL PERIPHERAL
                C RESISTANCE AND ARTERIAL VOLUME EXCESS
                      TRC=TD/A
                      RTP=(PA-PRA)/FCO
25                    CA=TRC/RTP
                      VAE=PA*CA
                      RETURN
                      END
```

```
PROGRAM SIMULAT    73/730  OPT=0 TRACE                    FTN 4.8+577

      1              PROGRAM SIMULAT(INPUT,OUTPUT,UT,TAPE6=UT)
                  C THIS PROGRAM SIMULATES THE EFFECTS OF ANTI-HYPERTENSIVE
                  C DRUG THERAPY IN A MODEL OF THE CARDIOVASCULAR SYSTEM.
                  C*************************************************************
      5           C*      SECTION 1 - STORAGE                                  *
                  C*************************************************************
                        REAL KXBL,KXHH,KXVL,
                        DATA PI/3.1415927/
                  C*************************************************************
     10           C*       SECTION 2 - INITIALIZATION                          *
                  C*************************************************************
                        DT=10.
                        FLAG=0.0
                        T=0.0
     15                 TFIN=600000.0
                  C INITIALIZE GAINS USED IN SIMULATION **********************G
                        GATR=0.0001
                        GANS=0.025
                        GACP=0.1
     20                 GARL=0.1
                        GASV=0.3
                        GXBL=GXHH=GXVL=0.2
                  C INITIALIZE CONTROLLER TIME CONSTANTS **********************T
                        TATR=0.0005
     25                 TANS=0.0005
                        TACP=0.000005
                        TARL=0.000005
                        TXBL=TXHH=TXVL=0.000005
                  C*************************************************************
     30           C*THIS SECTION CALCULATES THE VALUES OF SEVERAL              *
                  C*PARAMETERS AND INITIAL VARIABLES FROM THE INPUT DATA       *
                  C*************************************************************
                  C TIME INTERVALS INPUT
                          READ*,TS,HR
     35                 TS=TS/60000.
                        TD=1./HR-TS
                  C ECHOCARDIOGRAPHIC DATA INPUT
                          READ*,DLVS,DLVD
                  C CARDIAC OUTPUT CALCULATION
     40                 VLVD=7./(2.4+DLVD)*DLVD**3.
                        VLVS=7./(2.4+DLVS)*DLVS**3.
                           SV=VLVD-VLVS
                        FCO=SV*HR
                  C HAEMODYNAMIC PRESSURES INPUT
     45                   READ*,PSP,PD,PRA
                  C PRESSURE ESTIMATES.
                        TAU=TS*TD*HR/(PI-TD*HR)
                        ANG=PI*TS/(TS+TAU)
                        PS=PD+(PSP-PD)*SIN(ANG)
     50                 PSA=PD+(PSP-PD)*(1.-COS(ANG))/ANG
                        A=ALOG((PS-PRA)/(PD-PRA))
                        PDA=PRA+(PS-PD)/A
                        PA=HR*(TS*PSA+TD*PDA)
                  C ESTIMATION OF ARTERIAL COMPLIANCE TOTAL PERIPHERAL
     55           C RESISTANCE AND ARTERIAL VOLUME EXCESS.
                        TRC=TD/A
                        RTP=((PS-PD)*TRC+TS*(PSA-PRA))/SV
```

```
      PROGRAM SIMULAT    73/730  OPT=0 TRACE                    FTN 4.8+577

                  CA=TRC/RTP
                  VAE=PA*CA
           60     C*PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP*
                  C*PRINT INITIAL DATA AND CALCULATED VALUES *
                  C*PPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPPP*
                        PRINT*,TS,TD
                        PRINT*,SV,HR,FCO
           65           PRINT*,PS,PDA,PA
                        PRINT*,PSP,PD,PSA
                        PRINT*,PRA,A,TAU
                        PRINT*,TRC,RTP,CA,VAE
                        PRINT*,'    '
           70     C*************************************************************
                  C*                     SECTION 3                             *
                  C*THIS SECTION BEGINS THE SIMULATION OF THE DYNAMICS OF      *
                  C*THE CARDIOVASCULAR SYSTEM STARTING WITH INITIALIZATION.    *
                  C*************************************************************
                        ANSM=ATRM=ACPM=ARLM=1.0
                        ANSN=ATRN=ACPN=ARLN=1.0
                        CVB=CVX=CV=CA*100.
                        CIS=CA*100.
                        FCO=FVI=FCO
           80           FIF=0.
                        FIN=FUOD=FUO=1.0
                        GARLZ=GARL
                        HRB=HRX=HR
                        J=5000
           85           L1=L2=L3=L4=L5=0
                        PAD=PA
                        PDRB=PDRX=PDRZ=PDR=60.0
                        RFAC=25.0/PA
                        RIF=0.18
           90           RVL=RTP*RFAC
                        RVR=RVL/3.
                        RVB=RVX=RV=RVL-RVR
                        RAB=RAX=RAZ=RA=RTP-RVL
                        RIF=PC=(PRA+PA*RVL/RA)/(1.+RVL/RA)
           95           PVD=PV=PRA+(PA-PRA)*RVR/RTP
                        SLB=SLX=1./(PA-PDR)
                        SVB=SVX=SVZ=SV
                        SVM=1.0
                        TCP=SECOND(CP)
          100           VVE=PV*CV
                        VIF=CIS*PIF
                        XBL=XHH=XVL=0.
                        XBLD=XHHD=XVLD=0.0
                        XBLM=XHHM=XVLM=1.0
          105     C DRUG THERAPY SECTION ***********************************XD
                  C DRUG DOSAGE LEVELS AND FREQUENCY
                           XBLI=5.0
                           XHHI=5.0
                           XVLI=5.0
          110              KXBL=3.0
                           KXHH=3.0
                           KXVL=3.0
                  C END DRUG DOSAGE
                  C ITERATION BEGINS HERE ***********************************I
```

```
      PROGRAM SIMULAT    73/730  OPT=0 TRACE                    FTN 4.8+577

115             50 CONTINUE
              C CIRCULATING DRUG LEVEL DYNAMICS
                    TANG=PI*T/1440.0
                    IF ( T .GE. 5760. ) GO TO 70
                  XBL=XBLI*(1./(1.+EXP(-T/120.))-.5)*2.0
120               XHH=XHHI*(1./(1.+EXP(-T/120.))-.5)*2.0
                  XVL=XVLI*(1./(1.+EXP(-T/120.))-.5)*2.0
                    GO TO 80
                70 CONTINUE
                    XBL=XBLI
125                 XHH=XHHI
                    XVL=XVLI
                80 CONTINUE
                    XBLM=1.+GXBL*(XBL-XBLD)
                    XHHM=1.+GXHH*(XHH-XHHD)
130                 XVLM=1.+GXVL*(XVL-XVLD)
              C CARDIOVASCULAR EFFECTS OF THE ANTI-HYPERTENSIVE DRUGS
                  GARL=GARLZ*(-0.25*XBLM+1.25)
                  HRB=HRX*(-0.25*XBLM+1.25)
                  SVZ=SVX*(-0.25*XBLM+1.25)
135               SLB=SLX*(0.5*XHHM+0.5)
                  CVB=CVX*(0.05*XVLM+0.95)
                  PDRZ=PDRX*(-0.25*XVLM+1.25)
                  RAZ=RAX*(-0.5*XVLM+1.5)
                  RVB=RVX*(-0.10*XVLM+1.10)
140           C END DRUG THERAPY SECTION
              C*AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA*
              C*THIS SECTION BEGINS THE CONTROL ANALYSIS *
              C*AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA*
                100 CONTINUE
145           C URINE OUTPUT FUNCTION ***********************************UO
                  PDRB=PDRZ*(0.3*ATRM+0.7)
                  PDR=PDRB*(0.3*ANSM+0.3*ARLM-0.6*ACPM+1.0)
                  SL=SLB*(-0.2*ANSM-0.5*ARLM+0.3*ACPM+1.4)
                  FUO=(PA-PDR)*SL
150           C END RENAL FUNCTION
              C CARDIAC FUNCTION ****************************************CC
                  SVB=SVZ*(0.5*SVM+0.5)
                  SV=SVB*(0.2*ANSM+0.05*ARLM+0.05*ACPM+0.7)
                  HR=HRB*(0.50*ANSM+0.05*ARLM+0.35*ACPM+0.10)
155               FCO=HR*SV
              C END CARDIAC FUNCTION
              C THE CIRCULATION *****************************************C
                  RAB=RAZ*(0.2*ATRM+0.8)
                  CV=CVB*(-0.2*ANSM-0.3*ARLM+0.1*ACPM+1.4)
160               RA=RAB*(0.3*ANSM+0.5*ARLM-0.05*ACPM+0.25)
                  RV=RVB*(0.2*ANSM+0.4*ARLM-0.05*ACPM+0.45)
                  RTP=RA+RV+RVR
                  PIF=VIF/CIS
                  PV=VVE/CV
165               PA=FCO*(RA+RV)+PV
                  PRA=PA-FCO*RTP
                  PC=(PV+PA*RV/RA+PIF*RV/RIF)/(1.+RV/RA+RV/RIF)
                  FIF=(PC-PIF)/RIF
                  FVI=FCO-FIF
170           C END CIRCULATION
              C BARORECEPTOR CONTROL*************************************B
```

```
      PROGRAM SIMULAT    73/730  OPT=0 TRACE                FTN 4.8+577

                ANSN=1.-GANS*(PA-PAD)
            C END BARORECEPTOR
            C CARDIOPULMONARY CONTROL*********************************CP
      175       ACPN=1.+GACP*(PV-PVD)
                SVN=1.+GASV*(PV-PVD)
            C END CARDIOPULMONARY
            C AUTOREGULATION ***********************************************A
                ATRN=1.+GATR*(FCO-FCD)
      180   C END AUTOREGULATORY CONTROL FUNCTION
            C LOCAL RENAL CONTROL ******************************************R
                ARLN=1.-GARL*(FUO-FUOD)
            C END RENAL CONTROL
            C IMPLICIT FUNCTION CALLS ********************************IMPL
      185         L1=L1+1
                CALL IMPL( ATRN,ATRM,1,1.0E-3 ) , RETURNS (100)
                L2=L2+1
            C CHECK ON CONVERGENCE
                IF ( L2 .GT. 10500 ) GO TO 450
      190   CALL IMPL( ARLN,ARLM,2,1.0E-3 ) , RETURNS (100)
                L3=L3+1
            CALL IMPL( ACPN,ACPM,3,1.0E-3 ) , RETURNS (100)
                L4=L4+1
            CALL IMPL( ANSN,ANSM,4,1.0E-3 ) , RETURNS (100)
      195       L5=L5+1
            CALL IMPL( SVN, SVM, 5,1.0E-3 ) , RETURNS (100)
            C*************************************************************
            C*          DYNAMIC EQUATIONS                                *
            C*************************************************************
      200   FCD=FCD+TATR*(FCO-FCD)*DT
            FUOD=FUOD+TARL*(FUO-FUOD)*DT
            PAD=PAD+TANS*(PA-PAD)*DT
            PVD=PVD+TACP*(PV-PVD)*DT
            XBLD=XBLD+TXBL*(XBL-XBLD)*DT
      205   XHHD=XHHD+TXHH*(XHH-XHHD)*DT
            XVLD=XVLD+TXVL*(XVL-XVLD)*DT
            VIF=VIF+FIF*DT
            VVE=VVE+(FIN-FUO-FIF)*DT
      C END SYSTEMS ANALYSIS
      210   C*************************************************************
            C*       SECTION 4 - PRINTOUT SECTION                        *
            C*************************************************************
                J=J+1
            IF ( J .LT. 144 ) GO TO 400
      215       TIME=T/1440.
            PRINT (6,350) TIME,PA,HR,SV,FCO,VVE,VIF,FUO,CV,PDR,SL,RTP
              350 FORMAT(1X,F5.1,3F7.1,3F7.0,F6.2,2F6.0,2F7.4)
            PRINT*,T,PAD,PVD,FUOD,FCD,XBLD,XHHD,XVLD
            PRINT*,RTP,RV,RA,RAB,CV,CV,PC,PIF,PRA
      220   PRINT*,ATRM,ARLM,ACPM,ANSM,SVM,L1,L2,L3,L4,L5,TCP
            C     PRINT*,'     '
                 J=L2=L3=L4=0
            C CHECK ON TIME USAGE
              400 TCP = SECOND(CP)
      225       IF ( TCP .GT. 200. ) GO TO 450
                T=T+DT
                IF (T .GT. TFIN) GO TO 450
                IF (FLAG .EQ. 0.0) GO TO 50


               450 PRINT (6,*) L1,'L2=',L2,L3,L4,L5,TCP,XBLD,XHHD,XVLD
      230      500 STOP
                END
```

```
 SUBROUTINE IMPL       73/730  OPT=0 TRACE                    FTN 4.8+577

 1          C*****************************************************************
            C*IMPLICIT FUNCTION SUBROUTINE                                    *
            C*****************************************************************
                  SUBROUTINE IMPL(AXX,AXXX,XX,EX) , RETURNS (NN)
 5                  IF(ABS(AXX-AXXX)-EX) 570,570,550
              550   AXXX=0.50*AXXX+0.50*AXX
                    RETURN NN
              570   AXXX=AXX
                    RETURN
10                  END
```

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