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HAEMODYNAMIC CHANGES IN THE ARTERIAL CIRCULATION OF THE LOWER LIMBS IN PATIENTS WITH CLAUDICATION

By

NICOS SIMOU ANGELIDES, M.D. (Athens)

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The work for this thesis was done in the Academic Surgical Unit and Cardiovascular Unit of St. Mary's Hospital Medical School.

VOLUME 1

A B S T R A C T

This work was initiated in 1976 with the initial aim of measuring the simultaneous changes of flow in the thigh and in the calf, in order to understand the haemodynamic changes in the arterial circulation in the limbs of patients with claudication. Such had not been previously performed.

In Part I of the thesis the relevant literature of the haemodynamic changes that occur in the arteries and veins of the lower limb, at rest, during and after exercise in health and in the presence of vascular disorders, as well as methods related to the measurement of ankle pressure and muscle flow, are reviewed (Chapter 1). Special attention is paid to methods using isotope clearance from muscle and to attempts made by various workers to produce haemodynamic models of the lower limb.

Part II of the thesis deals with the simultaneous measurements of changes in flow in the muscles of the thigh and calf and to ankle pressure during and after exercise in order to understand the haemodynamic changes which occur in normal limbs and limbs with stenosing arterial disease (Chapter 2 and Chapter 3, Clinical Studies I and IV). The distinct patterns of flow observed, which were characteristic for the various types of arterial lesions resulted in the development of a method that could determine the site and severity of arterial lesions irrespective of whether these were single or multiple, occlusive or simply stenotic (Chapter 3, Clinical Studies I, II and III). Although arteriography is the only precise method available for determining the anatomical extend of the disease, the method developed by the author can provide a measurement of function which supplements arteriography, (particularly in the presence of single or multiple stenoses). This may

prove a useful test in patients with combined aortoiliac and femoro-popliteal stenoses (Chapter 3, Clinical Studies I, II and III).

In Part III of the thesis a haemodynamic model was developed (Chapter 4) and was subsequently validated enabling the author to demonstrate how inflow, outflow and pressure distal to a single arterial lesion can change with exercise (Chapter 5 and 6, Clinical Study V). Finally the effect of venous disorders on the haemodynamic model has been investigated in two pilot studies which indicate the direction future research should follow (Chapter 6, Clinical Study VI and VII).

Part IV of this thesis consists of a general discussion about the significance of the results and ends with recommendations for future work to study the venous circulation (Chapter 7) and a new advanced haemodynamic model (Appendix A15) that could allow the study of changes in limbs with combined aortoiliac and femoropopliteal lesions.

PREFACE

The purpose of the work described in this thesis was to understand the haemodynamic changes in the arterial circulation in the lower limb in patients with claudication.

A review of the literature related to methodology and the current knowledge about flow and pressure patterns in the normal and discarded arterial system is presented in Part I.

The methods of simultaneous ^{99m}Tc muscle clearance from the thigh and calf, ankle pressure measurements and the clinical studies to investigate the haemodynamic changes that occur during and after exercise are presented in Part II.

How these studies led to the development of a method to determine the site and severity of arterial lesions irrespective to whether these were single or multiple, occlusive or stenotic is presented in the same part (Part II).

The development of a haemodynamic model and clinical studies used for its validation are reported in Part III.

Finally, a general discussion and conclusions constitute Part IV.

The work for this thesis was initiated and completed in the Vascular Laboratory, Academic Surgical Unit and Cardiovascular Unit at St. Mary's Hospital, Medical School. The investigations and clinical studies were performed during a two-year scholarship in Vascular Surgery awarded by the British Council (1976-1977). The writing of the thesis was subsequently completed in 1978-79.

CLAIMS TO ORIGINALITY OF THIS THESIS AS A CONTRIBUTION TO THE SCIENCE AND PRACTICE OF SURGERY

The work in this thesis was initiated when very little information was available about the simultaneous changes of flow in the thigh and in the calf in the presence or absence of peripheral arterial disease. Functional information about the severity of arterial stenoses, especially when multiple, is difficult to obtain even with biplane angiography.

It has been demonstrated by the work in this thesis (Part II) that there are characteristic patterns of flow in the thigh and calf of normal limbs, limbs with aortoiliac, femoropopliteal and combined aortoiliac and fermoropopliteal lesions after exercise; that these characteristic changes of flow can be explained in terms of changes in pressure, peripheral resistance and the presence of a redistribution of blood in the various vascular beds. This is the first time that a redistribution of blood amounting to a "steal" of blood by the thigh from the calf in patients with combined aortoiliac and femoropopliteal lesions as well as in patients with pure superficial femoral artery occlusion has been demonstrated.

The simultaneous measurement of the hyperaemic index of the thigh and calf provided a means by which not only the site but also the degree of single or multiple stenoses could be determined.

The experience obtained from the above enabled the Author to develop a haemodynamic model that could explain how inflow, outflow and pressure distal to a single arterial lesion change with exercise using

isotope clearance values from the calf during three short tiptoe exercises, involving 5, 10 and 20 tiptoe movements. This is the first time a model that could provide such information from relatively simple measurements has been presented (Part III).

The work in this thesis has been done by the author with the exception of the angiograms performed by Dr. D. Sutton; the preparation of the ^{99m}Tc which was done by the staff of the Medical Physics Department and the writing of the computer programs which was done by Dr E. Shapiro.

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P A R T I

CHAPTER 1

REVIEW OF LITERATURE

1.1 INTRODUCTION

Pressure and flow are related and depend on the resistance of the arterial tree. The behaviour of these three haemodynamic components in health and in the presence of peripheral arterial disease has been studied by several workers, using various invasive and non-invasive methods.

In this section of the thesis a brief historical review of the development of the various methods used to measure flow is presented first (Section 1.2). Special detailed emphasis is given to the development of isotope clearance techniques to measure flow and to the use of Doppler ultrasound to measure pressure in the lower limbs, because these are the least invasive and most suitable methods for the work undertaken (Sections 1.3 and 1.4); they allow continuous monitoring of flow as well as frequently repeated measurements of pressure.

The current knowledge of the flow and pressure patterns in the normal and diseased arterial and venous system of the lower limb are subsequently reviewed.

Finally, reference is made to various mathematical and haemodynamic considerations used by previous workers to explain the changes in flow, pressure and resistance in the circulation of the lower limb (Section 1.6). This was an essential prerequisite to the study of simultaneous flow measurement in the thigh and calf (Part II) and the development of the haemodynamic model (Part III) in this thesis.

1.2 METHODS USED IN THE MEASUREMENT OF BLOOD FLOW

The development of methods of measuring blood flow in man was slow and difficult. This is clear from the large number of techniques that have

been devised and subsequently discarded or have found a limited application. Current methods can be separated into two groups : (i) those measuring blood flow in single vessels and (ii) those measuring tissue flow.

Methods for measuring flow in single vessels employ indicator dilution techniques, electromagnetic flowmeters, ultrasonic flowmeters, thermal dilution probes and microvascular flow techniques.

The Fick principle is the basis of the indicator dilution techniques. In its simplest form flow $F = \frac{Q}{A - V}$

where Q is the amount of a substance added to or removed from blood by an organ in unit time, A is the arterial inflow concentration and V is the venous outflow concentration; thus the Fick principle is dependent on the difference in concentration of an indicator in the blood entering and leaving an organ. An indicator must be innocuous and not vasoactive; it must not leave the vasculature between the point of injection and the point of sampling and there must be complete and uniform mixing with the bloodstream beyond the point of injection.

The most notable application of the Fick principle has been the measurement of cardiac output using oxygen as an indicator. Because the direct method is very invasive, requiring right heart catheterisation and systemic arterial cannulation (Cournard, 1945; Guyton et al; 1973), a variety of indirect methods have been devised using carbon dioxide, acetylene or nitrous oxide as indicators (Guyton et al., 1973). The Fick principle has also been used to measure renal, hepatic and cerebral

flow in single vessels by appropriate adaptation, by constant-rate infusion of a suitable indicator into the limb artery (i.e. femoral artery) and continuous sampling from the limb vein (i.e.femoral vein). A major practical difficulty is the recirculation of the indicator, which sets limits to the duration of flow measurements (Overbeck et al., 1969; Jorfeldt and Wahren, 1971). Many indicators have been used for this using non-diffusible dyes such as Evan's blue and indocyanine green, heat, plasma or dextran with sensing of electrical conductivity or optical transmission, gamma - emitting radionuclides and hydrogen. A great variety of sampling equipment has been devised such as intravascular sensing by a fibre-optic catheter or the less invasive external spectrophotometric analysis (Singh et al., 1970) and thermistors for thermal dilution (Fegler, 1957; Wilson et al., 1972; Forrester et al., 1972; Guyton et al., 1973).

The principle of the electromagnetic flowmeter is simple but its application is limited to exposed vessels during operative procedures (Berger and Gessner, 1966; Cappelon, 1978; Mills, 1972). Electromagnetic flowmeters measure flow instantaneously, are direction sensitive and can be clinically implanted for long-term measurement (Bergel and Gessner, 1966; Mills, 1972). They can also be miniaturised for cathetertip mounting (Taylor, 1973) and have been used in the human heart, aorta and venae cavae as a clinical research tool (Mason et al., 1970). The greatest practical difficulty is the necessity for careful preparation and calibration. The instrument settings must be adjusted to the haematocrit and the baseline must be repeatedly determined during long-term measurements by arresting blood flow.

Instruments based on the Doppler ultrasound principle detect changes in velocity (Franklin et al., 1961; Bergel, 1972). Measurements are not invasive, and quantitative changes can be observed within the

interval of the cardiac cycle. However, the absolute measurement of velocity can be achieved only by uniformly insonating the whole vessel and obtaining a mean velocity or a velocity profile from which the mean velocity can be calculated (Reneman et al., 1973). Calculations of the actual flow can only be possible, if the angle of the ultrasonic beam to the axis of the vessel and the diameter of the lumen are known. The latter has only recently been achieved by complicated equipment combining B mode imaging and gated Doppler ultrasound (Gill, 1978). The equipment is still in prototype form and is not available for general use. Despite the above, the detection of changes in blood velocity for the measurement of blood pressure (see Section 1.4) and determination of the presence of arteriosclerotic disease (Yao, 1970; Nicolaides et al., 1976; Angelides et al.,1978) has proved useful in recent years.

Thermal dilution probes have been described in a variety of shapes and forms. Their principle is that a pulse of thermal indicator is released at an upstream point on the probe and an indicator-dilution curve recorded by means of a probe-mounted thermistor downstream (Fronek and Ganz, 1960; White et al., 1967). More promising are the isothermal flowmeters, in which high frequency-response electronic circuiting maintains catheter-tip temperature constant in the presence of varying flow (Grahn et al., 1969). Unfortunately the frequency response of thermal flowmeters is still limited by the heat capacity of the probe, including the thermistors (Mills, 1972; Taylor, 1973)

Finally, several microvascular flow techniques have been used, for measuring flow in single vessels. They employ purely optical methods using high-speed cinematography or electronic counting through an optical or flying - spot television system (Rushmer, 1966; Zweifach, 1973).

The measurement of blood flow in organs and tissues can also be achieved by venous occlusion plethysmography, thermal dilution, methods of estimating proportional distribution among tissues and organs, selective uptake techniques and finally tissue clearance techniques.

Venous occlusion plethysmography is characterised by its simplicity (Greenfield, 1960). It is noninvasive, but has several possible sources of error : incomplete venous occlusion, inadequate size of distal vessels to accommodate the arterial inflow without the generation of back pressure, and imperfections in the volume sensing device. The most useful and historical type is the temperature - controlled water plethysmography. A variety of air-filled plethysmographs have been used also, but they gave little advantage. In contrast, the mercury-in-rubber strain gauge (Strandness et al.,1961) is less bulky, more acceptable to the patient and accurate (Longhurst et al.,1974).

Calorimetry is the best known thermal method. It has been used to measure flow in the skin (Greenfield, 1960). An alternative to the traditional calorimeter has been the copper-tellurium heat flow disc, which is applicable to any part of the skin surface (Catchpole and Jepson, 1955).

Methods of eliminating proportional distribution among tissues and organs using indicators have been developed in order to quantify the distribution of left ventricular output in animals (Sapirstein, 1975). New versions of their approach has been developed using isotopes (Kaihara et al, 1968; Forsyth, 1972).

The selective uptake techniques rely on the Fick principle and

have been used for the measurement of blood flow in organs. The nitrous oxide method of measuring cerebral flow is one example (Kety and Schmitt, 1948). Others are the bromsulphthalein (Bradley et al., 1945) or indocyanine green (Banaszak et al., 1960) for measuring hepatic flow, and the para-amino hippurate or diodrast for measuring renal flow (Levisky and Levy, 1973).

Tissue clearance techniques are the most popular methods for measuring tissue flow. They have a special place in vascular physiology and clinical investigation because they are only slightly invasive and can provide continuous monitoring of changes in flow.

Isotope muscle clearance was the method most applicable to the work undertaken in this thesis and for this reason it is discussed in detail in the subsequent section.

1.3 THE DEVELOPMENT OF MUSCLE CLEARANCE TECHNIQUES IN THE LOWER LIMB

The estimation of blood flow in the limbs by using radioactive krypton (Smith and Morales, 1944) and radioactive sodium (Smith and Quimby, 1945) was first attemped in the early forties, and was based on the principle that the local uptake of radioactive tracers administered in the general cirulation could be used to calculate flow. However, this method had the disadvantage of subjecting the entire body to radiation. In addition the mathematical analysis of the saturation curves was extremely complex. Although Smith and Morales were able to obtain approximate quantitative results by assuming a constant arterial concentration of radioactive krypton, Smith and Quimby did not attempt an analysis of their sodium uptake curves, but used them as a qualitative test of the peripheral circulation.

Subsequently, attempts were made to estimate the arterial blood flow in the limbs by measuring the rate at which a tracer substance (^{24}Na) disappeared from the site of an intramuscular injection (Kety, 1948; 1949). The application of this method was based upon the following assumptions:

(i) the tissue was homogenous so that complete mixing occurred.

(ii) the equilibrium between blood and tissue was immediate, and

(iii) the isotope was removed from the site of the injection by blood only.

Kety's mathematical analysis of the clearance of the injected ^{24}Na demonstrating how the clearance rate could be a measure of the local tissue circulation (Appendix A1) has been the model upon which subesquent work in this field was based. This analysis suggested that the tissue deposit of ^{24}Na should decrease along a single exponential curve which, if plotted semi-logarithmically, should yield a straight line whose slope (K) was a measure of the ability of the local circulation to remove freely diffusible substances(See Appendix A1).

The responces of K to alterations in the circulation were studied by Kety with some procedures designed to speed or slow the local circulation. The application of a tight tourniquet about the thigh was invariably and immediately followed by a sharp reduction in K to practically zero. Release of this tourniquet after ten minutes was associated with a K more than twice the normal which was undoubtedly a reflection of reactive hyperaemia. Exercise of the gastrocnemius for one minute by a repetitive extension and flexion of the ankle was accompanied and followed by a considerable increase in K. The local vasoconstrictor action of adrenaline was demonstrated by adding 0.1mg of the hydrochloride to the $^{24}NaCl$ before injection. This resulted

in a decrease of K to less than one-sixth the resting value (Kety,1949).

Subsequently, the ^{24}Na clearance technique was used to study muscle blood flow in patients with intermittent claudication (Walder, 1953; 1955). The patients were asked to exercise by repeatedly rising themselves up on the toes of the leg under investigation, once every second. They continued to exercise for two minutes unless stopped by pain. When they stopped they remained standing until the resting ^{24}Na clearance rate was re-established (Walder, 1958). In the case of patients suffering from peripheral vascular disease the ^{24}Na clearance curve showed little or even not any flow through gastrocnemius muscle during exercise. As soon as the patients stopped exercising the ^{24}Na clearance was re-established and there was a period of several minutes when the clearance rate was higher than the initial resting period. This high rate gradually subsided until eventually the resting conditions were re-established (Walder, 1958).

Sodium-24, the isotope initially employed, proved to be unsatisfactory and the inactive gas ^{133}Xe was introduced instead, for the investigation of muscle blood flow (Lassen et al.,1964). Sodium-24, was a hydrophilic particle which did not cross the cellular membrane to enter the capillaries and be removed by blood. Xenon-33 was lipophilic and therefore the cellular membrane did not constitute a barrier; thus, a more even distribution of the ^{133}Xe could be expected. Other advantages of the inert gas were the high rate of diffusibility within the tissues, the low radiation energy and its rapid elimination from the body which permitted a lower radiation exposure (Lassen et al., 1964). When both isotopes were injected simultaneously the ^{24}Na clearance rate was slower than the ^{133}Xe. This was presumed to be because of the impeded transfer of the ^{24}Na (Lassen et al., 1964). This experiment was subsequently criticised using the argument that the high

clearance rates obtained with ^{133}Xe were rarely seen under physiological conditions (Walder and Makin, 1969).

In contrast to ^{24}Na, the partition coefficient of ^{133}Xe could be estimated (see below and Appendix A2) and the results of clearance rates could be expressed in absolute values, i.e. in ml of blood per 100 grams of tissue per minute. In vitro and in vivo studies were made of the equilibrium distribution of ^{133}Xe in various organs and tissues of the dog (Conn, 1961). It was found that the affinity of haemoglobin for ^{133}Xe was appreciably greater than that of water. Therefore, acceptable accuracy for blood flow determinations depended on the use of a partition coefficient corrected at least for haemoglobin concentration. The muscle to blood partition coefficient (λ) was found to be 0.7 (or 70 percent) in vivo for blood with haematocrit of 40 at body temperature. Fundamental to the calculations was the assumption of maintenance of complete or almost complete diffusion equilibrium, thus

$$C_{muscle} = \lambda\, C_{blood} \tag{1.1}$$

where Cmuscle was the concentration of ^{133}Xe in the muscle and Cblood was the concentration in the blood. The value of the partition coefficient (λ) obtained in vivo at body temperature was given by the following equation

$$\frac{\text{Conc.of } ^{133}\text{Xe per gram muscle}}{\text{Conc.of } ^{133}\text{Xe per gram blood}} = 0.73 \tag{1.2}$$

Since the specific gravity of muscle was 1.05, the above ratio could be expressed as follows:

$$\frac{\text{Conc. of } ^{133}\text{Xe per gram muscle}}{\text{Conc. of } ^{133}\text{Xe per ml blood}} \approx 0.7 \tag{1.3}$$

Calculations of muscle blood flow in ml of blood per 100 grams of tissue per minute were generally based on the assumption that the muscle to blood partition coefficient λ was 0.7, the same as found for skeletal muscles in dogs by Conn. This assumption was subsequently criticised by the argument that it was uncertain to what degree the value of λ was the same in human subjects because of the higher and variable fat content (Lindbjerg , 1966). This higher fat content appeared to be caused by adipose tissue cells located in the perivascular connective tissue between the muscle bundles. Local variations in muscle tissue composition especially with respect to fat content could produce a non-homogeneous perfusion of ^{133}Xe leading to an underestimate of the muscle blood flow. In such cases the muscle to blood partition coefficient λ would be greater than 0.7 (Lindbjerg, 1966) and values up to 1.0 have been suggested (Clausen and Lassen, 1971).

Lassen's method was based on the following assumptions:

(i) the injection of the tracer did not interfere with the steady state of molecules in the tissue (muscle)

(ii) the tissue itself was homogeneous

(iii) uniform tissue labeling occurred.

(iv) recirculation of the tracer could be neglected, and

(v) regardless of the haematocrit the same partition coefficient (λ = 0.7) could be used in all cases. This was despite the variation of the coefficient caused by a higher solubility in red cells than in plasma.

Lassen's formula (Lassen et al.,1964) relating blood flow to the clearance rate of ^{133}Xe and its partition coefficient was:

$$M.B.F. = -100.\ \lambda.\ \ln 10.\ D \quad (ml/100gm/min) \qquad (1.4)$$

where, M.B.F. is the muscle blood flow, 100 is the multiplication factor

converting the observed decimal logarithms on the logarithmically recorded clearance curve to the natural (Naperian) system and D is the slope of the logarithmic disappearance curve. Since 100. λ. ln10 $\approx$ 161, this factor was used in practice and therefore muscle blood flow was given by the following equation:

$$M.B.F. = - 161 . D \text{ (ml/100 gm/min)} \qquad (1,5)$$

The details of Lassen's mathematical analysis are given in Appendix A2. This analysis was based on a single exponential decay of the clearance rate of ^{133}Xe which was injected into the muscular tissue. However, it had been noted that a single exponential curve did not exist and that there was more than one slope leading to a double or multiexponential curve which could be resolved into single exponential components (Dobson and Warner, 1957), (See also Appendix A3). However, several workers were in agreement that flow calculations based on the initial slope provided a reasonable approximation particularly at high flow rates (Lassen, 1967; Tonnesen, 1968a; 1968b; Tonnesen and Sejrsen, 1970; Clausen and Lassen, 1971).

The procedure followed by Lassen in order to study the effect of alterations in blood flow on the isotope clearance rate was as follows:- A cuff placed just above the knee was rapidly inflated to a pressure of about 250 mm of mercury. During the induced ischaemia the patients were asked to move the foot up and down using their crural muscle only. When intermittent claudication occurred the cuff was rapidly released and the ^{133}Xe clearance was recorded for five to ten minutes. A more "physiological" type of exercise employed later was walking on a plane horizontal level in a corridor (Lassen and Kamp, 1965). The patient walked 10 meters to and fro at a fixed rate of 4.8 km per hour for 2 minutes. Most of the patients with intermittent claudication

had to stop after about one and a half minutes. Subsequently, walking on the treadmill was introduced and standardised (Albert et al., 1966). The speed was 4.6 km per hour at an angle of elevation of 9^{o}. Patients with intermittent claudication were required to walk until pain in the leg stopped them. The control subjects walked for 4 minutes or until approximately 70 per cent of the ^{133}Xe was washed out, whichever came first. In other clinical studies the test varied according to the speed, inclination of the treadmill, period and type of exercise (e.g. combination of ischaemia produced by cuff and walking or just walking alone) (Tonnesen, 1968; Siggaard - Andersen et al., 1967; 1969; Corman et al., 1970; Larsen, 1973).

Other freely diffusible tracers such as ^{79}Kr and ^{131}I-antipyrin had been tested also (Lassen et al., 1964). However, quantitative values for blood flow were not obtained as their partition coefficients were unknown. More recently muscle blood flow was studied with ^{99m}Tc injected into the gastrocnemius as sodium pertechnate. (Cutajar and Marston 1970; Cutajar et al., 1971, Appleberg and Lewis, 1975). The data were expressed as a half-life ($T\frac{1}{2}$). The type of exercise used by Cutajar was similar to that introduced by Walter (Walter, 1958) : The clearance rate was first obtained at rest and then the patient was asked to exercise by tiptoeing at 2 second intervals. The exercise continued for 2 minutes unless the patient was stopped by claudication. After exercise the patient remained standing and post-exercise measurements were made for 4 to 5 minutes. Technetium - 99m was found to be a convenient tracer and the results demonstrated different clearance patterns between normal volunteers and patients with occlusive peripheral arterial disease. These are discussed in detail subsequently (Chapter 1, Section 1.5). Technetium -99m clearance from the hamstring muscle compartment was compared to ankle pressures in patients with aortoiliac disease (Appleberg and Lewis,1975). The patients walked on a horizontal treadmill at a standard speed of 4 km

per hour for 5 minutes or until claudication occurred. Clearance was expressed as a percentage of the initial radioactivity. Ankle systolic pressures were recorded simultaneously. A positive correlation was found between the isotope clearance and the ankle systolic pressures.

The information obtained from the above studies and its usefulness in understanding the haemodynamics of the circulation of lower limbs in health and disease will be discussed again in a subsequent section of this thesis (Chapter 1, Section 1.5).

1.4 THE USE OF DOPPLER ULTRASOUND IN THE MEASUREMENT OF PRESSURE

Although the direct method of measuring arterial blood pressure is the most accurate technique, it is not practical or desirable to insert needles and catherers into the arterial system for routine tests. Indirect methods of measuring arterial blood pressure are preferable. However, in the lower limb methods of detecting the presence of flow distal to a cuff which is being deflated have been tedious. It was not until Doppler ultrasound provided a simple means of detecting blood flow in small arteries such as the posterior tibial and dorsalis pedis that the measurement of the systolic pressure at the ankle became easy (Strandness et al., 1967). This method was extensively used to determine arterial pressure in the lower limb particularly distal to an area of arterial occlusion where the pressure was too low for pulses to be palpable (Yao et al., 1968; 1969; Allan and Terry, 1969). The coefficient of variation of ankle pressures has been shown to be 7 percent at 40 mm Hg and 3 percent at 160 mm Hg (Nicolaides, 1979).

It was realised that the width of the cuff was of great importance in the lower limbs, particularly in the thigh. The use

of a small cuff resulted in the recording of falsely high pressures. Ideally the cuff width should be at least one and a half times the diameter of the part where the pressure is to be measured (Sumner and Strandness, 1969).

The information obtained from measuring flow and ankle pressures in normal and arteriosclerotic patients and its value in understanding the haemodynamics of the circulation in the lower limbs will be discussed in the next section of this thesis.

1.5 FLOW AND PRESSURE PATTERNS IN LOWER LIMB

1.51 Flow and Pressure Patterns in Arteries of Normal Lower Limbs

1.511 At Rest

Blood flow at rest was quantitatively measured in several muscles of the lower limb by means of ^{133}Xe. The results obtained by several workers were in agreement (Lassen et al., 1964; Lassen and Kamp, 1965; Albert et al., 1966; Tonnesen and Sejrsen 1970). Values obtained for blood flow in different muscles were of the following order: tibialis anterior 1.7 $\pm$ 0.3, gastrocnemius 2.2 $\pm$ 0.7 and quadriceps 2.5 $\pm$ 1.6 ml of blood per 100 grams of tissue per minute.

Because the ankle systolic pressure varies with the brachial pressure, the pressure index was introduced as a more reproducible measure of the resistance to flow (Yao, 1970). The pressure index is defined as the ratio of the ankle systolic pressure over the brachial systolic pressure. In normal lower limbs the value of the pressure index was between 1.0 and 1.3 (Yao, 1970). The discrepancy between ankle and brachial pressure in normal limbs at rest has not been fully explained. It is established that although the mean pressure in the arteries of the leg is lower than in the aorta, the systolic

pressure is actually higher (Fig.1.1) (Remington and Wood, 1956; MacDonald, 1960). However, this does not explain why in some limbs the pressure at the ankle should be 30 percent greater than the pressure in the arm. Another suggestion is that the configuration of the tibia and fibula just above the ankle is such that for the same pressure in the brachial and posterior tibial arteries, a higher pressure is required in the pneumatic cuff to occlude the vessels at the ankle. Confirmation of these facts by direct measurement became essential.

1.512 During exercise

Blood flow in the calf during exercise, detected by means of muscle clearance techniques in normal limbs, was found to be significantly increased in comparison to the resting level. In normal subjects walking on a plane horizontal level at 4.8 km per hour, blood flow in the gastrocnemius increased by 10 to 20 times the resting value. This increase occurred during the first 30 seconds and the flow remained constant thereafter during the remaining period of the exercise (Lassen and Kamp, 1965). In normal individuals the maximum steady state for muscle blood flow appeared to be achieved in 30 to 48 seconds. (Tonnesen, 1964; Clausen and Lassen, 1971). A discrepancy in calf muscle blood flow was reported in normal individuals of different ages. In young subjects the average flow during exercise in the gastrocnemius was 30.3 $\pm$ 14.1 ml per 100 grams per minute, whereas in older individuals it was 21.4 $\pm$ 5.4 (Lassen and Kamp, 1965).

By using ^{99m}Tc muscle clearance technique it was found that the half life ($T\frac{1}{2}$) of the injected isotope during exercise was always less than 3 minutes (average 2.2 $\pm$ 0.6) in normal individuals with an average age of 48.6 years (Cutajar et al.,1971). In general,

difficulties were encountered in measuring blood flow during exercise. It had been noted several years earlier that strong isometric exercise could lead to complete cessation of flow in normal limbs (Grand, 1938). Similarly, the tension in the muscle when standing on one limb influenced and decreased the muscle blood flow (Walter,1958; Lassen and Kamp,1964). The markedly increased cardiac output during exercise could influence arterial inflow in the lower limbs (Fenn, 1953; Ekblom and Hermansen, 1968), whereas the decreased renal and hepatic flow observed during exercise was part of the total redistribution of blood flow (Bucht et al.,1953; Rowell et al.,,1966). Indeed, several hypotheses have been made concerning the redistribution of blood during exercise. It was suggested that some of the increased blood flow observed within the actively contracted muscles could be due to a shifting of blood from the skin or from non-exercising muscles (Blair et al., 1961).

Ankle systolic pressure measurementsby means of Doppler ultrasound have not been recorded during exercise for lack of method. However, they have been obtained immediately after exercise and have been equal to or above the brachial systolic pressure in normal limbs (Carter, 1968; Yao, 1970), even after walking on the treadmill up to 8 km per hour (Strandness and Bell, 1964). In one report a slight decrease in ankle systolic pressure was demonstrated in normal individuals immediately after running (Stahler and Strandness, 1967).

1.513. After Exercise

Muscle blood flow in the calf was invariably increased just after exercise in normal limbs. Average maximum values measured by ^{133}Xe after a combination of induced ischaemia and foot exercise were 54.9 ml per 100 grams per minute in those younger than 50 years and

51.8 ml per 100 grams per minute in those older than 50 years. (Lassen et al., 1964). Immediately after exercise blood flow in the gastrocnemius was similar to that measured during exercise (20 to 40 ml per 100 ml per minute) (Lassen and Kamp, 1965). However, occasionally blood flow after exercise was found to be greater than that measured during exercise (Cobb et al.,1969). One explanation suggested was that the flow during exercise was decreased by the mechanical effect of the contracting muscle, whereas it was unimpeded after exercise (Cobb et al.,1969). Another possible explanation suggested was that flow in the calf appeared higher during the post-exercise period due to a shifting of blood towards the thigh and thus decreasing blood flow in the calf during exercise (Lassen and Kamp, 1965). None of these "normal" subjects who showed this decreased flow in the calf during exercise with a higher flow rate immediately after exercise had been investigated by arteriography and it is impossible to exclude any mild clinically undetectable arterial stenosis.

The post-exercise half-life ($T_{\frac{1}{2}}$) of the ^{99m}Tc injected in the gastrocnemius of normal individuals (4.3 minutes $\pm$ 2.0) was always greater than the half-life during exercise (2.2 min $\pm$ 0.6). This implied that the clearance rate during exercise was greater than during the early post-exercise period (Cutajar et al., 1971).

In normal individuals blood flow in the calf measured by means of muscle clearance techniques decreased rapidly after the end of exercise, reaching the pre-exercise level, within one or two minutes (Lassen and Kamp, 1965; Albert et al., 1967; Tonnesen and Sejren, 1970; Cutajar et al., 1971).

Another way of measuring reactive hyperaemia , introduced by Hillestad, is the concept of the total excess of blood. (Hillestad 1963a; 1963b; 1963c). This is the amount of blood that flows in excess

of the resting level during the period of reactive hyperaemia. It is usually calculated from the area under the curve of flow plotted against time (Fig. 1.2). The total excess of blood after exercise was found to be 7.0 ± 3.5 ml per 100 ml of muscle. Most of this flow in normal limbs occurred during the first post-exercise minute. It was found that the total excess of blood after a period of ischaemia was proportional to the time the circulation was occluded up to a maximum of 5 minutes. For more prolonged periods of ischaemia the total excess of blood was slightly increased (Hillestad, 1963a; 1963b; 1963c; Zelis et al., 1970).

It was found that the maximum post-exercise hyperaemia was linearly related to the amount of exercise (Albert et al., 1966). However, this relationship was not simple. Thus, by using ^{133}Xe clearance and a calf exercise, on an ergograph which mimicked that of walking, it was shown that blood flow increased proportionately to the intensity of muscle exercise until half of the total capacity for muscular exertion was reached; beyond this point there was not any further increase in flow even if the muscular effort was increased (Tonnesen, 1964). Similar conclusions were reported by others (Clausen and Laseen, 1971). An explanation given for this interesting observation was that the stable levels of muscle blood flow observed after a certain increase in the intensity of the exercise are consequent upon the inability of the intermuscular vessels to establish a greater flow, having already reached their maximum possible degree of vasodilatation. Another explanation given was that when the cardiac output reached a maximum it imposed limitations to the arterial inflow in the limb. (Pirnay et al., 1971; 1972).

1.52 Flow and Pressure Patterns in Arteries of Arteriosclerotic Lower Limbs

1.521 At Rest

Blood flow in the calf estimated by means of muscle clearance studies at rest did not show any significant difference between normal limbs and limbs with peripheral arterial disease. Using ^{133}Xe it was found that the average resting blood flow in the calf of patients with peripheral arterial disease was 1.4 ml per 100 grams of tissue per minute in the tibialis anterior and 1.1 ml per 100 grams per minute in the gastrocnemius (Lassen et al., 1965). Values obtained by others ranged between 1.2 and 3.6 per 100 grams per minute (Albert et al., 1966; Tonnesen, 1970; Corman et al., 1970; Hirai; 1974). These values were similar to those found in normal limbs (Section 1.5).

In patients with rest pain, muscle blood flow in the calf varied during the 24 hours. The maximum blood flow at rest was 3.6 $\pm$ 3.0 ml per 100 ml per minute and lasted from 11.00 to 19.00 hours with a peak about 14.00 to 15.00 hours; the lowest flow was found between midnight and 04.00 hours (Bartoli, 1970). This finding gave a possible explanation of the frequent rest pain at night.

In patients with severe ischaemic changes, ulceration or gangrene in the foot, muscle blood flow in the calf was also found to be within the normal range (McEwan et al., 1970).

Although pressure index (P.I.) was equal or greater than 1.0 in normal limbs, it was almost always less than 1.0 in limbs with occlusive peripheral arterial disease (Carter, 1968; 1969; Yao et al., 1969; Fronek et al., 1973a; 1973b;). In general, there was not any

significant difference between the resting pressure indices in single aortoiliac and single femoropopliteal arterial disease. In contrast, when multiple arterial lesions were present, the resting pressure indices were found to be significantly lower (Carter 1969; Yao, 1970).

The pressure index is related to the degree of the functional disability; it was 1.11 ± 0.10 in normal limbs; 0.59 ± 0.15 in limbs with intermittent claudication; 0.26 ± 0.13 in limbs with rest pain and only 0.05 ± 0.08 in limbs with impending gangrene (Yao, 1970).

1.522 During Exercise

Blood flow in the calf measured by means of isotope clearance during exercise was as a rule lower in patients with peripheral arterial disease than in normal individuals (Walter, 1958; Lassen et al., 1964; Lassen and Kamp, 1965; Albert et al., 1966; 1968; Wolf et al., 1972).

Average blood flow in the gastrocnemius measured with ^{133}Xe was found to be 4.5 ± 1.6 ml per 100 grams per minute. This value represented an overall slight increase above the resting levels. However, in several cases blood flow had decreased almost to zero during exercise (Lassen and Kamp, 1965; Coffman and Mannick, 1965).

By using ^{99m}Tc in limbs with arterial occlusions it was found that the half life ($T\frac{1}{2}$) of the isotope during exercise was twice that of normal limbs (Cutajar et al., 1971).

Subsequently, it was shown that a negative linear correlation existed between muscle blood flow in the calf and the severity of exercise (Tonnesen, 1968). In patients with peripheral arterial disease the decrease in calf muscle flow during exercise became less after they had undergone exercise training. It was suggested that the functional capacity of the collateral circulation had increased (Skinner and Strandness, 1967a; 1967b; Larsen and Lassen, 1967).

It has already been stated in the previous section that ankle systolic pressure was significantly lower than the pre-exercise levels. This observation is associated with the familiar finding that the foot becomes white during exercise (Yao et el., 1970).

1.523 After Exercise

The reactive hyperaemic response in limbs with peripheral arterial occlusion was found to be completely different from that in normal limbs. In general, a lower maximum blood flow with a prolonged hyperaemic response was observed (Shepherd, 1950a; 1950b; Snell et al.,1960; Hillstead, 1963a; 1963b; 1963c; Myers, 1964; Fronek et al.,1973a; 1973b).

By using ^{133}Xe it was shown that the average duration of the post-exercise hyperaemia in the calf was abnormally prolonged (10.4 minutes) in patients with occlusive arterial disease (Albert et al., 1966). It was also shown that the maximum hyperaemic response occurred several minutes after the end of exercise (Lassen and Kamp 1965; Albert et al.,1966; Tonnesen,1967). Depending on the degree of the circulatory insufficiency and on the intensity of the exercise the maximum blood flow in the calf observed in patients with intermittent claudication after exercise ranged from 4.5 to 28 ml per 100 ml per minute with a delay of up to 22 minutes (Elsner and Carlson, 1962). Xenon-133 was used to demonstrate the effect of ischaemic exercise on the blood flow in calf muscles of patients with superficial femoral occlusion and the effect of thromboendarterectomy (Bell and Short, 1968; 1971). It was found that the peak blood flow and time to peak blood flow were 28.3$\pm$ 11.3 ml/100 ml and 1.80 $\pm$ 0.79 minutes before operation; they were 49.8 $\pm$ 19.8 ml/100 ml and 0.57 $\pm$ 0.47 minutes after operation.(Bell and Short,1971).

By means of ^{99m}Tc muscle clearance it was found that the post-exercise half-life of the isotope ($T\frac{1}{2}$) was 8.7 ± 3.1 minutes in patients with peripheral arterial occlusions. This was a significant decrease compared to normal limbs (4.3 ± 2.0 minutes) (Cutajar et al., 1971.

In patients with occlusive arterial disease the ankle systolic pressure decreased significantly just after exercise and it returned to the resting levels over a variable period of time (Yao et al.,1970). In patients with superficial femoral artery occlusion, ankle systolic pressure decreased by less than 50 per cent of the resting values and recovered completely within 5 minutes. In patients with severe intermittent claudication it decreased by more than 50 per cent and recovered within 5 to 15 minutes. Finally, in patients with multiple occlusions the ankle systolic pressure decreased to undetectable levels just after exercise and the recovery time was prolonged by more than 15 minutes (Yao et al.,1970). Similar results have been reported by others (Winsor, 1950; Strandness and Bell, 1964; Carter, 1968; 1969; Fronek et al.,1973a; 1973b).

1.53 Flow and Pressure Patterns in Veins of Normal Lower Limbs

1.531 At Rest

Flow in the superficial veins of the lower limb during motionless standing was zero. However, recordings with an electromagnetic flowmeter on the long saphenous vein demonstrated that slight movements of the body and even speech or laughter initiated short flow waves in a proximal direction (Bjordal, 1972a; 1972b).

In the supine position venous flow in limbs was phasic with respiration. The main factor respobsible was the increased intra-abdominal pressure during inspiration (Lewis et al.,1972). In

particular, flow in the femoral vein was found to be very sensitive to variations of the intra abdominal pressure; it decreased with inspiration, Valsalva manoeuvre, and external compression of the abdomen (Lewis et al.,1972; Sigel et al.,1973).

Pressure was stable and corresponded to the hydrostatic pressure. In the supine position mean venous pressure measured at the ankle was found to be 11.7mm Hg; in the sitting position 56.0mm Hg and during motionless standing 86.8mm Hg (Pollack and Wood, 1949).

During motionless standing the pressure was the same in the superficial and deep veins, provided that the measurements were obtained at the same level, (Hojengard and Sturup, 1952; Ludbrook, 1963; 1966a; 1966b). In one study it was demonstrated that the pressure in the deep veins was higher than in the superficial by 1mm Hg; it was argued that this small pressure gradient was adequate to keep the valves in the perforating veins closed (Arnoldi, 1965; 1966;1969).

1.532 <u>During Exercise</u>

Flow and pressure were found to vary according to the phase of the walking cycle (Pollack and Wood, 1949; Stegall, 1966, Bjordal, 1972a; 1972b).

Recordings with an electromagnetic flowmeter and simultaneous pressure measurements in the long saphenous vein demonstrated that the volume and the velocity of flow varied during walking according to changes in pressure: during calf muscle relaxation, i.e. the foot- - lifting phase, the pressure decreased. In contrast, during the foot descending phase there was a gradual increase in pressure due to the hydrostatic effect. This reached a maximum during the foot-on-the-

ground phase when the calf muscles contracted. During the relaxation phase the direction of flow was from the long saphenous to the deep veins via the perforating veins. Flow within the perforating veins ceased during muscular contraction when flow towards the heart reached its maximum value (Bjordal, 1972a; 1972b).

In general, during the walking cycle the direction of flow is towards the heart both in the superficial and deep veins and in an inward direction in the perforating veins (Fig. 1.3)

In the late forties Pollack and Wood demonstrated that marked pressure changes occurred in the long saphenous vein at the ankle in response to a single step: pressure increased by 10 mm Hg (from 85 to 95 mm Hg) just before the heel was lifted off the ground. As the foot came off the ground completely it showed an average fall of 70 mm Hg. During this phase calf muscles relaxed whereas thigh muscles contracted forcing the valves below the knee to close rapidly. Subsequently, as the heel touched the ground and the calf mucles contracted an icnrease in pressure occurred to an average of 68mm Hg. When the heel was on the ground it decreased again to an average of 46mm Hg. Finally, within 11 to 37 seconds of motionless standing the pressure increased to the resting level, (85 mm Hg) (Pollack and Wood, 1949).

Direct pressure recordings carried out in the deep veins of the normal limb demonstrated that in the posterior tibial vein the pressure increased more (155 mm Hg) than in the popliteal vein (84mm Hg) during calf muscular contractions. These changes suggested that during the contracting phase, blood flow was directed from the posterior tibial to the popliteal vein. Subsequently, during the relaxation phase the decrease in pressure was less in the popliteal (51mm Hg) than in the posterior tibial vein (30 mm Hg). This difference in

pressure forced the valves below the knee to close rapidly preventing reflux (Arnoldi, 1965; 1966; 1969).

Mean venous pressure was found to decrease during the first 3 to 12 steps of walking. The decrease was not associated to the severity of the exercise. Thus, walking at 2.7, 4.0 and 5.3 Km per hour decreased venous pressure to 22.3 - 25.6 mm Hg. Venous pressure returned rapidly to the resting levels within 30 seconds after the end of the exercise (Pollack and Wood 1949).

The results of direct pressure measurement carried out during exercise by several workers can be summarised as follows: during a steady walk the mean pressure both in the superficial and deep veins of the lower limb is reduced well below the hydrostatic level (Arnoldi, 1966; 1969; Ludbrook, 1966a;1966b).

1.54 Flow and Pressure Patterns in Veins of Limbs with Superficial Venous Insufficiency

1.541 Saphenofemoral Incompetence only (Primary varicose Veins)

The flow in the superficial veins of the lower limb in a patient who is completely motionless is zero. However, it was found that slight movements initiated small flow waves which directed blood distally, in contrast to the proximal direction of flow in normal limbs (Bjordal, 1972a; 1972b). This retrograde flow during quiet standing in the incompetent superficial system was observed by others and was also thought to be the result of minor muscular contractions (Folse, 1970a; 1970b; Strandness and Sumner, 1975).

Simultaneous flow and pressure recordings demonstrated that in limbs with saphenofemoral incompetence the volume and velocity of

flow varied during the walking cycle according to the pressure changes: during the foot - lifting phase there was a decrease in pressure at the ankle and a simultaneous increase in flow distally. As the foot descended the pressure at the ankle increased and the flow decreased. When the leg was carrying the full body weight the pressure reached its maximum and the flow distally was at the minimum (Bjordal, 1971; 1972a; 1972b). In general, during the walking cycle the direction of flow is towards the heart in the deep veins; it is in a retrograde direction in the superficial veins and in an inward direction in the perforating veins (Fig. 1.4). This concept was demonstrated fluoroscopically in the late twenties by McPheeters and his associates. They injected lipiodol into the proximal part of a varicose long saphenous vein. When the patient was relaxed in a reclining position, the solution remained at the point of injection. However, an increase in the intra abdominal pressure caused the solution to break into several globules which moved distally. When the patient moved into a semi- reclining position the solution passed down the entire length of the saphenous vein. Repeated increase in the intra-abdominal pressure succeeded in producing a to-and-fro motion of globules in the long saphenous vein; they did not pass into the deep circulation through the perforating veins. When the patient was asked to move the foot at the ankle the globules entered the deep veins. Finally, they moved proximally when the patient was asked to push the foot against the examiner's hand to stimulate the pumping action of the calf muscles (McPheeters et al., 1932).

In limbs with saphenofemoral incompetence only, the pressure was stable at rest and corresponded to the hydrostatic pressure. Pressure patterns did not show any significant difference between normal limbs and limbs with primary varicose veins under resting consitions (Pollack et al.,1949). However, marked differences were found during walking. The average fall in pressure during exercise was 37mm Hg in limbs with

saphenofemoral incompetence whereas it was 64mm Hg in normal limbs. After the end of exercise, pressure returned to the resting levels within 2.8 seconds in the former and within 31 seconds on average in the latter (Pollack et al.,1949).

1.542 Incompetence of Saphenofemoral Junction and Calf Perforating Veins

Blood flow in the incompetent perforating veins in the calf was zero when the patient was relaxed and motionless. However, slight body movements were accompanied by corresponding to-and-fro flow waves (Bjordal, 1972a; 1972b).

During the walking cycle the direction of venous flow in the incompetent perforating veins varied according to the phasic changes in pressure: during the foot-lifting phase flow was directed inwards: it was directed outwards during the foot-on-the-ground phase. This bidirectional flow in the perforating veins was associated with the phasic changes in flow which occurred simultaneously in the incompetent long saphenous vein. During the relaxation phase flow in the long sahpenous vein was retrograde and blood entered the deep veins via the perforating veins (diastolic inflow). Subsequently, during calf muscle contraction the increased pressure in the deep veins expelled blood into the superficial system through the perforating veins (systolic outflow). It was found that the systolic outflow was less than the diastolic inflow (Bjordal, 1972a; 1972b).

In general, during the walking cycle the direction of flow in the deep veins is towards the heart and bidirectional in the long saphenous and incompetent perforating veins. However, the resultant mean flow is retrograde in the long saphenous vein and in an inward direction in the perforating veins (Fig 1.5).

Direct pressure measurements carried out simultaneously in the superficial and deep venous system at the ankle demonstrated that the average pressure was 76 mm Hg in the former and 78 mm Hg in the latter. This difference in pressure suggested that during motionless standing a positive pressure gradient of 2 mm Hg existed between the posterior tibial and the long saphenous vein (Arnoldi, 1966; 1969). However, blood flow in the incompetent perforating veins was zero when the patient was completely relaxed and motionless (Bjordal, 1972a; 1972b). The positive gradient demonstrated by Arnoldi could well be the result of minor muscular contractions. During the walking cycle the pressure in the posterior tibial vein increased on average to 118 mm Hg while in the long saphenous vein it increased to 108 mm Hg. This difference in pressure permitted sudden shifting of blood from the deep to the superficial venous system (Arnoldi, 1966). Subsequently, during muscle relaxation a mean pressure of 30 mm Hg was recorded in the posterior tibial while it was 43mm Hg in the long saphenous vein. This reversed difference in pressure permitted an inward flow (Arnoldi, 1966).

The above results were confirmed by other studies in which direct pressure measurements were carried out simultaneously in the deep and superficial venous system (Hojensgard and Sturup, 1952; Ludbrook, 1966a; 1966b). The effect of the haemodynamic changes described is that in limbs with saphenofemoral incompetence and incompetent calf perforating veins, the fall in the venous pressure at the ankle is much less than in normal limbs. The average fall in pressure during exercise was 7mm Hg in limbs with incompetence of saphenofemoral junction and calf perforating veins whereas it was 55mm Hg on average in normal limbs. After the end of exercise pressure returned to the resting levels within 2.1 seconds in the former and within 37 seconds in the latter (Arnoldi, 1966).

1.55 Flow and Pressure Patterns in Veins of Limbs with Deep Venous Insufficiency

In limbs with deep venous insufficiency, occlusion of the deep veins and destruction of the valves occur as a result of deep venous thrombosis. In the majority of limbs recanalisation of the occluded segment occurs, but the destruction of the valves is permanent (Bauer, 1942; Ludbrook, 1966a; 1966b; Sakaguchi et al.,1972; Barnes et al.,1973a, 1973b).

At rest flow is approximately zero. During muscle contraction the direction of flow is towards the heart and during relaxation retrograde (Bjordal, 1972). Flow in the long saphenous vein depends on whether the valves are competent or not. When competent, blood is directed into the sahpenous via the perforating veins. When incompetent, blood moves in a to-and-fro way without any significant net direction of flow (Bjordal, 1972a; 1972b).

In general, when both the deep and the superficial venous systems are incompetent the direction of flow during walking is bidirectional in the deep, the superficial and the perforating veins. However, the resultant mean flow in the perforating veins is in an outwards direction (Fig 1.6).

Pressure at rest can vary moderately in limbs with deep venous insufficiency. This depends on whether deep venous occlusion is present or not as well as on the degree of the collateral circulation by-passing the occlusion. Direct pressure measurements carried out in limbs with unilateral iliofemoral thrombosis show that in the supine position the resting pressure within the femoral vein is 5.5 $\pm$ 10.5 mm Hg higher in the occluded than in the normal limb during the acute phase. This difference in pressure is less pronounced (0.6 $\pm$ 1.4mm Hg)

when the collateral circulation develops (Negus and Cockett, 1967). Pressure patterns at rest do not show any significant difference between normal limbs and limbs with deep venous insufficiency when recanalization of the deep veins occurs (Pollack et al., 1949; De Camp et al., 1951; Husni, 1970).

In limbs with deep venous insufficiency, marked variations in pressure are found during walking: in limbs with acute iliofemoral thrombosis an increase in the mean pressure within the femoral vein has been noted (Negus and Cockett, 1967). In limbs with incompetent deep veins which were not occluded, the pressure in the long saphenous vein at the ankle fluctuates. The recorded fluctuation is three times greater than in normal limbs. After the end of the exercise, pressure returns to the resting level within 1.5 seconds in the diseased limbs and within 37 seconds in the normal (Pollack et al., 1949; Arnoldi, 1965; Negus and Cockett, 1967; Hjelmstedt, 1968a; 1968b; Bjordal, 1972a; 1972b). A positive correlation is found between the mean venous pressure during exercise and the extent of the occlusive process (Hjelmstedt, 1968a; 1968b).

The effect of the haemodynamic changes described is that in limbs with deep venous insufficiency the fall in the venous pressure at the ankle is much less than in normal limbs. In some patients pressure can even increase above the resting levels. Venous claudication occurs when it exceeds the systolic pressure. Venous claudication can also occur without an increase in venous pressure during exercise in patients with both deep venous incompetence and occlusive arterial disease. In such patients, the fall in arterial pressure during exercise results in a systolic pressure which is lower than the venous pressure at the ankle.

1.6 MATHEMATICAL AND HAEMODYNAMIC CONSIDERATIONS OF THE ARTERIAL AND VENOUS SYSTEM

Several workers have produced hydrostatic and electrical models of the circulation of the lower limb in order to understand and explain the haemodynamic changes that occur in health and in the presence of arterial or venous disease. The basis of these models is the relationship between pressure, flow and resistance (Flow = Pressure/ Resistance) which is the same, irrespective of whether the model is a hydrostatic or an electrical one. Although this basic principle is a common characteristic, the models produced vary considerably because of the large number of arteriosclerotic and venous abnormalities that occur and because different authors applied them to different parts of the circulation of the lower limb (Green et al.,1944; Longland,1953; Gaucer et al.,1965; Ehrenfeld et al., 1968; Holt, 1969; Rushmer, 1970; Strandness and Sumner,1975; Sumner and Strandness,1970; 1975).

The study of the blood supply to the lower leg is facilitated by dividing it into two major segments : (a) the small arteries, arterioles, capillaries and venules lying within the calf muscles plus those veins which return blood to the inferior vena cava and (b) the cognate arteries (iliac, femoral, superficial femoral, and collaterals) which transport blood to the calf (Strandness and Sumner, 1975; Sumner and Strandness, 1975).

When a main artery is severely stenosed or occluded, blood flow distal to the lesion is maintained through the collateral vessels. The total resistance to flow can be obtained by combining the resistance of the diseased main artery to the resistance of the collateral vessels. Thus,

$$Rcs = \frac{Rs \times Rc}{Rs + Rc}$$

where Rs = resistance of the main artery

Rc = resistance of the collateral vessels

Rcs = total resistance

It has been argued (Strandness and Sumner, 1975) that under normal conditions Rs is very small and therefore Rcs is also very small because it depends on the resistance of the patent main artery, while the resistance of the collateral circulation is immaterial. Under abnormal conditions, i.e. when the main artery is severely stenosed or occluded, Rs increases towards infinity; the combined resistance Rcs increases also and depends on the resistance Rc of the collateral vessels. Therefore it can be assumed that the more well developed the collateral circulation is, the less is the resistance imposed to the blood flow and the less the value of the total resistance Rcs (Strandness and Sumner, 1975).

Sumner and Strandness studied the changes in peripheral resistance at rest and after exercise in limbs with and without arterial disease by measuring calf flow with strain gauge plethysmography and by using an estimate of the mean ankle pressure and of the mean systemic arterial pressure calculated from the brachial systolic and diastolic and ankle systolic pressure (Sumner and Strandness, 1975). They found that at rest the flow in the calf was the same in normal limbs and in limbs of claudicants, but the peripheral resistance in claudicants was lower. After exercise the peripheral resistance decreased to very low levels. They also demonstrated that similar changes occurred in the resistance of the thigh. They argued that the calculations of calf resistance were valid, but the changes in the resistance in the thigh were probably artificial, because the true resistance of the thigh could only be calculated if blood flow in the thigh was measured, which they did not do. It became obvious that simultaneous measurements of flow

in the thigh and in the calf were essential in any attempt to measure collateral rssistance.

On the basis of Green's (Green et al.,1944) and Longland's (Longland, 1953) work, Strandness and Sumner (Strandness and Sumner, 1975) attempted to explain the heamodynamic behaviour of the collateral circulation by using an electrical model. In this model (Fig 1.7) the main artery and the collateral vessels were considered to be two parallel components of the arterial supply to the limb. The muscular arteries were taken to be the connecting channel between the main artery and the collaterals.

According to this model, when the pressure Pa_1 in the main artery is greater than the pressure Pc_1 in the collateral vessels the flow of blood is diverted from the main artery into the collaterals through the anastomic vessels. When Pa_1 is lower than Pc_1 the flow of blood is diverted from the collaterals into the main artery. Finally, when Pa_1 equals Pc_1 the flow of blood through the anastomotic vessels is zero.

In a normal limb Pa_1 is equal to Pc_1 and the flow of blood through the anastomotic vessels is zero. This implies that the ratio of the resistance of the collateral vessels (Rc_1) over the resistance of the muscular bed (Rcd) supplied by the collaterals is equal to the ratio of the resistance of the main artery (Ra) over the resistance of the muscular bed (Rd) supplied by the main artery (Rc_1/Rcd = Ra /Rd).

In a limb with stenosis of the main artery (e.g. superficial femoral artery) the above ratios are not equal. The direction of flow in the anastomotic vessels where resistance (Rc_2) is fixed depends on the ratio of the resistance of the superficial femoral artery over the resistance of the muscular bed in the calf (Ra /Rd) and on the ratio

of the resistance of the profunda femoris artery over the resistance of the muscular bed in the thigh (Rc_1/Rcd). When the ratio Ra/Rd is greater than the ratio Rc_1/Rcd the pressure in the popliteal artery is lower than in the profunda. Therefore, the flow of blood is diverted through the collaterals to the popliteal artery and to the calf muscles.

Assuming that the main artery, (i..e superficial femoral artery) is occluded, Strandness's electrical model can be modified as in figure 1.8. (Strandness and Sumner, 1975). In this model, the resistance of the collateral vessels and the resistance of the muscles in the calf are in series, parallel to the thigh vascular resistance. Since the collateral resistance is always greater than the resistance in the profunda it can be assumed that the resistance of the calf muscles will decrease at rest as part of the compensatory mechanism. (Sumner and Strandness, 1975).

Different workers using various techniques have demonstrated that in limbs with single arterial lesions, peripheral blood flow at rest is normal in claudicans but is decreased in patients with ischaemic rest pain (Hillestad, 1963a; 1963b; 1963c; Pentecost, 1964; Folse, 1965; Strandell and Shephers, 1968; Larsen abd Lassen, 1969; Sumner and Strandness, 1969). This is because the peripheral resistance is lower at rest compensating for the stenosis or occlusion by allowing an increased flow through the stenosis of the main artery or the colletral circulation (Sumner and Strandness, 1970). During exercise, peripheral blood flow increases in claudicants, but the increase is less than that which occurs in normal limbs (Shepherd, 1970; Hillestad, 1963a; 1963b; 1963c; Pentecost, 1964; Lassen and Kamp, 1965; Sumner and Strandness, 1969; Wolfesal, 1972). In patients with rest pain, exercise

may result in no increase in blood flow because the resistance of the muscle bed is already at its lowest (Sumner and Strandness, 1969). This explains why blood pressure distal to the arterial lesion is decreased in claudicants and even more so in patients with rest pain (Hillestad, 1964; 1963b; 1963c; Sumner and Strandess,1969; Yao,1970; 1973; Wolf, 1972). Exercise ordinarily results in a further decrease in peripheral pressure resulting in an even higher pressure gradient (Strandness and Bell, 1964; Sumner and Strandness,1969; Carter,1971; 1972; Wolf et al., 1972).

In limbs with multiple lesions, although blood flow in the more distal tissues may be normal at rest, it may decrease to even lower levels during exercise producing a white foot as a result of minimal perfusion (DeWeese, 1960; Allwood,1962; Lassen and Kamp, 1965; Yao, 1970). Blood pressure below fixed obstructions will be reduced at rest and will fall to even lower levels during exercise due to the increased pressure gradient (Strandness and Bell, 1964; Sumner and Strandness,1969; Yao, 1970). Finally, it has been suggested that one vascular bed can steal from another only when the artery supplying both beds is functionally obstructed (Ehrenfeld et al., 1968; Sumner and Strandness, 1972; Strandness and Sumner, 1975).

The study of haemodynamic behaviour of the venous system is facilitated by regarding the venous system as consisting of collapsable and rigid tubes. Such a vertical tube model was produced by Gauer and Thron (Gauer and Thron,1965) and was later improved by Rushmer (Rushmer, 1970). This model (Fig. 1.9) consisted of rigid and collapsable tubes containing fluid, the total volume of which was not enough to fill the collapsable part of the system. Under the influence of the hydrostatic pressure the fluid dilates the lower part of the collapsable tube leaving the upper part collapsed because of the atmospheric pressure.

In this model, pressure measurements revealed that pressure was zero (equal to atmospheric pressure) in the collapsed upper part. Pressure in the patent lower part was identical to the pressure in the rigid tube provided that the level was the same. (Fig 1.9). Pressure at the upper part of the rigid tube (at the level of the occluded part) was found to be lower than the atmospheric pressure (-40mm Hg) (Fig.1.9). The negative pressure in the upper segment of the rigid tube occurred because the occluded upper segment prevented free communication with the collapsable tube.

A horizontal - tube haemodynamic model is presented in figure 1.10 (Holt, 1969). This model consisted of a reservoir from which fluid could pass through a system of horizontal rigid and collapsable tubes connected in series. The collapsable tube was enclosed within a chamber in which pressure could vary. The rigid tubes were subjected to the atmospheric pressure. However, pressure P_1 and P_2 within the rigid tubes could be regulated by varying the height of the reservoir and could be measured in the two vertical tubes of the haemodynamic model connected in parallel with the rigid tubes (Holt,1969).

The following assumptions were taken into consideration so that the horizontal tube model could explain flow within the tubes in a similar way to blood flow within the veins: (i) pressure within the chamber was taken to be equal to the atmospheric pressure and (ii) pressure P_1 in the proximal rigid rube was taken to be greater than pressure P_2 within the distal rigid tube. Under these assumptions flow was found to be directly proportional to the pressure gradient (P_1-P_2).

Subsequently, when the pressure P_2 in the distal rigid tube decreased below the pressure within the chamber the tube towards the distal end of the chamber collapsed; the rest of the collapsable tube

remained patent.

When tne pressure P_2 and the pressure Pc within the chamber remained constant, tnen an increase in pressure P_1 in the proximal rigid tube produced a proportional increase in flow.

In this haemodynamic model the distal rigid tube can be considered to be within the thorax and the pressure chamber through which the collapsable tube passed, the abdominal cavity. It was shown, that when the pressure P_2 in the distal rigid tube was decreased below the chamber's pressure, then the distal portion of the collapsable tube was occluded. This can simulate the collapse of the inferior vena cava just below the diaphragm. It was also shown that flow through the proximal rigid tube depended on the relationship of the pressure P_1 in this tube and the chamber's pressure, Pc. This observation can explain adequately why blood flow in the femoral vein is so sensitive to variations of the intra-abdominal pressure. According to the above, flow in the femoral vein is expected to decrease with inspiration (i.e. lower intra-abdominal pressure) and to increase with expiration (i.e. higher intra-abdominal pressure). In recent years this has been verified using Doppler ultrasound (Lewis, 1974).

In contrast to the horizontal - tube haemodynamic model, different changes were observed in the vertical - tube haemodynamic model when it was tilted horizontally. It was found that when the collapsable and the rigid parts of this model were at an equal horizontal level, then the pressure was equal at all points. This observation suggests that the peculiar behaviour of the hydrostatic pressure on the venous blood flow (i.e. in upright position) results from the collapsable nature of the veins; it also suggests that the amount of

blood in the body is insufficient to distend the entire vascular tree completely.

The models described above summarise the relevant theories of the haemodynamic changes that occur in the circulation of the lower limb available at the time the author undertook the investigations presented in this thesis.

P A R T II

SIMULTANEOUS MEASUREMENTS OF CHANGES IN FLOW IN THE MUSCLES OF THE THIGH AND CALF

CHAPTER 2

EXPERIMENTAL METHODS
USED IN PART II

2.1 INTRODUCTION

The methods used in Part II of the thesis are described in this chapter.

The ^{99m}Tc clearance method was used, because ^{99m}Tc was available and easy to handle and because absolute values of flow were not required. Recirculation of ^{99m}Tc was also negligible (Appendix A7). Ankle systolic pressure measurements, by using Doppler ultrasound and cuffs, are simple and reproducible. Although the pressure measured this way may not be exactly the absolute pressure in the posterior tibial artery, it was useful to the study as changes in pressure were of more interest so that they could be compared to changes in flow obtained by the ^{99m}Tc clearance method.

Angiography did not involve the author, but was part of patients' management in the Cardiovascular Unit.

2.2 SIMULTANEOUS ^{99m}Tc MUSCLE CLEARANCE IN THE THIGH AND CALF AT REST AND AFTER EXERCISE

2.21 Procedure

All patients rested for 20 minutes in bed before starting the test at a constant room temperature ($26^{o}C$). Forty μCi of ^{99m}Tc in the form of sodium pertechnate diluted in 0.2 ml of saline were injected into the thickest part of the gastrocnemius and quadriceps. A sharp needle was used with an external diameter of 0.4 mm. The needle was inserted at an angle of 45^{o} to the skin and at a depth of 3 cm. The plunger of the syringe was withdrawn each time before the injection in order to ensure that intravascular administration of the radioactive isotope did not occur. The probes of two Pitman 235-isotope localisation monitors (See Appendix A4) were placed at a constant distance of 2 cm from the

skin over the site of the injections (Fig 2.1). The position was marked to enable accurate replacement of the probes after exercise. The output from the detectors was recorded continuously on a CR 552 pen recorder (Figs. 2.1 and 2.2).

The effect the one injection of ^{99m}Tc had on the radioactivity measured at the other site of injection was negligible (See Appendix A7). For reproducibility and comparison with ^{133}Xe see appendices A8 and A9.

Clearance curves were recorded for 10 minutes at rest. The patient then walked on a horizontal treadmill (Fig 2.3) at 4.5 km per hour for a maximum period of 3 minutes or until claudication occurred. Immediately after exercise he walked quickly back to bed and clearance curves were recorded for 20 minutes. The total period between the end of exercise and the beginning of the recording was always less than 30 seconds.

2.22 Calculation of T and expression of Results

Percentage clearance per minute (T) at any minute was obtained from the following equation:

$$T = \frac{f(t) - f(t+1)}{f(t) + f(t+1)} \times 200 \qquad (2.1)$$

where f(t) was the radioactivity measured at time t and f(t+1) was the radioactivity measured one minute later. The radioactivity cleared during one minute was $f(t) - f(t+1)$. The mean radioactivity during the same minute was $\frac{f(t) + f(t+1)}{2}$ and therefore the percentage radioactivity cleared per minute was given by equation 2.1.

T was calculated at minute intervals during the resting and the post-exercise periods. Thus, 10 values of T were obtained at rest and 20 after exercise for each clearance curve. Because this involved a total of 30 T values from the thigh and 30 from the calf the calculations were done using a computer (See Appendix A14). The values of T from the thigh and calf were plotted against time on the same graph. This enabled a visual comparison of the simultaneous changes occurring at both sites (Fig 2.4).

2.23 Other Parameters Measured

The calculation of Total excess of T, Maximum value of post-exercise T, Hyperaemic Index, Time of onset of maximum value of post-exercise T and Total period of increased post-experience T were obtained from the graphs of T against time (Fig 2.4).

The Total excess of post-exercise T (A) was first claculated. This was the area representing the post-exercise hyperaemia (shaded area in Fig 2.5) . This area could be calculated by measuring the height of the curve every minute from the line representing the resting level and taking their mean (Fig 2.5).

The Hyperaemic Index (H.I) was defined as the ratio of the total excess of post-exercise T (A) over the maximum value of T (M) during the same post-exercise period (Fig 2.6).

$$H.I. = \frac{A}{M} \qquad (2.2)$$

A,M, and H.I. were calculated by computer from the values of T obtained every minute during the pre and post-exercise periods.

The time of onset of maximum value of post-exercise T and the total period of increased post-exercise T were obtained from the graphs

of T against time and both were expressed in minutes.

2.3 SIMULTANEOUS ^{99m}Tc MUSCLE CLEARANCE IN THE THIGH AND CALF BEFORE, DURING AND AFTER EXERCISE

Because the probes of the 235-isotope localization monitors were heavy and could not be used during exercise, lighter probes (80 g each) were obtained. They were attached on two Dual Channel Analysers - model 45-24 (see Appendix A5). These light probes were strapped on the thigh and on the calf over the site of the injection (Fig 2.7).

The same procedure already described (see section 2.21) was used but it became possible to obtain a clearance curve during exercise also. Although T was calculated according to equation 2.1 (p. 60) a different computer program was used (see Appendix A14) because of the extra readings (one every minute) obtained during exercise.

2.4 PRESSURE MEASUREMENTS

2.41 Procedure

The same resting and exercise procedure was used as for the measurement of ^{99m}Tc clearance: all patients rested for 20 minutes before starting the test. A 15 cm cuff was applied around the right arm: two similar cuffs were applied around the ankles, 2 cm above the malleoli. By using a Parks 806 directional Doppler to detect flow in the posterior tibial artery (see Appendix A6) systolic pressures were measured at rest in the following order: right brachial pressure - right ankle pressure - left ankle pressure. The patient then walked on the treadmill (Fig 2.3) at 4.5 km per hour for a maximum period of 3 minutes or until claudication occurred. The cuffs remained in position during exercise so that post-exercise systolic pressure could be measured with minimum delay.

Immediately after exercise the patient walked quickly to the bed and the pressure measurements were carried out in the same order. If the post-exercise ankle systolic pressure was found lower than at rest, measurements continued at minute intervals until the pressure reached the resting value (Recovery). The recovery time was recorded.

2.42 Expression of Results

Results were expressed as:

(i) Resting Pressure Index, which was defined as the ratio of the ankle systolic pressure over the brachial systolic pressure both measured at rest.

(ii) Post-exercise Pressure Index, defined as the ratio of the ankle systolic pressure over the brachial systolic pressure both measured during the first minute after exercise.

(iii) Recovery Time, defined as the time in minutes which was necessary for the decreased pressure after exercise to reach the resting level

2.5 AORTOGRAPHY

Single plane aortography was used as the objective arbiter of the level and anatomical extent of the arterial lesions. It was done in all the patients studied but not in the healthy volunteers. A lumbar aortogram was performed in 83 per cent of the patients and a retrograde percutaneous aortogram in the remaining. In both cases films were taken serially starting at the pelvis and proceeding to the ankles. All aortograms were performed by Dr. D. Sutton as part of the routine management of the patients.

2.6 STATISTICAL METHODS

The significance of differences of the clearance changes in the different groups was determined using student's t test.
This was justified because the data was normally distributed.

CHAPTER 3

CLINICAL STUDIES

3.1 INTRODUCTION

The purpose of the clinical studies presented in this Chapter was to investigate the haemodynamic changes that occur during and after exercise in normal and arteriosclerotic limbs.

In addition an attempt was made to assess the value of changes in muscle blood flow after exercise in determining the severity and site of arterial lesions.

Four clinical studies have been undertaken using the methods described in the previous chapter (Chapter 2).

3.2 CLINICAL STUDY I: Simultaneous muscle clearance in the thigh and Calf, and ankle pressures at rest and after exercise

3.21 Aims

Study I, was designed to answer the following questions:

a) *Are there any distinct patterns of flow in the thigh and calf in normal limbs, limbs with aortoiliac, femoropopliteal and combined aortoiliac and femoropopliteal occlusions?*

b) *How can the patterns of flow changes after exercise be explained in terms of observed changes in pressure and probable changes in peripheral resistance?*

c) *Is there any redistribution in the flow of blood in limbs with peripheral disease?*

d) *How can the changes in flow and pressure after exercise be used to build a mathematical model of the arterial circulation in the lower limb?*

e) *Are there any distinct patterns of the thigh and calf Hyperaemic Indices in normal limbs, limbs with aortoiliac, femoropopliteal and combined aortoiliac and femoropopliteal occlusive disease?*

3.22 Material

Twenty healthy volunteers (30 limbs) and 114 patients (136 limbs) with peripheral vascular disease were studied. Limbs were graded into 4 groups according to the state of the aortoiliac and femoropopliteal segments.

Group A -(normal limbs)

In this group 30 limbs of 20 normal volunteers without any evidence of arterial disease were selected using the following criteria: Ankle pressure was increased after exercise and the post-exercise pressure index was greater than the resting pressure index, confirming the absence of stenosing arterial disease. The mean age was 26.4 ± 3.1 years.

Group B - (limbs with iliac occlusion only)

In this group 35 limbs of 32 patients were included. Femoral pulses were absent or weak and iliac occlusion was shown on the aortogram. The patients' mean age was 64.5 ± 4.7 years.

Group C - (limbs with superficial femoral artery occlusion only)

In this group 46 limbs of 38 patients were included. Pulses over the posterior tibial and dorsalis pedis arteries were absent. An occlusion of the superficial femoral artery longer than 10 cm was shown on the aortogram. The mean age was 59.8 ± 5.1 years.

Group D - (limbs with combined aortoiliac and femoropopliteal lesions)

In this group 25 limbs of 24 patients were carefully selected so that either the aortoiliac or femoropopliteal segment showed more than 70 per cent stenosis or occlusion while the other site was always occluded.

Femoral pulses were weak or absent while the pulses over the posterior tibial and dorsalis pedis arteries were always absent. The patients' mean age was 67.4 ± 4.2 years.

3.23 Results

3.231 T, Maximum T, Time of onset of Maximum T, Ankle Systolic Pressures Normal Limbs (Group A)

The changes of T in the thigh and the calf of normal limbs before and after exercise are shown in figure 3.1. Thigh and calf T were stable and comparable at rest. They showed a fivefold increase immediately after exercise and both returned to the resting level within 3 minutes. The maximum increase in T was observed during the first post-exercise minute. Thigh and calf T were comparable during the whole of the post-exercise period.

The mean ankle and brachial systolic pressures at rest were 132 ± 15 and 130 ± 12 mm Hg respectively. Immediately after exercise both were increased: mean ankle systolic pressure 147 ± 22 mm Hg; mean brachial systolic pressure 144 ± 24 mm Hg. As a result, the values of the resting and post-exercise pressure indices were 1.0 ± 0.10 and 1.0 ± 0.17 respectively. The recovery time in normal limbs was zero.

For comparison, the mean changes of thigh T, calf T and ankle systolic pressure in normal limbs before and after exercise are shown in figure 3.2. The increase in pressure after exercise occurred when the maximum thigh and calf T were observed.

Limbs with Iliac Occlusion only (Group B)

Changes of T in the thigh and in the calf of limbs with iliac occlusion only are shown in figure 3.3. Thigh T and calf T were stable and comparable at rest. Immediately after exercise thigh and calf T showed a threefold increase and both returned to the resting level within 10 minutes. The maximum increase in T was observed during the first post-exercise minute. Thigh T and calf T were comparable during the whole of the post exercise period.

Thus the pattern of ^{99m}Tc clearance in group B was much the same as in group A but the increase in T after exercise was less and the time needed for this to disappear was longer (figs 3.1 and 3.3).

The mean ankle systolic pressure was less than the brachial systolic pressure at rest. They were 85 $\pm$ 13 mm Hg and 140 $\pm$ 24 mm Hg respectively. Immediately after exercise the mean ankle systolic pressure decreased (40 $\pm$ 11 mm Hg) whereas the brachial systolic pressure increased (148 $\pm$ 19 mm Hg). As a result of these changes the values of the resting and post-exercise pressure indices were 0.58 $\pm$ 0.12 and 0.32 $\pm$ 0.10 respectively. The maximum decrease in the ankle systolic pressure was observed during the first post-exercise minute. The mean recovery time was 7.3 minutes.

The mean changes of thigh T, calf T and ankle systolic pressure in limbs with iliac occlusion only are shown in figure 3.4. The decrease in pressure after exercise occurred when thigh T and calf T were decreased. All returned to resting level after a period of 10 minutes.

Limbs with Superficial Femoral Artery Occlusion Only (Group C)

The changes of T in the thigh and in the calf of limbs with superficial femoral artery occlusion only are shown in figure 3.5. Although the clearance pattern at rest was the same, a completely different pattern was observed during the post-exercise period. Thigh T showed a threefold increase immediately after exercise while calf T decreased below the resting level. The decrease of T persisted until there was a fall in thigh T. The maximum value of T in the thigh was observed immediately after exercise. Thigh T returned to the resting level within 5 minutes when a delayed maximum increase in calf T occurred. Thereafter calf T decreased gradually until it reached the resting level 14 minutes after exercise.

Thus the clearance pattern of ^{99m}Tc was different in the thigh and calf. In the former, it was similar to that observed in normal limbs; in the latter, it diminished immediately after exercise rising to a maximum 6 minutes later and returning to the resting level during the subsequent 8 minutes (fig 3.5).

The mean ankle systolic pressure was lower than the brachial systolic pressure at rest: they were 84.8 $\pm$ 9 mm Hg and 123 $\pm$ 17 mm Hg respectively. Immediately after exercise the mean ankle systolic pressure decreased (49 $\pm$ 11 mm Hg), while the brachial systolic pressure increased (141 $\pm$ 13 mm Hg). As a result of these changes the values of the resting and post-exercise pressure indices were 0.71 $\pm$ 0.09 and 0.42 $\pm$ 0.13. The maximum decrease in the ankle systolic pressure was observed during the first post-exercise minute. The mean recovery

time was 3.8 minutes.

The mean changes of thigh T, calf T and ankle systolic pressure in the limbs with superficial femoral artery occlusion only are shown in figure 3.6. The decrease in pressure and in calf T occurred simultaneously. In contrast, a marked increase in thigh T was observed during the same post-exercise period.

Limbs With Combined Aortoiliac and Femoropopliteal Lesions (Group D)

The changes of T in the thigh and in the calf of limbs with combined aortoiliac and femoropopliteal lesions are shown in figure 3.7. Thigh T and calf T were the same at rest but different during the post-exercise period. Thigh T showed a threefold increase immediately after exercise whereas there was not any clearance in the calf (T = zero). The maximum increase in thigh T occurred during the first post-exercise minute and then thigh T decreased gradually. Calf T increased gradually and reached a maximum value during the tenth post-exercise minute when thigh T reached the resting level. Thereafter calf T decreased gradually until it reached the resting Level 19 minutes after exercise.

Thus the clearance pattern in the thigh was comparable to that in limbs with iliac occlusion only (Group B).

The mean ankle and brachial systolic pressures at rest were

100 ± 17 mm Hg and 170 ± 21 mm Hg respectively. Immediately after exercise the mean ankle systolic pressure decreased to an undetectable level while the brachial systolic pressure increased (178 ± 24 mm Hg). The ankle systolic pressure remained undetectable for an average period of 2.9 minutes. As a result of these changes the mean resting pressure index was higher (0.52 ± 0.09) than the post-exercise pressure index (0.18 ± 0.08). The mean recovery time was 17.6 minutes.

The mean changes of thigh T, calf T and ankle systolic pressure in the 26 limbs with combined aortoiliac and femoropopliteal lesions studied are shown in Figure 3.8. The decrease in pressure to an undetectable level was associated with the zero clearance in the calf and the increased T in the thigh. The recovery of ankle systolic pressure and increase in calf T were observed simultaneously.

3.232 Hyperaemic Index

The mean values of the Hyperaemic Index in the thigh and in the calf of the limbs in groups A, B,C and D are shown in table 3.1. In normal limbs (group A) thigh and calf Hyperaemic Indices were comparable. In limbs with iliac occlusion only (group B), the Hyperaemic Index in the thigh was comparable to the Hyperaemic Index in the calf; both were three times greater than in normal limbs. In limbs with superficial femoral artery occlusion only (group C) the mean Hyperaemic Index in the calf was three times greater than in the thigh; the latter was comparable to the thigh and calf Hyperaemic Indices in normal limbs. Finally, in limbs with combined aortoiliac and femoropopliteal lesions (group D) the mean Hyperaemic Index in the calf was two times grater than in the thigh. The thigh Hyperaemic Index was comparable to the thigh and calf Hyperaemic Indices in limbs with iliac occlusion only (Group B).

In order to demonstrate how the measurements of the two Hyperaemic Indices (thigh and calf) in each limb can separate the four groups (A to D), the Hyperaemic Index in the calf has been plotted against the Hyperaemic Index in the thigh (Figure 3.9) as a form of bivariate analysis. This was done with individual limbs. The means from table 3.1 were also plotted and are shown as large black dots (Figure 3.9).

3.24 Discussion

3.241 T, Maximum T, Time of Onset of Maximum T, Ankle Systolic Pressure

(a) Are there any distinct patterns of flow in the thigh and calf in normal limbs, limbs with aortoiliac, femoropopliteal and combined aortoiliac and femoropopliteal occlusion?

Although muscle blood flow in the thigh and calf in patients with occlusive arterial disease at rest was not different from normal limbs distinct patterns of changes in flow were found after exercise in the four groups studied (A to D). Thus, in normal limbs (group A) there was a marked and short lived hyperaemic response after exercise both in the thigh and in the calf. In patients with iliac occlusion only (group B) the pattern was much the same, but the hyperaemic response after exercise was diminished and prolonged equally in the thigh and in the calf. In patients with superficial femoral artery occlusion only (Group C) there was a marked and short lived hyperaemic response in the thigh, but the flow in the calf was diminished immediately after exercise with a delayed hyperaemic response. Finally, in patients with combined aortoiliac and femoropopliteal lesions (group D) there was a low and prolonged hyperaemic response in the thigh, but flow in the calf was absent immediately after exercise. In these patients (group D) the hyperaemic response in

the calf showed a more delayed and prolonged pattern than in patients with superficial femoral artery occlusion (group C). These patterns are so distinct that they may be used to identify the site of arterial occlusion.

b) How can the patterns of flow changes after exercise be explained in terms of observed changes in pressure and probable changes in peripheral resistance?

The concept concerning blood flow is that the normal limb can be regarded haemodynamically as a "standpipe system" in which pressure is maintained along the whole length of the axial vessels and flow is fed out of these vessels into vascular beds of varying resistance. In a simple standpipe, pressure takes only one value, but for an elastic system of vessels fed by an intermittent pump it is necessary to consider mean pressure. If any or all of these resistances fall, as in the hyperaemia caused by exercise, flow is increased. In consequence, the mean pressure along the standpipe may be sustained or may fall overall, the degree to which this takes place being determined by central delivery and thus by cardiac output. The change in the mean pressure is the result of a fall in the diastolic pressure because of the reduced peripheral resistance. This simple view of the limb adequately explains the findings in normal limbs; flow is increased, systolic pressure is increased, mean pressure is decreased according to the above and diastolic pressure must be decreased.

When aortoiliac occlusion was present the results suggest that the blood flow pattern was the same as in a normal limb but was "throttled" by the occlusion so that blood flow was insufficient to

permit normal reactive hyperaemia.

When there was femoropopliteal block only, the hyperaemia was normal in the thigh, but flow in the calf was diminished initially and was followed by a delayed hyperaemia. The only conceivable explanation of the diminished flow in the calf immediately after exercise when there is maximum vasodilation of the muscle bed in that area, is a fall in pressure in the axial vessels distal to the occlusion as demonstrated by the decrease in ankle systolic pressure. This in turn must be the consequence of a similar fall in the pressure gradient across the collateral circulation due to the fall in mean pressure proximally (see also the mathematical analysis of an electrical analogue which supports the above and which derives pressure (voltage) changes from flow (current) changes p.79). As the hyperaemia in the thigh is decreasing there is an increase in the peripheral resistance of the thigh muscle bed which results in an increase in the mean pressure in the profunda, thus restoring the pressure gradient in the collateral vessels. This then permits hyperaemia in the calf where maximum dilatation is still present.

The changes that occurred in patients with combined aortoiliac and femoropopliteal lesions can be explained along similar lines. However, the aortoiliac lesion is responsible for an aortofemoral gradient which becomes even more pronounced immediately after exercise producing a lower pressure in the profunda, a prolonged reactive hyperaemia in the thigh and a more delayed onset of calf hyperaemia.

c) *Is there any redistribution in the flow of blood in limbs with peripheral arterial disease?*

In the limbs with iliac occlusion only the increase in flow per unit volume of muscle was the same both in the thigh and in the calf

after exercise. Equal perfusion pressure should have been present distal to the occlusion within the main arteries supplying the thigh and the calf as their lumen was normal. The occurring vasodilatation during exercise within the peripheral vascular beds was responsible for the post-exercise hyperaemic response in the thigh and in the calf, but the collateral circulation limited the amount of blood flow into the limb and therefore caused the diminished hyperaemic response (Fig 3.3).

In limbs with superficial femoral artery occlusion the increase in flow which occurred in the thigh after exercise was the same as in normal limbs, but flow in the calf was diminished. A large amount of blood was available through the main arteries of the thigh and thus vasodilatation during exercise was responsible for the marked and short-lived post-exercise hyperaemic response (Fig 3.5). The collateral circulation through the thigh bypassing the occlusion limited the amount of blood flow 'demanded' by the vasodilated peripheral vascular bed of the calf at the end of exercise. However, when the flow in the thigh was decreased towards the resting level, an increased flow occurred in the calf producing the observed delayed hyperaemic response (Fig 3.5). The decrease in flow in the calf immediately after exercise and the observation that the hyperaemic response occurred when the flow in the thigh decreased towards the resting level suggested that a redistribution of blood was occurring in the limb during the early post-exercise period. This was more pronounced in limbs with combined aortoiliac and femoropopliteal lesions.

Therefore, the concept of calf claudication in femoropopliteal obstruction is of blood being "dumped" into a large vasodilated proximal muscle mass. The calf is deprived and can only begin to receive blood

to permit it to clear the isotope as the hyperaemia in the thigh decreases.

d) How can the changes in flow and pressure after exercise be used to build a mathematical model of the arterial circulation in the lower limb?

A mathematical model of the circulation of the lower limb should be such that it can explain all the changes in flow and pressure as a result of exercise that have been observed by others and in the present study. However, in the present study changes in flow per unit volume of muscle and changes in the ankle systolic pressure have been measured only. Therefore it is necessary to make certain assumptions concerning changes in response to exercise. Until direct measurements of mean pressure and of the various resistances of the different vascular beds in the limb at rest and after exercise are available, such a model will be the best approximation, provided it can explain all the observed changes.

Figure 3.10 shows a diagramatic representation of the arterial tree and its electrical analogue in a limb with superficial femoral artery occlusion. The resistance of the occluded superficial femoral artery (R_2) is infinitely high and the fixed resistances of the external iliac (R_1') and of the main arteries distal to the occlusion are very small. Therefore they can both be omitted and the electrical model can be redrawn as in figure 3.11. The mathematical analysis is based on the simplified electrical model (Fig 3.11b) and is carried out assuming that constant pressure (voltage) is present in the aorta.

Let R_1 = Resistance of common iliac artery (Fixed) (see Fig. 3.10)

R_1' = " " external " " (")

R_2 = " " superf. femoral " (")

R_3 = " " profunda femoris" (Fixed)

R_4 = " "collateral arteries (")

R_5 = " " main calf " (")

R_t = " "thigh muscle bed (variable)

R_c = " " calf muscle bed (")

V = Assumed constant pressure (voltage) in aorta

The resistance of the occluded superficial femoral artery (R_2) is infinitely high and the resistance of the external iliac (R_1') and of the main arteries distal to the occlusion (R_5) are fixed are very small. All three can be omitted (fig 3.11a) and the electrical model can be redrawn as in Figure 3.11b.

Let I = Total flow of blood (current)

i_t = Muscle blood flow in thigh (current)

i_c = Muscle " " " calf (")

V = Pressure in aorta (voltage)

V_A = " at point A (fig 3.11b)

The total resistance is:

$$(R_1 + R_3) + \frac{R_t (R_4 + R_c)}{R_t + R_4 + R_c}$$

According to Ohm's Law

$$I = \frac{V}{(R_1 + R_3) + \dfrac{R_t (R_4 + R_c)}{R_t + R_4 + R_c}} \qquad (1)$$

But $I = i_c + i_t$ (2)

Pressure (voltage) V_A at point A is:

$$V_A = i_t R_t = i_c (R_4 + R_c) \quad (3)$$

Therefore:

$$i_t = i_c \left(\frac{R_4 + R_c}{R_t}\right) = \frac{R_4 + R_c}{R_t} \cdot (1 - i_t) \quad (4)$$

This can be developed into

$$i_t = \left(\frac{R_4 + R_c}{R_t} \cdot I\right) - \left(\frac{R_4 + R_c}{R_t} \cdot i_t\right)$$

$$i_t + \left(\frac{R_4 + R_c}{R_t} \cdot i_t\right) = \frac{R_4 + R_c}{R_t} \cdot I$$

$$i_t \left(1 + \frac{R_4 + R_c}{R_t}\right) = \frac{R_4 + R_c}{R_t} \cdot I \quad (5)$$

Solving the equation for i_t

$$i_t = \frac{R_4 + R_c}{R_4 + R_c + R_t} \cdot I$$

Substituting I with equation (1)

$$i_t = \left(\frac{R_4 + R_c}{R_4 + R_c + R_t}\right) \cdot \frac{V \cdot (R_4 + R_c + R_t)}{R_t (R_4 + R_c) + (R_1 + R_3)(R_4 + R_c + R_t)}$$

(6)

which is

$$i_t = (R_4 + R_c) \times \frac{V}{R_t(R_4+R_c)+(R_1+R_3)(R_4+R_c+R_t)} \quad (7)$$

and

$$i_t = \frac{(R_4+R_c) \times V}{R_f(R_4+R_c) + R_4(R_1+R_3) + (R_1+R_3)(R_c+R_t)} \quad (8)$$

Substituting i_t with $i_c(R_4 + R_c)/R_t$ from equation (4)

$$i_c = \frac{R_t \times V}{R_f(R_4+R_c) + R_4(R_1+R_3) + (R_1+R_3)(R_c+R_t)} \quad (9)$$

The changes that occur in i_t and i_c as a result of changes in R_t and R_c after exercise can be illustrated with an example.

Let fixed resistances and constant aortic pressure be

$R_1 = 1\ \Omega$, $R_3 = 2\ \Omega$, $R_4 = 10\ \Omega$ and $V = 100$ V.

Before exercise (resting conditions)

Let $R_t = R_c = 10\ \Omega$. Then from equation (8)

$$i_t = \frac{2000}{30+200+60} = \frac{2000}{290} = 6.9 \text{ A}$$

and from equation (9)

$$i_c = \frac{1000}{290} = 3.45 \text{ A}.$$

Immediately after exercise

Let $R_t = 1\ \Omega$ and $R_c = 1\ \Omega$. Then from equation (8)

$$i_t = \frac{1100}{30+11+6} = \frac{1100}{47} = 23.4 \text{ A}$$

and from equation (9)

$$i_c = \frac{100}{47} = 2.1 \text{ amp}$$

(C) At the time when Peak Flow occurs in the calf

Let R_t = 10 ohm and R_c = 4 ohm

Then from equation (8)

$$i_t = \frac{1,400}{30 + 110 + 42} = 7.69 \text{ amp}$$

and from equation (9)

$$i_c = \frac{1,000}{200} = 5 \text{ amp}$$

Thus the chages which occur in the thigh muscle (R_t) and calf muscle (R_c) resistancesduring exercise can explain the changes in flow that occur in patients with superficial femoral occlusion (Fig 3.5). The effect of these changes on pressure can be illustrated also:

In the same model (Fig 3.11b), the pressure at point (A) proximal to the occlusion is:

$$V_A = i_t \cdot R_t$$

Similarly, at point (B) distal to the occlusion the pressure is:

$$V_B = i_c \cdot R_c$$

Thus before exercise $V_A = 10 \times 7 = 70$ volt

$V_B = 10 \times 3.5 = 35$ volt

Immediately after exercise $V_A = 22 \times 1 = 22$ volt

$V_B = 2 \times 1 = 2$ volt

3.242 Hyperaemic Index

e) *Are there any distinct patterns of the thigh and calf Hyperaemic Indices in normal limbs, limbs with aortoiliac, femoropopliteal and combined aortoiliac and femoropopliteal occlusive disease?*

Distinct patterns of values of the Hyperaemic Indices (thigh and calf) were found in the four groups studied (A to D). The graphic form of bivariate analysis used has demonstrated that the Hyperaemic Indices can separate the four groups without any overlap (Fig 3.9). This separation means that in patients with claudication and occlusive lesions the Hyperaemic Indices can determine whether the disease consists of a single lesion confined to either the femoropopliteal or the aortoiliac regions or whether it is double involving both the femoropopliteal and aortoiliac segments.

3.3 CLINICAL STUDY II: Hyperaemic Index in Limbs with Combined Aortoiliac and Femoropopliteal Stenosis

3.31 Aims

It has been demonstrated in the previous section (Section 3.2) that the Hyperaemic Index can determine the site of single occlusions or combined aortoiliac and femoropopliteal severe lesions. The purpose of the present clinical study (study II) was to answer the following question:

f) To what extent can the Hyperaemic Index determine the site and severity of combined aortoiliac and femoropopliteal stenosis?

Hypothesis: The mean calf Hyperaemic Index of the four groups (A to D) studied in the previous section was plotted against the mean thigh Hyperaemic Index of the same groups and the four points obtained were joined by lines as shown in figure 3.12.

(i) It can be argued that the points representing limbs with combined aortoiliac and femoropopliteal stenosis would be inside the ABCD quadrangle and their position would be determined by the relative severity of the lesions.

(ii) Points of limbs with femoropopliteal stenosis greater than aortoiliac would be in ACD triangle and of limbs with aortoiliac stenosis greater than femoropopliteal stenosis would be in ABD triangle.

(iii) Limbs with stenotic lesions greater than 70 per cent would be in BDC triangle and with stenotic lesions less than 70 per cent in ABC triangle. Thus limbs in triangle p would have a femoropopliteal stenosis greater than 70 per cent which is more severe than the aortoiliac stenosis. Limbs

in triangle q would have aortoiliac stenosis greater than 70 per cent which is more severe than the femoropopliteal stenosis. Limbs in triangle r would have less than 70 per cent femoropopliteal stenosis which is more severe than the aortoiliac stenosis. Finally, limbs in triangle s would have less than 70 per cent aortoiliac stenosis which is more severe than the femoropopliteal stenosis.

Substantiating this hypothesis would be a means of providing an answer to question (f).

3.32 Material

Twenty-eight patients (33 limbs) with claudication and combined aortoiliac and femoropopliteal stenoses of any degree were studied. They were selected according to the aortogram which was part of their in-patient investigation. The degree of stenosis seen in the AP plane was expressed as a percentage of the normal size lumen. This was based on measurements of an adjacent area of the angiographically normal vessel. Lesions were classified as 0-10%, 10-40%, 40-70%, more than 70% stenosis or occlusion.

Simultaneous muscle clearance curves were recorded from the thigh and calf and the Hyperaemic Index was calculated according to the methods described in section 2.23 (p.61). The results were expressed graphically by plotting the Hyperaemic Index of the calf against the Hyperaemic Index of the thigh.

3.33 Results

The results of the thigh and calf Hyperaemic Indices are expressed graphically (Fig 3.13). The degree of stenosis in the

aortoiliac and femoropopliteal segments in relation to triangles p, q, r, s as postulated in the hypothesis and the arteriographic findings are shown in Table 3.2.

3.34 Discussion

The results in this section support the hypothesis. All the points representing limbs are inside the ABCD quadrangle. The arteriographic findings in Table 3.2 suggest that points in triangles s and q have stenosis which is more severe in the aortoiliac than in the femoropopliteal segment. Limbs in triangles p, and r have stenosis which is more severe in the femoropopliteal than in the aortoiliac segment. Limbs in triangle p have femoropopliteal stenosis greater than 70 per cent and in triangle q aortoiliac stenosis greater than 70 per cent. Finally, limbs in triangle r have femoropopliteal stenosis less than 70 per cent and limbs in triangle s, aortoiliac stenosis less than 70 per cent.

Although one is fully aware of the inherent error in grading lesions on single plane arteriography, the results suggest that the methods used to express the Hyperaemic Indices in this study may provide a less invasive means of expressing the site and severity of arterial lesions although it cannot match the definition of the anatomical extent shown on the arteriogram. The study in the next section of this thesis was designed to test this further.

In conclusion the question posed can be answered as follows:

g. *Can the Hyperaemic Index determine which is the more severe lesion in combined aortoiliac and femoropopliteal stenosis?*

The answer is yes, considering the limitations of single plane arteriography in the present study.

3.4 CLINICAL STUDY III. The Hyperaemic Index in Limbs with Peripheral Arterial Disease-Prospective Study

3.41 Aims

The results obtained from the last two sections (3.2 and 3.3) suggest that the Hyperaemic Indices obtained simultaneously from the thigh and calf can determine the state of the aortoiliac and femoropopliteal segments, i.e. whether occluded or stenosed; whether the stenosis was greater or less than 70 per cent and finally in limbs with combined aortoiliac and femoropopliteal lesions which of the two was most severe. By superimposing the results of clinical study I in section 3.2 (Fig 3.9) with the results of clinical study II (Fig 3.13) figure 3.14 is obtained. Limbs with double stenotic lesions only are inside the ABCD quadrangle while all limbs on the lines and outside the quadrangle (shaded areas) have occlusions.

The previous two studies (studies I and II) were in patients selected according to the arteriographic findings. In this section of the thesis a prospective study was undertaken. Patients with claudication, admitted to the ward for investigation were studied by simultaneous clearance of ^{99m}Tc from the thigh and calf and the state of the aortoiliac and femoropopliteal segments was predicted before arteriography was performed . The findings were then compared with arteriography. Thus, the aim of this study was to substantiate the findings of the previous studies.

3.42 Material

Twenty-three consecutive patients (44 limbs) with claudication, admitted to the ward for investigation with a view to operation were studied.

Simultaneous muscle clearance curves were obtained from the thigh and calf and the Hyperaemic Index was calculated according to the methods described (Section 2.23, p. 61). The results were expressed graphically by plotting the Hyperaemic Index of the calf against the Hyperaemic Index of the thigh. The state of the aortoiliac and femoropopliteal segments was thus predicted before arteriography was available. Aortography was subsequently performed and was used as the objective arbiter of the state of the vessels. The degree of stenosis seen on the AP plane was expressed as a percentage of the normal size lumen. This was based on measurements of adjacent areas of the angiographically normal vessel. Lesions were classified as 0-10, 10-40, 40-70, greater than 70 per cent, stenosis, and occlusion.

Sixteen patients (24 limbs) had an operation. This was decided by the consultant surgeon in charge who had no knowledge of the results of the isotope studies. His decision to operate was based on the clinical and angiographic findings. The 16 patients were restudied two weeks after the operation in order to see the effect that the reconstructive procedures had had on the Hyperaemic Indices.

3.43 Results

The results of the Hyperaemic Indices are expressed graphically in figure 3.15 and the degree of arterial stenosis suggested by them in table 3.3. The state of the aortoiliac and femoropopliteal segments in the same limbs as subsequently demonstrated by the aortogram are shown in table 3.4. Comparing table 3.3 with table 3.4 it can be seen that the prediction of the lesions were correct in 40 out of 44 limbs (Table 3.5)

Sixteen patients (24 limbs) had a reconstructive operation (fig. 3.16). Femoropopliteal vein bypass graft was performed in four

(limbs 1,2,3 and 4 of fig. 3.16). Unilateral iliac endarterectomy and profundoplasty in 1 limb (18) and an aortoiliac endarterectomy or dacron bypass graft to the aortoiliac segment in the remaining limbs. With the exception of 4 limbs which had the femoropopliteal vein bypass graft, all limbs which had an aortoiliac reconstruction had occlusion or greater than 70 per cent stenosis in the aortoiliac segment. All stenoses were above the BC line (Fig 3.16). The effect of the operation on the Hyperaemic Indices was to move all points towards ACD triangle and towards point A. (Fig 3.17). The points that remained above the BC line represented limbs which had severe combined aortoiliac and femoropopliteal disease pre-operatively, while after operation they were left with femoropopliteal occlusion and some residual aortoiliac stenosis.

3.44 Discussion

g) To what extent can the ^{99m}Tc clearance predict the presence and the extent of occlusive lesions in patients with peripheral arterial disease?

The results indicate that it is possible to predict the degree of stenoses in femoropopliteal and aortoiliac segments, expressed as normal, less than 70 per cent stenosis, more than 70 per cent stenosis and occlusion accurately in 90 per cent of limbs. In patients with single segmental disease (i.e. limbs number 1,2,3,4,19,20,21 and 22 of fig 3.16) the Hyperaemic Indices became normal after successful reconstruction (Fig 3.17).

h) What is the value of ^{99m}Tc clearance method in limbs with combined aortoiliac and femoropopliteal disease?

The results indicate that this method can determine not only the degree of stenosis in each segment in terms of the four categories

above (i.e. normal, less than 70 per cent, more than 70 per cent stenosis and occlusion) but also which of the two is the more severe. In patients with double segment disease reconstructing one segment changed the Hyperaemic Indices to a pattern compatible to the residual disease (Fig 3.16 and 3.17)

The results of the Clinical Studies I, II and III led to the production of a diagnostic chart (Fig. 3.18). According to this chart it is possible to classify limbs with claudication to any of 12 possible categories (a-h, r-q: see key of Fig. 3.18).

3.5 CLINICAL STUDY IV. Simultaneous ^{99m}Tc Muscle Clearance in the Thigh and in the Calf Before, During and After Exercise

3.51 Aim

It has already been mentioned (see section 2.22) that it became possible to obtain a clearance curve during exercise by using light probes which could be strapped on the leg (Fig 2.7). These probes were available at the later stages of this study and therefore the number of patients investigated was limited. However, an attempt has been made to answer the following question:

i) Are there any distinct patterns of changes in flow during exercise determined by ^{99m}Tc muscle clearance?

3.52 Material

5 healthy volunteers (5 limbs) and 23 patients (25 limbs) with peripheral vascular disease were studied. The normal volunteers were selected using the following criteria: (i) The ankle systolic pressure was increased after a 3-minute walk on the treadmill at 4.5 Km per hour, and (ii) the post-exercise pressure index was greater than the resting pressure index.

The patients with peripheral arterial disease had been admitted to the hospital for aortography as part of their routine management.

Limbs were graded into 4 groups:

Group 0 : 5 limbs of 5 normal volunteers

Group 1 : 5 limbs of 5 patients with iliac occlusion only.

Group 2 : 5 limbs of 5 patients with a long superficial femoral artery occlusion only.

Group 3 : 10 limbs of 8 patients with combined severe (more than 70 percent stenosis or occlusion) aortoiliac and femoropopliteal lesions.

The methods described in sections 2.2 and 2.3 were used. All the normal volunteers and the patients walked on the treadmill at 4.5 Km per hour for a period of 3 minutes or until claudication occurred.

3.53 Results

The changes of T in the thigh and in the calf of a normal limb, a limb with iliac occlusion only, a limb with superficial femoral artery occlusion only and a limb with combined severe aortoiliac and femoropopliteal lesions, before, during and after exercise are shown in Figure 3.19, 3.21, 3.23 and 3.25 respectively. The mean values of thigh T and calf T and their standard deviations before, during and after exercise are shown in figure 3.20 for group 0 (normal limbs); in figure 3.22 for group 1 (limbs with iliac occlusion only); in figure 3.24 for group 2 (limbs with superficial femoral artery occlusion only) and in figure 3.26 for group 3 (limbs with combined severe aortoiliac and femoropopliteal lesions).

Before and after exercise, the changes of T in the thigh and in the calf were similar to those described in a previous section (see section 3.22). During exercise, they were as follows: In normal limbs (group 0) there was a comparable increase in thigh T and calf T after the onset of exercise (Figs 3.19 and 3.20). They both reached a maximum value (sixfold increase) within 30 seconds and remained stable thereafter during the rest of the period of exercise. (Fig 3.19 and 3.20).

In limbs with iliac occlusion only (group 1), thigh and calf T showed a comparable fivefold increase within 30 seconds after the onset of exercise, then, they started to decrease gradually but they did not reach the resting level at the end of walking (Fig. 3.21 and 3.22).

In limbs with superficial femoral artery occlusion only (group 2) there was a different pattern of changes in thigh T and calf T during exercise : Thigh T showed a fivefold increase within 30 seconds and remained stable thereafter. Calf T showed a similar increase initially, then, it started decreasing and was lower than the resting level during the third minute of walking (Figs. 3.23 and 3.24). In 2 out of 5 limbs studied, claudication occurred during the third minute of walking.

Finally, in limbs with combined severe aortoiliac and femoropopliteal lesions (group 3) a different pattern of changes in thigh T and calf T was found also: Thigh T showed a fivefold increase within 30 seconds from the beginning of exercise which was followed by a gradual decrease towards the resting level (Figs. 3.25 and 3.26). Calf T showed a comparable fivefold increase initially,; it was followed by a rapid decrease, to below the resting level, during the second minute of exercise. Calf T was very low during the third minute of exercise. (Figs. 3.25 and 3.26). In all the limbs studied, claudication occurred during the third minute of walking.

3.54. Discussion

i) Are there any distinct patterns of changes in flow during exercise determined by ^{99m}Tc muscle clearance?

The answer is yes.

In the control group of normal limbs there was a marked hyperaemic

response both in the thigh and calf. The maximum value of T was reached 30 seconds after the onset of walking and remained unchanged thereafter.

In limbs with iliac occlusion only the pattern was diminished but equal in the thigh and the calf: A hyperaemic response was established 30 seconds after the onset of walking; it started to diminish but did not disappear at the end of the exercise.

In limbs with superficial femoral artery occlusion only, there was a different pattern of flow in the thigh and in the calf: The former showed a flow pattern similar to that in normal limbs; the latter showed an initial hyperaemic response, which however, disappeared by the third minute of walking; at the end of walking little flow was found in the calf (Figs. 3.23, 3.24).

Finally, in limbs with combined aortoiliac and femoropopliteal lesions the flow pattern in the thigh was similar to that in limbs with iliac occlusion only, while the flow pattern in the calf was less than the resting level by the second minute of walking; during the third minute of exercise, when claudication occurred, very little flow was found in the calf (Figs. 3.25 and 3.26).

P A R T III

THE DEVELOPMENT AND VALIDATION OF A HAEMODYNAMIC MODEL

CHAPTER 4

DEVELOPMENT OF THE HAEMODYNAMIC MODEL

4.1 INTRODUCTION

Although the method described in Part II provided distinct patterns of diagnostic value in patients with peripheral occlusive disease it had a disadvantage : two injections were required and because of technical limitations one lower limb only could be studied at a time. The information was mainly obtained during the period after exercise with the patient in a horizontal position in order to avoid interference from venous disorders.

It became evident that a method which could allow both lower limbs to be studied at the same time would be of great value for the clinical assessment of patients. This new method had to be performed with the patient standing with one injection in each calf. However, because of the standing position the possibility of interference by the venous system had to be investigated.

In Part III of the thesis a theoretical haemodynamic model was developed as a hypothesis, concerning the haemodynamic changes prevailing in the arterial system during tiptoeing. The haemodynamic model was then validated by testing it on normal volunteers and on patients with peripheral arterial and venous diseases.

The haemodynamic model is described in this chapter.

4.2 THEORETICAL CONSIDERATIONS AND DEVELOPMENT OF HAEMODYNAMIC MODEL

4.21 Two-pool Haemodynamic Model

In order to elucidate the position and the significance of

single arterial lesions the arterial tree of the lower limb is considered to be composed of two pools of blood, one above and one below the arterial lesion (Fig.4.1). Pool 1 is an infinite pool of blood above the lesion. Pool 2 is a limited pool containing the amount of blood (Q_o) between the arterial lesion and the point of an intramuscular injection of ^{99m}Tc in the calf. The calf is chosen as the site of injection so that the isotope clearance is measured distal to vascular lesions amenable to reconstruction.

It is assumed that during a period of repeated elevations of the heel from the ground (tip-toeing) a constant proportion (a) of the blood contained in pool 2 leaves via exit B (Fig 4.1) during each tip-toe cycle. It is also assumed that an amount X (n) of blood is brought into this pool (pool 2) during the nth tip-toe cycle. Thus, (a) is a fraction of the amount of blood (Q_n) in pool 2 at time n. At the beginning of the exercise the amount of blood in pool 2 is Q_o.

At the end of the 1st cycle

$$Q_1 = Q_o - aQ_o + X_1 \qquad (4.1)$$

i.e. the amount of blood in pool 2 at rest (Q_o), minus the amount that left pool 2 (aQ_o), plus the amount that entered pool 2 (X_1).

Equation (4.1) can be rewritten as:

$$Q_1 = (1-a)\ Q_o + X_1 \qquad (4.2)$$

At the end of the 2nd cycle:

$$Q_2 = (1-a)\, Q_1 + X_2 \qquad (4.3)$$

Substituting Q_1 from equation (4.2), equation (4.3) can be rewritten as:

$$Q_2 = (1-a)\left[(1-a)\, Q_o + X_1\right] + X_2 \qquad (4.4)$$

or

$$Q_2 = (1-a)^2\, Q_o + (1-a)X_1 + X_2 \qquad (4.5)$$

Similarly, at the end of the 3rd cycle:

$$Q_3 = (1-a)\, Q_2 + X_3 \qquad (4.6)$$

Substituting Q_2 from equation (4.5), equation (4,6) can be rerwritten as:

$$Q_3 = (1-a)\left[(1-a)^2\, Q_o + (1-a)\, X_1 + X_2\right] + X_3 \qquad (4.7)$$

or

$$Q_3 = (1-a)^3\, Q_o + (1-a)^2 X_1 + (1-a)\, X_2 + X_3 \qquad (4.8)$$

So, at the end of the n^{th} cycle:

$$Q_n = (1-a)^n\, Q_o + (1-a)^{n-1}\, X_1 + (1-a)^{n-2} X_2 \ldots + X_n \qquad (4.9)$$

Assuming that the same amount of blood enters pool 2 during each tiptoe cycle then:

$$X_1 = X_2 = X_3 = \ldots\ldots\ldots\ldots X_n = \lambda$$

and

$$Q_n = Q_o\ (1-a)^n + \left[\frac{1-(1-a)^n}{a}\right]\lambda \qquad (4.10)$$

Let, W_n be the amount of blood that has left pool 2 via B (Fig. 4.1) from the beginning of the first to the end of the n^{th} tiptoe cycle.

This W_n is the total amount of blood ($n.\lambda$) that has entered pool 2, plus the initial amount of blood in it at rest (Q_o), minus the amount of blood Q_n that remains in pool 2 at the end of the n^{th} tiptoe cycle.

$$W_n = n\lambda + Q_o - Q_n \qquad (4.11)$$

Substituting Q_n from equation (4.10)

$$W_n = n\lambda + Q_o - Q_o(1-a)^n - \frac{1-(1-a)^n}{a}\lambda \qquad (4.12)$$

Let, $1-a = \beta$

$$W_n = n\lambda + Q_o - Q_o\beta^n - \frac{(1-\beta^n)}{a}\lambda \qquad (4.13)$$

or

$$W_n = \frac{\lambda}{a}(an-1+\beta^n) + Q_o(1-\beta^n) \qquad (4.14)$$

The amount of blood (W_n) that leaves pool 2 via B from time t=0 to time t=n (i.e. by the end of the n^{th} cycle) is proportional to the total percentage clearance between t=0 and t=n (i.e. total percentage clearance=Dn),

Therefore,

$$W_n = K.D_n \qquad (4.15)$$

Where K is the muscle to blood partition coefficient for the isotope used.

Substituting W_n from equation (4.14)

$$K.D_n = Q_o \ (1-\beta^n) + \frac{\lambda}{a} (an-1+\beta^n) \qquad (4.16)$$

After five tiptoe cycles:

$$KD_5 = Q_o(1-\beta^5) + \frac{\lambda}{a} (5a-1+\beta^5) \qquad (4.17)$$

After ten tiptoe cycles:

$$KD_{10} = Q_o(1-\beta^{10}) + \frac{\lambda}{a} (10a-1+\beta^{10}) \qquad (4.18)$$

After twenty tiptoe cycles:

$$KD_{20} = Q_o \ (1-\beta^{20}) + \frac{\lambda}{a} (20a-1+\beta^{20}) \qquad (4.19)$$

Solutions for (a) (Q_o) and (λ) can be derived from the above equations (See Appendix A10).

Thus,

$$a = \frac{63D_{20} - 466D_{10} + 900D_5}{250(9D_5 - 2D_{10})} \qquad (4.20)$$

$$Q_o = \frac{K\,D_5(10a - 1 + \beta^{10}) - D_{10}(5a - 1 + \beta^5)}{(1-\beta^5)(10a - 1 + \beta^{10}) - (1 - \beta^{10})(5a - 1 + \beta^5)} \qquad (4.21)$$

$$\lambda = \frac{[K\,D_5 - Q_o(1 - \beta^5)]}{10a} \qquad (4.22)$$

(a), (Q_o) and (λ) can be calculated provided D_5, D_{10}, D_{20} and K are known.

a, Q_o and λ can be used to calculate the total amount of blood Q_n in pool 2 at the end of each tiptoe cycle. The same parameters (a, Q_o and λ) can be used also to calculate the total amount of blood W_n which leaves pool 2 at the end of each tiptoe cycle.

Q_n in pool 2 can either increase or decrease with each cycle, depending on the values of a, Q_o and λ. Theoretically, this increase or decrease in Q_n should be continued indefinitely during exercise. However, in practise, after a limited number of tiptoe cycles Q_n reaches a steady value (Qfinal).

Qfinal can be determined from the following equation:

$$Qfinal=\frac{\lambda}{a} \tag{4.23}$$

W_n will always increase at the end of each tiptoe cycle. This increase in W_n is a function of the values of a, Q_o and λ, and should therefore vary in normal limbs and in limbs with peripheral arterial disease. W_n can be calculated from equation 4.11.

The number (n) of tiptoe cycles at the end of which Qfinal is obtained approximately can be calculated from equation 4,10. This equation can be rewritten as follows:

$$Q_n = Q_o.\beta^n + \frac{\lambda}{a}(1-\beta^n) \tag{4.24}$$

If, $Q_n = \infty$

then, $\beta = (1-a) = 0$

and

$$Q_\infty = Q_o.0 + \frac{\lambda}{a}\{1-0\}=\frac{\lambda}{a} \tag{4.25}$$

Therefore, Q_n in order to reach a proportion (e, say)(e.g. 90 per cent) of the final value

$$Q_n \geqslant e\frac{\lambda}{a} \tag{4.26}$$

Substituting Q_n from equation 4.24, equation 4.26, can be rewritten as:

$$Q_o.\beta^n + \frac{\lambda}{a}(1-\beta^n) \geqslant e\ \frac{\lambda}{a} \tag{4.27}$$

or

$$\beta^n(Q_o - \frac{\lambda}{a}) \geq e\ \frac{\lambda}{a} - \frac{\lambda}{a} \qquad (4.28)$$

or

$$\beta^n \geq \left[\frac{\frac{\lambda}{a}(1-e)}{\frac{\lambda}{a} - Q_o}\right] \qquad (4.29)$$

Taking logarithms, equation 4.29 can be rewritten as:

$$n \log \beta \geq \log \frac{\lambda}{a} + \log (1-e) - \log(\frac{\lambda}{a} - Q_o) \qquad (4.30)$$

or

$$n \geq \frac{\log \frac{\lambda}{a} + \log(1-e) - \log(\frac{\lambda}{a} - Q_o)}{\log \beta} \qquad (4.31)$$

Where n, is the number of tiptoe cycles which are needed so that Q reaches α proportion e, of its final value.

In order to elucidate the position and the significance of combined arterial lesions of the main channels in the lower limb, a heamodynamic model concerning three pools can be considered (Fig 4.2). This three-pool system could be analysed in a similar manner as the two-pool system (Fig 4.1). However, it was assumed that the supply of blood in the top pool of the two-pool system was of restricted capacity because, the main effect a proximal lesion would have on the lower pool would be a reduction in the value of λ, i.e. on the amount of blood entering the lower pool of the two-pool system. Thus, an approximation of the behaviour of the lower two pools in the three-pool system (Fig. 4.2) could be obtained by lowering the value of λ and examining the lower two pools only. Therefore, the same equations (4.20, 4.21 and 4.22) could be applied.

4.22 Effect of Venous Insufficiency on the Heamodynamic Model

The two-pool haemodynamic model describes the haemodynamic changes that occur in the arterial tree when the patient is tiptoeing in the erect position. From previous studies outlined in the introduction of this thesis (see sections 1.53, 1.54 and 1.55), the effect of a venous system which is normal, has superficial venous insufficiency or deep venous insufficiency will be different.

Because of the possibility that the co-existing venous disease will affect the results obtained, the presence or absence and type of venous disease was considered during the experiments for validation of the two-pool haemodynamic model.

C H A P T E R 5

METHODS FOR THE VALIDATION OF THE HAEMODYNAMIC MODEL

5.1 INTRODUCTION

The methods used for the validation of the haemodynamic model are described in this Chapter.

The ^{99m}Tc muscle clearance method was used as a measure of flow and particularly to determine changes in flow that occur during exercise. Ankle systolic pressure measurements were carried out by using cuffs and Doppler ultrasound to detect flow in the posterior tibial artery. The Doppler ultrasound was also used to determine the presence of reflux at the saphenofemoral and saphenopopliteal junctions and in the popliteal vein. Ambulatory venous pressure measurements were carried out to determine the presence of venous insufficiency and to differenciate between deep and superficial venous insufficiency. Finally, aortography and ascending venography were employed on arterial and some venous patients respectively.

5.2 METHODS EMPLOYED, CALCULATION AND EXPRESSION OF RESULTS

5.21 Procedure

Forty μCi of ^{99m}Tc as sodium pertechnate diluted in 0.2 ml of saline were injected into the thickest part of both gastrocnemius muscles, the patient being in bed. A sharp needle was used with an external diameter of 0.4 mm. The needle was inserted at an angle of 45^{o} to the skin and to a depth of 3 cm. The plunge of the syringe was withdrawn each time before injection in order to ensure that intravascular administration of the radioactive material did not occur. The point of the injection was marked to enable accurate replacement of the probes. The patient then stood up steadying himself against a horizontal bar (Fig. 5.1 and 5.2). The probes of two Pitman 235-isotope

localisation monitors were placed at a constant distance from the skin over the site of the injections. Care was taken so that the limbs were always placed apart in order to avoid any interaction from the two radiation sources and full collimation was used (collimators in the extended position). The output from the detectors was recorded continuously on a double-pen CR-552 recorder (Figs. 5.1 and 5.2).

All patients rested for 20 minutes in a constant room temperature ($26^{o}C$) before starting the test. Clearance curves were obtained in the standing position for 5 minutes at rest; the patient was then asked to exercise by going up on tiptoe as high as possible and down again at 2-second intervals keeping the knees straight (Fig. 5.3). Initially he was asked to carry out 5, 10 and 20 movements respectively leaving adequate rest intervals, three to five minutes, between each session so that the post-exercise hyperaemic response could subside and resting clearance levels re-establish themselves. The radioactivity was recorded continuously during the 5, 10 and 20 movements of tiptoe and during the resting intervals. The above sequence was repeated twice after the patient remained standing motionless for 5 minutes.

Each movement consisted of two components:

(a) the upward component on tiptoe which was characterised by a rapid fall of the recording pen towards the base-line. This was due to an increased distance of the radiation sources away from the probes.

(b) the downward component (i.e. the heel on the ground) which was characterised by a rapid reversed movement of the recording pen away from the baseline which was due to the return of the radiation sources to the original

distance from the probes. However, the recording pen was steadying itself at a lower level at the end than at the beginning of any session of 5, 10 and 20 movements, the difference being proportional to the amount of radioactivity cleared during the exercise (Figs. 5.4a, 5.4b and 5.4c).

When the light (80g) probes and the Dual Channel Analysers (Model 45-24) became available they were used instead of the Pitman isotope localisation monitors. The same procedure already described was used (Figs. 5.5 and 5.6) but they gave a much smoother clearance curve (Fig. 5.7). In 5 patients both instruments (235-isotope localisation monitors and Dual Channel Analyser) were used simultaneously. The parameters a, Q_0 and λ were found to be the same (see Appendix A13) (Fig. 5.7).

5.22 Calculation and Expression of Results

From the clearance curves obtained the total percentage clearance (D_5, D_{10} and D_{20}) during 5, 10 and 20 tiptoe movements respectively was calculated as shown in figure 5.8. From these measurements a, Q_0 and λ were calculated using the equations developed in the previous chapter (Ch.4, p.102). Thus,

$$a = \frac{63D_{20} - 466D_{10} + 900D_5}{250(9D_5 - 2D_{10})} \qquad (4.20)$$

$$Q_0 = \frac{K\,D_5(10a-1+\beta^{10}) - D_{10}(5a-1+\beta^5)}{(1-\beta^5)(10a-1+\beta^{10}) - (1-\beta^{10})(5a-1+\beta^5)} \qquad (4.21)$$

$$\lambda = \frac{[KD_5 - Q_0(1-\beta^5)]}{10a} \qquad (4.22)$$

The partition coefficient of ^{99m}Tc for muscle is 0.8 (Veal, 1977). Since $K \propto Q_o$ [see equation (4.21)] a 10 per cent error in K leads to only 10 per cent error in the estimation of the amount of blood in pool 2 (Fig. 4.1).

Q_n, Qfinal, n and W_n were calculated using the equations developed in Section 4.21. Thus,

$$Q_n = Q_o.\beta^n + \frac{\lambda}{a}(1-\beta^n) \qquad (4.10)$$

$$Qfinal = \frac{\lambda}{a} \qquad (4.23)$$

$$n \geq \frac{\log(\frac{\lambda}{a}) + \log(1-e) - \log(\frac{\lambda}{a} - Q_o)}{\log \beta} \qquad (4.31)$$

and $$W_n = n\lambda + Q_o - Q_n \qquad (4.11)$$

For the calculations of n, e in equation 4.31 was taken to be 0.9 (90 per cent).

5.3 PRESSURE MEASUREMENTS, PROCEDURE AND EXPRESSION OF RESULTS

5.31 Theoretical Considerations

In theory, the values of pressure P_5, P_{10} and P_{20} measured at the end of five, ten and twenty tiptoe cycles can be introduced instead of the total percentage clearance D_5, D_{10} and D_{20} measured during the same cycles respectively. However, in practice this is not possible for the following reasons:

Let, pressure after r movements on tiptoe be P_r. Let V_o be the volume of the arteries at rest and V_r be the "steady-state" volume which

is reached at the r^{th} movement on tiptoe. Similarly, let Q_o be the amount of blood in the arteries at rest and Q_r be the amount of blood in the arteries at the r^{th} movement on tiptoe.

P_r is a function of V_r and Q_r. Since,

$$V_r = C_r \cdot V_o$$

and

$$Q_r = K_r \cdot Q_o$$

where C_r and K_r are unknown constants, it can be deduced that P_r cannot be derived and thus pressures cannot be readily used in the haemodynamic model to determine a, Q_o and λ.

5.32 Procedure and Expression of results

Two 15 cm cuffs were applied around the ankles, 2 cm above the malleoli. By using two Parks-806 directional Doppler probes to detect flow in the posterior tibial arteries ankle systolic pressures were measured at rest (P_R) and after five (P_5), ten (P_{10}) and twenty (P_{20}) movements on tiptoe. Measurements were carried out simultaneously with the help of Mrs R. Bowers, an experienced technician of the Vascular Laboratory. If pressure was decreased below the resting level after any session of tiptoeing, measurements were continued at one-minute intervals until recovery of pressure occurred.

In the present study the absolute values of the ankle systolic pressure were used.

5.4 VENOUS DOPPLER ULTRASOUND

An 806-directional Doppler ultrasound (see Appendix A6) was

used to determine the presence of reflux at the saphenofemoral and saphenopopliteal junctions and in the popliteal vein.

The patients were examined standing. The probe was positioned over the femoral vein at the groin. This position was determined by localising the femoral artery and then by moving the probe medially until the typical venous flow was heard on manual compression of the thigh. The probe was adjusted so that the maximum audible signal was obtained. The changes of respiration, on valsalva manoeuvre and on manual calf compression and release were noted. Reflux at the saphenofemoral junction was diagnosed if there was retrograde flow during the valsalva manoeuvre and on release of calf compression provided this reflux was abolished by compression of the long saphenous vein at mid-thigh. The probe was then placed behind the knee which was slightly flexed while the patient's weight was on the opposite limb. The position of the probe was adjusted so that the signal from the popliteal artery was audible in addition to the signal from the popliteal vein on calf compression. The presence of retrograde flow on release of calf compression which was not abolished by digital compression of the short saphenous vein, indicated incompetence of the popliteal valves. Retrograde flow on calf release which was abolished by digital compression of the short saphenous vein indicated reflux at the saphenopopliteal junction.

5.5 AMBULATORY VENOUS PRESSURE MEASUREMENT PROCEDURES

A 21G (bore 20G) "butterfly" needle was inserted into a vein on the dorsum of the foot and was connected through an Akers transducer (Model 840) and a B.A.P. 001 amplifier to a potentiometric pen recorder (J. and J. Instruments, Model CR552mK2).

Venous pressure was measured with the patient standing still and then doing a tiptoe exercise for 30 seconds at a rate of one heel raising movement per second. This was repeated once after inflating a 2.5 cm pneumatic cuff at the ankle to a pressure of 140 mm Hg and a second time after inflating a 2.5 cm pneumatic cuff at the thigh to a pressure of 180 mm Hg. It has been demonstrated that the above pressures will allow occlusion of the superficial veins only, because of the small width of these cuffs (Nicolaides et al, 1971).

5.6 ASCENDING VENOGRAPHY

Ascending venography was done in order to determine the presence or absence of deep venous occlusion (Craig, 1977). All ascending venograms were performed by Dr D. Sutton.

CHAPTER 6

CLINICAL STUDIES FOR THE VALIDATION OF THE HAEMODYNAMIC MODEL

6.1 INTRODUCTION

The purpose of the clinical studies presented in this Chapter was:

1. to validate the haemodynamic model (see Section 4.2) by testing it on normal volunteers and on patients with peripheral arterial disease in the presence or absence of venous disease,

2. to investigate the haemodynamic changes that occur during exercise in normal and arteriosclerotic limbs, and

3. to study the effect that external compression has on the two-pool haemodynamic model in limbs with venous insufficiency.

6.2 CLINICAL STUDY V: VALIDATION OF THE TWO-POOL HAEMODYNAMIC MODEL

6.21 Aims

The aim of this study was:

(a) to validate the two-pool haemodynamic model,

(b) to investigate the haemodynamic changes that occur during exercise in limbs with single and combined arterial lesions, and

(c) to determine the diagnostic and clinical value of these measurements.

The following questions were posed:

(k) *Are the results of the measurements made compatible with the haemodynamic model?*

(l) *Can the two-pool haemodynamic model provide any useful information about blood flow in normal limbs and in limbs with peripheral arterial disease?*

(m) *Are the changes in pressure that have occurred compatible with the changes in flow detected?*

6.22 Material

18 healthy volunteers (29 limbs) and 56 patients (78 limbs) with peripheral vascular disease were studied. The normal volunteers were selected using the following criteria:

(a) the ankle systolic pressure was increased after a 3-minute walk on the treadmill at 4.5 Km per hour (see Section 2.4), and

(b) the post-exercise pressure index was greater than the resting pressure index.

The patients with peripheral arterial disease had been admitted to hospital for aortography as part of their routine management.

Limbs were graded into five groups:

Group 0 (normal limbs). In this group 29 limbs of 18 normal volunteers were selected according to the criteria mentioned above. The mean age of the normal volunteers was 23 ± 2.8 years.

Group Aa (limbs with iliac occlusion only). In this group 25 limbs of 17 patients were included. Femoral pulses were weak or absent and iliac occlusion was shown on the aortogram. The patients' mean age was 60 ± 3.2 years.

Group Ba (limbs with superficial femoral artery occlusion only). In this group 22 limbs of 15 patients were included. Pulses over the posterior tibial and dorsalis pedis arteries were absent. An occlusion of the superficial femoral artery longer than 10 cm was shown on the aortogram. Patients' mean age was 55 ± 4.2 years.

Group Ca (limbs with combined aortoiliac and femoropopliteal occlusions). In this group, 7 limbs of 7 patients were carefully selected so that both the aortoiliac and femoropopliteal segments showed occlusions on the aortogram. Femoral pulses were weak or absent while the pulses over the posterior

tibial and dorsalis pedis arteries were always absent. The patients' mean age was 59.2 ± 5.7 years.

Group Da (limbs with combined aortoiliac and femoropopliteal stenoses). In this group 24 limbs of 20 patients were included. Femoral pulses were normal or weak, while pulses over the posterior tibial and dorsalis pedis were either weak or absent. Combined aortoiliac and femoropopliteal stenoses of various degrees were shown on the aortogram. The patients' mean age was 51 ± 9.8 years.

All limbs were studied by ^{99m}Tc muscle clearance in the calf as described in Chapter 5 (see Section 5.2) and a, Q_o, λ, Q_n, Qfinal and n were calculated. For the calculations of n, e in equation 4.31 (see p.104) was taken to be 0.9 (90 per cent).

Ankle systolic pressures were also measured using the procedure described in Section 5.32 (p.111).

Finally, the presence of venous disease was excluded by Doppler Ultrasound using an 806 directional Doppler (Lewis and Yao, 1974). One limb of a normal volunteer and one limb of a patient with peripheral arterial disease had incompetence of the saphenofemoral junction and were not included in this study.

6.23 Results

The mean values of a and standard deviation in the five groups studied (Fig.6.1) were as follows:

Group O: 0.09 ± 0.03 (9 ± 3.2 per cent);

Group Aa: 0.12 ± 0.04 (12 ± 4.5 per cent);

Group Ba: 0.18 ± 0.03 (18 ± 3.4 per cent);

Group Ca: 0.22 ± 0.03 (22 ± 3.8 per cent)

and in Group Da: 0.16 ± 0.05 (16 ± 5.9 per cent).

The mean values of Q_o and standard deviation (Fig. 6.2) were:

Group O: 19.10 ± 1.80 ml per 100 ml of tissue;

Group Aa: 9.95 ± 1.93 " " " "

Group Ba: 3.75 ± 1.15 " " " "

Group Ca: 0.45 ± 0.31 " " " "

and in Group Da: 12.4 ± 4.2 ml per 100 ml of tissue.

The mean values of λ and standard deviation (Fig. 6.3) were as follows:

Group O: 2.10 ± 0.32 ml per 100 ml of tissue per tiptoe cycle

Group Aa: 0.72 ± 0.12 " " " " " " "

Group Ba: 0.41 ± 0.14 " " " " " " "

Group Ca: 0.07 ± 0.03 " " " " " " "

and in Group Da: 0.64 ± 0.48 ml per 100 ml of tissue per tiptoe cycle.

The results demonstrated that a better separation of the 5 groups (O to Da) was produced by Q_o and λ than a (Figs.6.1 to 6.3). In order to show the overlap between Groups O to Da the median and 95 per cent tolerance levels of Q_o and λ were calculated and are shown in figures 6.4 and 6.5.

By plotting the values of Q_o against the values of λ as a form of bivariate analysis (Fig. 6.6) the 5 groups were separated:

Normal limbs (Group O) and limbs with combined aortoiliac and femoropopliteal occlusions (Group Ca) were distributed along a straight

line (Fig. 6.6). The distribution of limbs with iliac occlusion only (Group Aa) and of limbs with superficial femoral artery occlusion only (Group Ba) was such that a "body" and two "tails" were formed graphically (Fig. 6.6). The great majority of limbs formed the "body" of each group (Aa and Ba). These limbs had aortographically a long occlusion of the iliac and of the superficial femoral arteries respectively. One of the "tails" was moving away from the "body" along the Q_o axis. Limbs forming this "tails" had aortographically a short proximal occlusion of the common iliac and of the superficial femoral arteries respectively. The other "tail" was parallel to the λ axis (Fig. 6.6). This "tail" was formed by limbs which had aortographically a long occlusion of the iliac and superficial femoral arteries respectively but with poor development of collaterals. Finally, limbs with combined aortoiliac and femoro-popliteal stenoses (Group Da) were distributed in a separate but broad area of the graph (Fig. 6.6).

The values of a, Q_o and λ in Group 0 (normal limbs) are shown in Table 6.1. The extent of the arterial lesion and the degree of stenosis according to lumbar aortography in relation to the values of a, Q_o and λ for every limb studied are shown in Table 6.2.

The mean values of a, Q_o and λ ($\bar{a}$, $\bar{Q}_o$ and $\bar{\lambda}$) for Groups 0 to Ca were used in order to calculate the mean values of Q_n ($\bar{Q}_n$) per tiptoe cycle. This is shown in figure 6.7 for Group 0 (normal limbs); in figure 6.8 for Group Aa (limbs with iliac occlusion only); in figure 6.9 for Group Ba (limbs with superficial femoral artery occlusion only) and in figure 6.10 for Group Ca (limbs with combined aortoiliac and femoro-popliteal occlusions). From these measurements the mean value of Qfinal ($\bar{Q}$final) and the mean number of tiptoe movements ($\bar{n}$) after which Qfinal was reached were also calculated. In normal limbs (Group 0), $\bar{Q}_n$ increased

and $\overline{Q}$final was reached by the seventh tiptoe cycle (Fig. 6.7). In limbs with peripheral arterial occlusions (Groups Aa, Ba and Ca), $\overline{Q}_n$ decreased during exercise irrespective of the site of the arterial occlusion. In Group Aa, $\overline{Q}$final was reached after 16 tiptoe cycles (Fig. 6.8); in Group Ba after 9 cycles (Fig. 6.9) and in Group Ca after 7 (Fig. 6.10). In limbs with combined aortoiliac and femoropopliteal stenoses (Group Da) $\overline{Q}_n$ and $\overline{Q}$final were not calculated because the means of a, Q_o and λ had very large standard deviations.

The mean values ($\overline{P}_R$, $\overline{P}_5$, $\overline{P}_{10}$ and $\overline{P}_{20}$) of the ankle systolic pressures P_R, P_5, P_{10} and P_{20} calculated in the five groups studied (O to Da) are shown in Figure 6.11. In Group O (normal limbs), $\overline{P}_5$ and $\overline{P}_{10}$ were greater than $\overline{P}_R$; in contrast $\overline{P}_{20}$ was slightly lower than $\overline{P}_R$. The latter resulted from a decrease in P_{20} observed in 32 per cent of the normal limbs studied (Table 6.3). In limbs with peripheral arterial disease, although $\overline{P}_5$, $\overline{P}_{10}$ and $\overline{P}_{20}$ were lower than $\overline{P}_R$ they showed a different pattern of decrease: In Group Aa (limbs with iliac occlusion only), they showed a step-ladder distribution [$\overline{P}_5 > \overline{P}_{10} > \overline{P}_{20}$]; in Group Ba (limbs with superficial femoral artery occlusion only) there was a rapid decrease in $\overline{P}_{10}$ but no significant difference between $\overline{P}_{10}$ and $\overline{P}_{20}$ [$\overline{P}_5 > \overline{P}_{10} \simeq \overline{P}_{20}$]; in Group Ca (limbs with combined aortoiliac and femoropopliteal occlusions) there was a rapid decrease in $\overline{P}_5$ but no significant difference between $\overline{P}_5$, $\overline{P}_{10}$ and $\overline{P}_{20}$ [$\overline{P}_5 \simeq \overline{P}_{10} \simeq \overline{P}_{20}$); finally, in limbs with combined aortoiliac and femoropopliteal stenoses (Group Da), a pattern similar to Group Ba was found, but with an overall higher pressure (Fig. 6.11).

The values of P_R, P_5, P_{10} and P_{20} for every limb studied in relation to the values of a, Q_o and λ are shown in Table 6.3.

6.24 Discussion

(k) *Are the results of the measurements made compatible with the two-pool haemodynamic model?*

The results demonstrated that the two-pool haemodynamic model is valid for single occlusive lesions and can provide information of the haemodynamic changes that occur in the lower limbs. In such limbs, the site of the arterial occlusion determines the amount of blood (Q_o) between the arterial lesion and the site of the injection expressed in ml per 100 ml of tissue. The greater the value of Q_o the more proximal is the arterial occlusion. Similarly, the degree of the collateral circulation and thus the severity of the arterial occlusion determines the amount of blood (λ) through the collaterals expressed as ml of blood that flows into 100 ml of tissue per tiptoe cycle. The higher the value of λ the greater is the degree of the collateral circulation (more proximally situated and shorter occluded segment). Thus the two-pool haemodynamic model apart from the anatomical information about the site of a single arterial occlusion may provide functional information about the collateral circulation.

In limbs with double arterial lesions which include Group Ca and Da, it was difficult to predict the site and severity of each arterial lesion exactly (Fig. 6.6). In these limbs, the proximal pool of the two-pool haemodynamic model is not infinite as described in Section 4.21. The capacity of this pool can take any value and so can λ. The magnitude will depend on the severity of the proximal lesion and the change occurring in thigh pressure. For this reason the two-pool haemodynamic model is not applicable to limbs with combined aortoiliac and femoropopliteal lesions and can provide only functional information of an apparent single lesion causing the observed change in ^{99m}Tc

clearance. To separate limbs with double lesions from normal limbs and from limbs with single lesions it is essential to analyse a three-pool haemodynamic model (see Section 4.21) which will require the recording of changes in flow in the thigh and in the calf simultaneously. (Appendix A15).

By using the two-pool haemodynamic model absolute values of blood flow are obtained. These depend on the value of the muscle to blood partition coefficient (K) for ^{99m}Tc which is taken to be equal to 0.8 (Veal, 1977; see also Appendix A12). Since the amount of blood (Q_o) in pool 2 is proportional to K (see equation 4.21) a 10 per cent error in K can lead to only a 10 per cent error in the estimate of Q_o and therefore cannot alter the significance of the results.

(1) *Can the two-pool haemodynamic model provide any information concerning the haemodynamic changes of blood flow in normal limbs and in limbs with peripheral arterial disease?*

It has been demonstrated (see Section 6.23) that in both normal and arteriosclerotic limbs rapid changes in flow occur during the initial tiptoe cycles until a steady state of flow is reached (Figs. 6.7 - 6.10). In normal limbs, the amount of blood Q_n at the end of each tiptoe cycle is greater than the initial amount of blood Q_o ($Q_n > Q_o$) (Fig. 6.7). In contrast, in arteriosclerotic limbs Q_n is less than Q_o ($Q_n < Q_o$) (Figs. 6.8 - 6.10).

Irrespective of the presence or absence of arterial disease, Q_n will change for a limited number, n, of tiptoe cycles until a steady value (Qfinal) is reached. This suggests that after a certain number of

tiptoe cycles very small changes in flow would occur during the remaining period of the exercise. In arteriosclerotic limbs, the number of tiptoe cycles which, are needed so that Qfinal is reached, is related to the capacity of pool 2 in the two-pool haemodynamic model and thus to the site of the arterial lesions (Fig. 6.8 - 6.10).

In normal limbs, the increase in the amount of blood in pool 2 at the beginning of the exercise occurs because there is less blood leaving than entering it (Table 6.4). The amount of blood entering is 2.1 ml per 100 ml of tissue per tiptoe cycle, while the amount of blood leaving during the first cycle is only 1.7 ml per 100 ml of tissue; thus, the amount of blood in pool 2 will increase from 19 ml per 100 ml of tissue at rest to 23 ml per 100 ml of tissue when a steady state will be reached. At this stage the amount of blood leaving per cycle will be $\overline{a} \times \overline{Q}$final i.e. 0.09 x 23 = 2.1 ml per 100 ml of tissue which is the same amount of blood that is entering pool 2 per tiptoe cycle (Table 6.4).

In arteriosclerotic limbs, the decrease in the amount of blood in pool 2 at the beginning of the exercise occurs because there is more blood leaving than entering it (Table 6.4). In limbs with iliac occlusion the amount of blood entering pool 2 ($\overline{\lambda}$) is 0.7 ml per 100 ml of tissue per tiptoe cycle, while the amount leaving during the first cycle is 1.2 ml per 100 ml of tissue; thus, the amount of blood in pool 2 will decrease from 10 ml per 100 ml of tissue at rest to 5.83 ml per 100 ml of tissue when a steady state will be reached. At this stage the amount of blood leaving per cycle will be the same as the amount of blood entering in pool 2 (Table 6.4). The changes that occur in Groups Ba and Ca can be explained along similar lines (Table 6.4).

(m) *Are the changes in pressure that have occurred compatible with the changes in flow detected?*

The increase in ankle systolic pressure that occurred in the normal limbs and the decrease observed in the arteriosclerotic limbs was noted during the early stages of the exercise before a steady state (Qfinal) was reached. The step-ladder decrease in pressure observed in limbs with aortoiliac occlusion is associated with the 16 tiptoe cycles required for a steady flow to be reached. In contrast, the rapid fall in pressure after 10 tiptoe cycles in limbs with single femoropopliteal occlusion and after 5 tiptoe cycles in limbs with combined aortoiliac and femoropopliteal occlusions is associated with the 9 and 7 tiptoe cycles required respectively for the Qfinal to be reached. In these limbs the steady state flow and steady state pressure were reached simultaneously.

In normal limbs, although there is an increase in ankle systolic pressure during the initial tiptoe cycles, a decrease finally occurs irrespective of the steady state value (Qfinal) of blood flow. This may be the result of a similar fall in the peripheral resistance but cannot be explained by the present haemodynamic model. Such a fall in ankle systolic pressure was not observed in normal limbs after a 3-minute walk on the treadmill (see Section 3.231). This may be associated with the fact that pressure measurements after tiptoeing were carried out immediately at the end of the exercise. Such a small transient fall in ankle systolic pressure in the first 30 seconds after severe exercise has been observed in normal limbs by others (Lassen, 1967; 1978).

6.3 CLINICAL STUDY VI: EFFECT OF VENOUS INSUFFICIENCY ON THE TWO-POOL HAEMODYNAMIC MODEL

6.31 Aim

It has been mentioned (see Section 4.22) that in the presence of venous insufficiency it is very probable that the measurements of λ will be affected because the inefficient muscle pump will not produce the high arteriovenous gradient found in normal limbs.

The aim of this study was to test the effect of venous insufficiency on the measurements of a, Q_o and λ in patients with normal arterial tree but with various degrees of venous insufficieny and in patients with combined arterial and venous diseases.

The following question, n, was posed:

(n) *What is the effect of venous insufficiency on the measurements of a, Q_o and λ in patients with normal or abnormal arterial tree?*

6.32 Material

32 patients (37 limbs) with normal arterial tree but with various degrees of venous insufficiency and 4 patients (4 limbs) with combined arterial and venous disease were studied.

The presence of arterial disease was excluded using the criteria mentioned in Section 5.22. Thus, (1) the ankle systolic pressure was increased after a 3-minute walk on the treadmill at 4.5 Km per hour and (2) the post-exercise pressure index was greater than the resting pressure index.

Patients with a normal arterial tree but with various degrees of venous insufficiency were graded into the following 3 groups:

Group Va: In this group 10 patients (15 limbs) were included. They had superficial venous insufficiency, i.e. saphenofemoral incompetence and varicose veins of the long saphenous system. The diagnosis was based on the following grounds: (1) veins were controlled by high thigh tourniquet; (2) Doppler ultrasound confirmed the presence of saphenofemoral incompetence and the absence of reflux at the saphenopopliteal junction; and (3) ambulatory venous pressure measurements showed moderate fall in pressure during exercise to a mean of 45mm Hg; on application of an ankle tourniquet to exclude the superficial veins ambulatory venous pressures showed a fall to less than 30mm Hg.

Patients' mean age was 28.0 ± 4.3 years.

Group Vb: In this group 12 patients (12 limbs) were included. They had saphenofemoral incompetence and incompetent calf perforating veins. The diagnosis was made by the fact that (1) the veins were not controlled by a high thigh tourniquet, a low thigh tourniquet nor a tourniquet just below the knee; (2) Doppler ultrasound confirmed the presence of reflux at the saphenofemoral junction and the absence of reflux at the saphenopopliteal junction; (3) finally, confirmation of the presence of incompetent calf perforating veins was obtained by venography.

Patients' mean age was 39.0 ± 5.2 years.

Group Vc: In this group 10 patients (10 limbs) were included. They

had deep venous incompetence. This was diagnosed on the following grounds: (1) all patients had a history of post-phlebitic limb; (2) Doppler ultrasound confirmed the presence of a marked reflux in the popliteal vein even after digital compression of the short saphenous vein; (3) ambulatory venous pressure measurements showed a high ambulatory venous pressure, greater than 60mm Hg even after occlusion of the superficial veins by a narrow cuff and (4) all patients had a venogram which demonstrated irregular deep veins. This irregularity suggested old thrombosis and recanalisation.

Patients' mean age was 47 ± 4.6 years.

The presence of arterial disease was based on the following grounds: (1) the ankle systolic pressure was decreased after a 3-minute walk on the treadmill; (2) the post-exercise pressure index was lower than the resting pressure index and (3) the diagnosis was confirmed by an aortogram which was used as the objective arbiter of the state of the arteries.

Patients with combined arterial and venous diseases formed the following group:

Group Vd: In this group 4 patients (4 limbs) were included. 3 out of 4 limbs studied had iliac occlusion only; the remaining one limb had a long superficial femoral artery occlusion shown on the aortogram. All the limbs studied had saphenofemoral incompetence and incompetent calf perforating veins. The diagnosis of the venous disease was made on the grounds mentioned in Group Vb, thus (1) the veins were not controlled by a high thigh tourniquet, a low thigh tourniquet nor a

tourniquet below the knee; (2) Doppler ultrasound confirmed the presence of reflux at the saphenofemoral junction but not at the saphenopopliteal junction; and (3) venography confirmed the presence of incompetent perforating veins. Patients' mean age was 51 ± 4.2 years.

All limbs were studied by the ^{99m}Tc muscle clearance method in the calf as described in Chapter 5 (see Section 5.2) and a, Q_o and λ were calculated.

6.33 Results

The results are shown in figure 6.12. They demonstrate that λ was affected by the venous disease despite the presence or absence of arterial lesions, whereas a and Q_o remained unchanged.

The mean value and standard deviation of λ was 1.90 ± 0.23 in Group Va (limbs with normal arterial tree and superficial venous insufficiency); 1.10 ± 0.34 in Group Vb (limbs with normal arterial tree, saphenofemoral incompetence and incompetent calf perforating veins); 0.32 ± 0.26 in Group Vc (limbs with normal arterial tree and deep venous incompetence) and -1.32 ± 0.56 in Group Vd (limbs with combined arterial and venous disease).

By plotting the values of λ against the values of Q_o for each limb studied Figure 6.12 is obtained. In this figure the position of Groups 0 (normal limbs), Aa (limbs with iliac occlusion only) and Ba (limbs with superficial femoral artery occlusion only) of the previous study V (see Section 6.2) are also included as shaded areas. In limbs with normal arterial tree and superficial venous insufficiency (Group Va) λ was slightly diminished in comparison to normal limbs (Group 0); it was

moderately diminished in limbs with normal arterial tree, saphenofemoral incompetence and incompetent calf perforating veins (Group Vb); finally, it was markedly diminished in limbs with a normal arterial tree and deep venous insufficiency (Group Vc). In all these limbs Q_0 was not affected by the presence of venous disease.

In the 4 limbs studied with combined arterial and venous diseases (Group Vd)(limbs No 38, 39, 40, 41 in Fig. 6.12) the findings suggested that in the presence of venous disease λ was also affected whereas Q_0 remained unchanged. In all these limbs, λ showed a negative value (Fig. 6.12). Thus, limbs No 38, 39 and 40 with iliac occlusion only should have been in the position occupied by Group Aa and limb No 41 with superficial femoral artery occlusion only should have been in the position occupied by Group Ba (Fig. 6.12).

6.34 Discussion

(n) *What is the effect of venous insufficiency on the measurements of a, Q_0 and λ in patients with normal or abnormal arterial trees?*

The results demonstrated that a and Q_0 are not affected, but λ is.

In limbs with a normal arterial tree but with various degrees of venous insufficiency the fall in λ might be the result of an increase in venous pressure during exercise, which in turn decreases the arteriovenous gradient.

Because only 4 limbs with combined arterial and venous diseases have been studied the results should be viewed with caution. However, they suggest that venous disease may result in a lower value of λ. The

negative values of λ obtained may well be the result of a negative arteriovenous gradient due to an ambulatory venous pressure higher than the arterial.

Further studies are required to confirm this.

The results also suggest that the two-pool haemodynamic model can be used as a diagnostic test in the absence of venous disease only. In the presence of venous disease it may be impossible to distinguish the existence of a second arterial lesion because there will be an overlap with Group Da (limbs with combined aortoiliac and femoropopliteal stenoses)(see Section 6.23).

6.4 CLINICAL STUDY VII: EFFECT OF EXTERNAL COMPRESSION ON THE TWO-POOL HAEMODYNAMIC MODEL IN LIMBS WITH VENOUS INSUFFICIENCY

6.41 Aim

It has already been shown (see Section 6.3) that in the presence of venous insufficiency the measurements of λ are probably affected because the inefficient muscle pump is unable to produce the high arteriovenous gradient found in normal limbs.

The last study (VII) was an attempt to test the effect of external compression on the measurements of a, Q_o and λ in patients with a normal arterial tree and various degrees of venous insufficiency.

The following question, o, was posed:

(o) *What is the effect of external compression on the measurements of a, Q_o and λ in limbs with a normal arterial tree and various degrees of venous insufficiency?*

6.42 Material and Methods

8 patients (8 limbs) which were included in the previous study were selected. Four of the limbs belonged in Group Vb; they had saphenofemoral imcompetence and incompetent calf perforating veins (limbs No.16, 18, 25 and 27 in Fig. 6.12). The remaining 4 limbs belonged in Group Vc; they had deep venous incompetence (limbs No.28, 30, 33 and 37 in Fig. 6.12).

Every limb was studied before and after the application of two elastic bandages 10" wide using the procedure described in Section 4.31. The bandages were applied on the whole limb firmly starting from the toes

up to the groin after the patient had been rested horizontally for 20 minutes with a 45^{o} leg elevation.

From the clearance curves obtained before and after the application of the external support a, Q_o and λ were calculated according to equations 4.20, 4.21 and 4.22 respectively (see Chapter 5, Section 5.2).

6.43 Results

The results are demonstrated in Table 6.5. They showed that the values of a and Q_o were not affected by the external compression. In contrast, λ was increased after the application of external support both in limbs with saphenofemoral incompetence combined with incompetent perforating veins and in limbs with deep venous insufficiency.

In order to demonstrate the results graphically as a form of bivariate analysis the values of Q_o before and after the application of external compression were plotted against the relative values of λ. This is shown in Figures 6.13a and 6.13b. The position of the limbs before the application of the external support is demonstrated in figure 6.13a, whereas in Figure 6.13b the position of the limbs after the application of external compression is shown. In these figures the position of normal limbs (Group 0)(see Section 6.22) is also included as a shaded area. The effect that external compression had on λ was to move the 8 limbs upwards, bringing them nearer to the shaded area (Fig. 6.13b).

6.44 Discussion

(o) *What is the effect of external compression on the*

measurements of a, Q_o and λ in limbs with a normal arterial tree and various degrees of venous insufficiency?

The results of this pilot study showed that a and Q_o are not affected by the application of external support but λ is. It has been suggested (see Section 6.3) that in limbs with venous insufficiency the fall in λ is the result of a low arteriovenous gradient found in these limbs. The increase in λ after the application of external compression may be the result of a relative increase in the arteriovenous gradient.

Further studies should be undertaken to determine the effect that elastic support may have on the measurements of a, Q_o and λ.

P A R T IV

GENERAL COMMENTS
AND CONCLUSIONS

C H A P T E R 7

GENERAL DISCUSSION, CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK

In this chapter the results from the various studies presented in this thesis are discussed as a whole, with recommendations of possible directions that future research should follow.

A review of the literature in 1976, when the work for this thesis was commenced, revealed that although isotope clearance techniques in the muscles of the lower limb are well established (Kety, 1949; Walter, 1955; 1958; Lassen et al., 1964; Lassen and Kampp, 1965; Grimby et al., 1967; Albert et al., 1966, 1969; Sumner and Strandness, 1969; Gutajar et al., 1971), simultaneous clearance of radioactive isotopes from the thigh and calf muscles after exercise had not been studied previously. The results confirm the observation repeatedly made that in patients with claudication from arterial occlusion, resting muscle blood flow is not different from normal. However, of more interest are the changes described after exercise and the possible light they can throw on the mechanisms of claudication.

The indicator used in this thesis is ^{99m}Tc in the form of sodium pertechnate, because it is readily available and easy to handle. Although the use of 99m Tc does not permit the determination of muscle blood flow in absolute values (i.e. ml/100 ml of muscle/min) because its partition coefficient is not known, however, it allows the measurement of changes in flow in arbitrary units (T). Five patients (five limbs) have been studied on five consecutive days in order to determine the reproducibility of the method. The coefficient of variation was 12 per cent immediately after exercise when T was high (20 per cent/min) and 3 per cent at rest when T was low (3-4 per cent/min) (see Appendix A8). The validity of ^{99m}Tc as a local radioactive tracer for the measurement of the flow of blood was tested by comparing it to the results obtained by ^{133}Xe clearance at rest and after exercise in five healthy volunteers.

They were studied (5 limbs) by both isotopes on two consecutive days. Similar changes in flow were demonstrated by both isotopes for increases in T up to 15 per cent/min. For higher flows, which occurred during the first minute after exercise, the ^{99m}Tc was lower than ^{133}Xe by 20 per cent (see Appendix A9).

In order to explain the pattern of changes in flow obtained in Part II of the thesis the normal lower limb can be regarded haemodynamically as a "sandpipe system" in which pressure is maintained along the whole length of axial vessels and flow is fed out of these vessels into vascular beds of varying resistance.

When aortoiliac occlusion is present, the results suggest that the flow pattern is the same as in a normal limb, but is "throttled" by the occlusion and blood flow via the collateral circulation is insufficient to permit normal reactive hyperaemia.

When there is a femoropopliteal block only, the hyperaemia is normal in the thigh, but flow in the calf is unchanged initially and is followed by a delayed hyperaemia. The only conceivable explanation of the unchanged flow in the calf immediately after exercise when there is maximum vasodilation of the muscle bed in that area, is a fall in pressure in the axial vessels distal to the occlusion as demonstrated by the decrease in ankle systolic pressure noted in these patients (see Chapter 3, Clinical Study I). This in turn must by the consequence of a similar fall in the pressure gradient across the collateral circulation due to increased blood supplying the thigh whose vascular bed has a decreased resistance. As the hyperaemia in the thigh is

decreasing, there is an increase in the peripheral resistance of the thigh muscle bed which results in an increase in the pressure in the proximal part of the collateral circulation, thus restoring the pressure gradient across the collateral vessels. This then permits hyperaemia in the calf where maximum dilation is still present.

The changes that occurred in patients with combined aortoiliac and femoropopliteal lesions (see Chapter 3, Clinical Study 1) can be explained along similar lines. However, the aortoiliac lesion is responsible for an aortoiliac gradient which becomes even more pronounced immediately after exercise producing a lower pressure in the profunda, a prolonged reactive hyperaemia in the thigh and a more delayed onset of calf hyperaemia.

Therefore, the concept of calf claudication in femoropopliteal occlusion is of blood being "dumped" into a large vasodilated proximal muscle mass. The calf is deprived and can only begin to receive blood to permit it to clear the isotope as the hyperaemia in the thigh decreases.

The different values of the Hyperaemic Indices found in the four groups of limbs studied (see Chapter 3, Clinical Study 1) can be used in patients with claudication to determine whether the disease consists of a single lesion confined to either the femoropopliteal or the aortoiliac regions or if it is a double lesion involving both the femoropopliteal and aortoiliac segments. However, the patients studied were selected with occlusive disease which can be diagnosed clinically by the weak or absent pulses. It has been argued that it would be worth investigating to what extent the Hyperaemic Indices

could determine the site and severity of combined aortoiliac and femoropopliteal stenoses. It is for this reason that Clinical Study II was undertaken (see Chapter 3).

Although one is fully aware of the inherent error in grading lesions on single plane arteriography, the results suggest that the method used to express the Hyperaemic Indices in this study may provide a less invasive means of determining the site and functional severity of arterial lesions although it cannot match the definition of the anatomical extent shown on the arteriogram. Clinical Study III was designed to test this further (see Chapter 3).

The results of this study indicate that it is possible to predict the degree of stenosis in the femoropopliteal and aortoiliac segments, expressed as normal, less than 70 per cent stenosis, more than 70 per cent stenosis and occlusion with a high accuracy. In addition in patients with double segment disease, this method can determine which of the two is the more severe.

The results of the Clinical Studies I, II and III (see Chapter 3) led to the production of the diagnostic chart in figure 3.18. According to this chart it is possible to classify any limb with claudication to any of the 12 areas.

Finally, in Clinical Study IV (see Chapter 3) it was found that distinct and characteristic patterns of changes in flow exist during exercise also in normal limbs and in limbs with aortoiliac, femoropopliteal and combined aortoiliac and femoropopliteal lesions. The results demonstrated that the redistribution of blood started during exercise in limbs with superficial femoral

artery occlusion (Fig. 3.23) and in limbs with combined aortoiliac and femoropopliteal lesions (Fig. 3.25).

Although the original aim of the isotope studies described in Chapter 3 was to understand the haemodynamic changes that occur with exercise, the simultaneous clearance of ^{99m}Tc from the thigh and calf developed into a diagnostic test. However, the method is unnecessary in patients with arterial occlusions because the diagnosis can be made clinically. Single stenoses can be assessed by the degree of reduction of ankle pressures after exercise. The main value of the method may be in supplementing arteriography in patients with combined aortoiliac and femoropopliteal stenoses.

In Part III of the thesis a theoretical two-pool haemodynamic model was developed as a hypothesis concerning the haemodynamic changes which occur in the arterial system during tiptoeing (see Chapter 4). The two-pool hameodynamic model was then validated by testing it in normal volunteers and in patients with peripheral arterial and venous disease (see Chapters 5 and 6). The results demonstrate that the two-pool haemodynamic model is valid for single occlusive lesions and can provide information about the haemodynamic changes that occur in the lower limbs(Chapter 6, Clinical Study V). In such limbs, the site of the arterial occlusion determines the amount of blood (Q_o) between the arterial lesion and the site of the injection (Fig. 4.1) expressed as ml per 100 ml of tissue. The greater the value of Q_o the more proximal is the arterial occlusion. Similarly, the degree of the collateral circulation and thus the severity of the arterial occlusion determines the amount of blood (λ) through the collateral circulation (Fig. 4.1) expressed as ml

blood that flows into 100 ml of tissue per tiptoe cycle. The higher the value of λ the greater is the degree of collateral circulation (more proximally situated and shorter occluded segment). Thus, apart from the anatomical information about the site of a single arterial occlusion, the two-pool haemodynamic model may provide functional information about the collateral circulation.

The parameters Q_o and λ were obtained in absolute values by using the partition coefficient of ^{99m}Tc (K = 0.8). The partition coefficient K was taken to be 0.8 as suggested by Veal (1977). Experiments performed in healthy volunteers in whom blood flow in the calf at rest and after exercise was estimated using strain-gauge plethysmography and and ^{99m}Tc clearance simultaneously suggested that 0.8 was valid for the first 20 minutes after the injection of 40 µCi in the gastrocnemius (see Appendix A12). It has already been argued that a 10 per cent error in K can lead to only a 10 per cent error in the estimate of Q_o because Q_o is proportional to K (see equation 4.12). Therefore, an error in K cannot alter the significance of the results which are based on the changes rather than on the absolute values calculated.

The results demonstrated that in both normal and arteriosclerotic limbs rapid changes in flow occur during the initial tiptoe cycles until a steady state of flow is reached (Figs. 6.7 to 6.10). In normal limbs the amount of blood Q_n at the end of each tiptoe cycle is greater than the initial amount of blood Q_o ($Q_n > Q_o$) (Fig. 6.7). In contrast, in arteriosclerotic limbs Q_n is less than Q_o ($Q_n < Q_o$) (Figs. 6.8 to 6.10). Irrespective of the presence or absence of arterial disease, Q_n will change for a limited number, n,of tiptoe cycles until a steady value (Qfinal) is reached. The number of tiptoe cycles after which Qfinal is reached is related to the capacity of pool 2 in the two-pool model and

thus to the site of the arterial lesions (Figs. 6.8 to 6.10).

In normal limbs, the increase in the amount of blood in pool 2 at the beginning of the exercise occurs because there is less blood leaving than entering it (Table 6.4). The amount of blood entering pool 2 ($\bar{\lambda}$) is 2.1 ml per 100 ml of tissue per tiptoe cycle, while the amount of blood leaving during the first cycle ($\bar{W}_1 = \bar{a} \cdot \bar{Q}_o$) is only 1.7 ml per 100 ml of tissue. Thus, the amount of blood in pool 2 at rest ($\bar{Q}_o$) will increase from 19 ml per 100 ml of tissue to 23 ml per 100 ml of tissue when a steady state will be reached ($\bar{Q}$ final). At this stage the amount of blood leaving pool 2 per cycle will be Wf = $\bar{a}$ .Qfinal, i.e. 0.09 x 23 = 2.1 ml per 100 ml of tissue which is the same amount of blood that is entering pool 2 during each tiptoe cycle (Table 6.4).

In arteriosclerotic limbs the decrease in the amount of blood in pool 2 at the beginning of exercise occurs because there is more blood leaving than entering it (Table 6.4). In limbs with iliac occlusion the amount of blood entering pool 2 ($\bar{\lambda}$) is 0.7 ml per 100 ml of tissue per tiptoe cycle, while the amount leaving during the first cycle is 1.2 ml per 100 ml of tissue. Thus, the amount of blood in pool 2 at rest ($\bar{Q}_o$) will decrease from 10.0 ml per 100 ml of tissue to 5.38 ml per 100 ml of tissue when a steady state will be reached ($\bar{Q}$final). At this stage the amount of blood leaving per cycle will be the same as the amount of blood entering pool 2 (Table 6.4). The changes that occur in groups Ba and Ca can be explained along similar lines (Table 6.4).

The increase in ankle systolic pressure that occurred in normal limbs and the decrease in arteriosclerotic limbs were noted during the early stages of the exercise, before a steady state ($\bar{Q}$final) was reached. The step-ladder decrease in pressure observed in limbs with aortoiliac occlusion is associated with the 16 tiptoe cycles before the steady state

was reached. In contrast, the rapid fall in pressure after 10 tiptoe cycles in limbs with single femoropopliteal occlusion and after 5 tiptoe cycles in limbs with combined aortoiliac and femoropopliteal occlusions is associated with the 9 and 7 tiptoe cycles required respectively so that the Qfinal would be reached. In these limbs the steady state flow and the steady state pressure were reached simultaneously.

Although there is an increase in ankle systolic pressure during the initial tiptoe cycle in normal limbs, a decrease finally occurs irrespective of the steady value of blood flow (Qfinal). This cannot be explained by the present haemodynamic model. Such a fall in ankle pressure was not observed in normal limbs after a three minute walk on the treadmill (see Chapter 3). This may be associated with the fact that pressure measurements after tiptoeing were carried out immediately at the end of the exercise. Such a small transient fall in ankle systolic pressure in the first 30 seconds after severe exercise has been observed in normal limbs by others (Lassen, 1978).

In limbs with double arterial lesions (Groups Ca and Da) it is not possible to predict the site and severity of each arterial lesion (Fig. 6.6) (Chapter 6, Clinical Study V). In these limbs the proximal pool of the two-pool haemodynamic model is not infinite (Fig. 4.2). The capacity of this pool which lies between the two lesions can take any value and so can λ. The value of λ will depend on the severity of the proximal lesion and the thigh pressure. For this reason the two-pool haemodynamic model is not applicable to limbs with combined aortoiliac and femoropopliteal lesions and can provide functional information only of an apparent single lesion causing the observed change

in ^{99m}Tc clearance. For a better separation of limbs with double lesions from normal limbs and from limbs with single lesions it is essential to develop a three-pool haemodynamic model (Fig. A15.1) which will require the recording of changes in flow in the thigh and in the calf simultaneously. The information obtained from the simultaneous clearance studies from the thigh and calf (See Chapter 3) and from the validation of the two-pool model (See Chapters 4, 5 and 6) encouraged the author to proceed with the development of a three-pool model (See Appendix A15).

In summary, the work in this thesis has provided the author with a better understanding of the haemodynamic changes that occur in the arterial system during exercise. Also, it has led to the development of tests which may prove of clinical value. In addition, the findings have pointed the direction future work should take. These are as follows:

The three-pool haemodynamic model should be validated by doing the standard tiptoeing exercise of 5, 10 and 20 movements, as used in the two-pool model, with the measurement of the simultaneous clearance from the thigh and calf. The decrease in radioactivity during each one of the three exercises (5, 10 and 20 tiptoe movements) will provide three values for the thigh and three values for the calf from which the values of a, $\bar{a}$, b, Q_o U_o and λ can be calculated (see Appendix A15). Subsequently, the possibility of expanding the three-pool haemodynamic model to incorporate the venous system should be explored.

Further work is also necessary to see what useful information can be obtained from the simultaneous changes of flow in the thigh and calf during exercise. Should this be so it may then become unnecessary to

study the post-exercise hyperaemia.

The Hyperaemic Index was used throughout this thesis which is a measure of time. Therefore, it should be investigated whether $\frac{I}{2}$ (The time taken for the hyperaemic response to decrease to half its peak level) can give similar results. Also, it should be investiagted whether the Hyperaemic Index or $\frac{I}{2}$ from the thigh and calf can give similar results by using reactive hyperaemia with a cuff at the upper thigh.

Finally, a method that would allow the study of reactive hyperaemia without the injection of an isotope should be sought. Photoplethesmography is a new method that allows the non-invasive measurements of changes in skin blood flow and it follows that it will be well worthwhile studying the reactive hyperaemic response in the skin of thigh and calf simultanelously.

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