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Analysis of the Systemic Arterial Circulation
by a Square Wave Infusion Technique

By

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A Thesis submitted in partial fulfillment
of the requirements for the degree of

Doctor of Philosophy

in the

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ABSTRACT

An attempt has been made to analyse the physical properties of the systemic arterial circulation by a standard engineering approach (transient analysis). This involved giving a square wave infusion of blood and interpretation of the pressure response.

Development of a technique to give a square wave infusion of blood was required. This resulted in an infusion-giving apparatus which was composed essentially of a syringe whose action was controlled by a large, servo-controlled motor. The square wave effect was achieved by an electro-magnetic clutch-brake combination. The latter was capable of full activation within a 30 millisecond time interval. The whole apparatus was able to give a perfect square wave within the tolerance of these limits.

Approximately 5% of the animals blood volume was slowly withdrawn into the infusion giving apparatus through a cannula in the right carotid artery. On activation of the electro-magnetic clutch, this blood was returned to the rabbit in the form of a square wave over a 2 - 3 second period. During this period, the heart was transiently arrested by vagus nerve stimulation. The pressure response of the arterial system to this square wave infusion of known flow rate was monitored in the right femoral artery with a pressure transducer. By relating the input flow pattern to the output pressure response, information could be

obtained about the physical properties of the system.

Direct pressure-flow studies across the whole systemic arterial circulation were found to be linear in the range of 90 to 40 mm Hg pressure. A 'critical closing pressure' was invariably present, and found to vary in value from 10 to 50 mm Hg. This necessitated a modification in the normal method of calculating total peripheral resistance to account for the true slope of the pressure-flow plot (herein called 'slope' resistance). It was found that the mean chord resistance value in a 5 to 6 lb. rabbit was approximately twice the magnitude of the mean slope resistance value (0.33 to 0.17 mm Hg/ml/min). Furthermore, these did not always vary in the same direction when a variety of different stresses were imposed on the circulation.

Compliance value calculations demonstrated a hysteresis effect. The mean compliance value of the systemic arterial circulation in a 5 - 6 lb. rabbit measured during inflation was 0.037 ml/mm Hg: measured during deflation, it was 0.054 ml/mm Hg. There was good correlation between the compliance values measured by the square wave infusion method and by a method using excised lengths of aorta.

An inertial component was found to be present which had an approximate mean value of 30 gm cm^{-4} in 5 - 6 lb. rabbits.

The general response of the systemic arterial circulation to a square wave infusion showed that it could primarily be

considered to act as a linear first order system. The transient pressure response to a step function in flow was a single exponential curve with a mean of 509 msec in inflation and 743 msec in deflation. More exact modelling required consideration of the systemic arterial circulation as a third order system to account for the small inertial component.

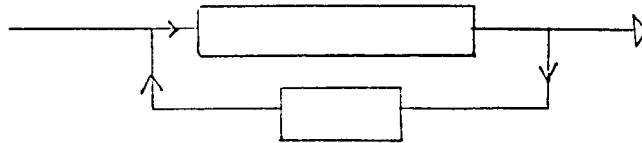
An electrical model was built whose response to a simulated square wave infusion of fluid, gave good correspondence to that obtained in the living rabbit. The correlation coefficient between cardiac output values measured by the square wave infusion technique and by the Fick method was +0.80.

The effects of various CO₂ concentrations, asphyxia, haemorrhage, nor-adrenalin infusion, and long-term cholesterol feeding on the rabbit systemic arterial circulation were investigated by this method.

CHAPTER I

INTRODUCTION

The circulatory system is composed of a number of tubes which act as conduits for the passage of blood. These tubes are acted upon by a complex variety of nervous, hormonal and physical influences. When viewed through the eyes of an engineer, the situation can be summarised in the diagram below.



The circulation functions as a complex control system, in which the principal controlled variable is blood flow to the critical organs. If it is desired to study either the effects of a single influence alone on the circulation ; or alternatively to begin to understand the complex mechanics of control in the circulation, then it is obviously important to have a good understanding of the purely physical characteristics of the circulation as represented by the unlabelled box in the diagram above. Basically, this is what the work to be described in this thesis is about viz: development of a method to allow rapid monitoring of the various physical factors involved when blood flows through the vascular bed.

Use was made of a standard engineering technique. The

engineer typically classifies any unknown physical system, as in the unlabelled box above, as a 'black box'. All Black boxes that behave in an approximately linear fashion, can be broadly classified according to their responses to standard stimuli. Such a standard stimulus is the 'square wave' used in this investigation. Such classification allows an understanding of the 'group' behaviour inside the box, and in some instances, gives a more penetrating insight into the fundamental make up of the box itself.

Stephen Hales (1677-1761), Vicar of Teddington, and author of 'Statistical Essays' (1733) containing a series of observations on animal and plant life, was the first to document any physical characteristics of the circulation. The part of his work which he called 'haemastaticks' began with a description of the first known method of measuring blood pressure.

"Experiment 1. In December, I caused a mare to be tied down alive on her back, she was 14 hands high, and about 14 years of age, had a fistula on her withers, was neither very lean, nor yet lusty; having laid open the left crural artery about 3 inches from her belly, I inserted into it a brass pipe whose bore was one sixth of an inch in diameter, and to that.... I fixed a glass tube, of nearly the same diameter, which was 9 feet in length: then untying the ligature on the artery, the blood rose in the tube 8 feet 3 inches.... when it was at its full height, it would rise

and fall at and after each pulse 2, 3, or 4 inches:"

He repeated this amazing performance on several more horses. It remained the only technique for measuring blood pressure until Poiseuille introduced the mercury manometer in 1828. It is perhaps of interest to note that he probably obtained this idea from his method of measuring sap pressure in plants.

He also performed various other experiments on the circulatory system. He took the intestines of a dog and measured the difference in resistance between the large arteries and the small 'capillary arteries'. He calculated the diameter of the latter at $1/3240$ th of an inch and noted that 'this is so fine, only single Blood globules can pass them into the veins'. He noted that passage of hot or cold water through these vessels could change their resistance and that the 'viscosity' of the perfusion fluid was an important factor. Filling the left ventricle of one of the exsanguinated horses with beeswax enabled him to calculate the stroke volume and cardiac output. He also designed an apparatus to measure the amount of air absorbed by breathing, and defined its site of absorption at the alveoli.

Stephen Hales was the first to suggest the importance of the elastic nature of the arterial wall. It had long been known to the early surgeons that haemorrhage from a large artery came out in vigorous, uneven, spurts, whereas bleeding from the finer vessels was much more even in character. Hales recognized that this could be

explained by the elastic properties of the arterial wall. It was known that the arteries expanded with each heart beat, and that this occupied only about one third of the pulse interval. During the remainder of the pulse interval, he surmised, the arteries would contract down again because of their elasticity, and propel the blood in a more continuous fashion into the smaller vessels of the periphery, thus accounting for the greater evenness of their flow.

It is hard to believe that such remarkable precision and objectivity could come barely fifty years after Harvey's death (1657). The end of the seventeenth century was a very significant period in the development of biological knowledge and Stephen Hales could not unjustly be considered as the father of modern haemodynamics.

The literature review which follows, considers current knowledge of the physical properties of the circulation in two sections. The first considers the fundamental physical properties of arteries in the systemic circulation. The second considers the composite physical behaviour of the whole system (i.e.: the 'group' behaviour of the black box).

1. THE FUNDAMENTAL PHYSICAL PROPERTIES OF ARTERIES IN THE SYSTEMIC CIRCULATION

Stephen Hales recognized that arteries in the living body have the fundamental physical properties of resistance and compliance (or 'elasticity', as he called it). A third property, inertance, due to the mass of blood contained in the arteries, also contributes to the fundamental physical behaviour of the system. These will now be considered in turn.

(i) RESISTANCE

Resistance is defined as the ratio of the pressure gradient across a system (ΔP), to the change in flow rate (ΔF). Thus:

$$R = \frac{\Delta P}{\Delta F} \quad \text{where } R = \text{resistance}$$

It has the dimensions of $M^1 L^{-4} T^{-1}$. There is no consistent unit of expression used in physiological work. It is variously expressed in terms of (1) dynes sec cm⁻⁵, or (2) mm Hg/ml/sec, or (3) mm Hg/ml/min. GREEN (1944) has commented concerning expression of resistance in terms of dynes sec cm⁻⁵ that 'it is not readily appreciated as such and it in no way increases its accuracy'. He proposed expression of resistance in terms of mm Hg/ml/min. This system has been adopted in this thesis. Viscous resistance has the exact equivalent of Ohmic resistance in electrical terms.

(a) POISEUILLE'S LAW

Although many of the factors concerned in this property were known to the English physician, Thomas Young (1809), it was not until 1842 that his French counterpart, J.L. Poiseuille, was able to put them on a firm physical basis. Poiseuille's initial interest was in measurement of pressure gradients across large arteries with his new mercury manometer. Contrary to the expectations of his time, he could not find any pressure gradient across even the smallest arteries which he could penetrate, and his attention was then drawn to the factors determining flow through the fine capillary vessels. Having no means to make blood incoagulable, he was forced to study water flow through glass capillary tubes. By meticulous experiment he was able to establish the following classical relationship between pressure and flow across rigid tubes:

$$Q = \frac{K.P.D^4}{L.}$$

Where Q = volume flow rate across tube

P = pressure gradient across tube

D = diameter of tube

L = length of tube

The factor K was clearly related to the viscosity of the fluid. Sir Isaac Newton (1687) had earlier done some experiments on the rotation of a cylinder in fluids of varying viscosities, and had proposed that the 'lack of slipperiness' (as he referred to viscosity) was due to laminae of the fluid moving over each

other at different rates. He suggested that perpendicular to the axis of motion, there was a velocity gradient of the fluid laminae: this gradient is now usually referred to as 'the rate of shear'. In recognition of this a fluid is said to be Newtonian when its viscosity does not vary with the rate of shear.

The theoretical solution of the relationship between pressure and flow in rigid tubes was provided in 1856 by Weideman, who derived it from the general equations of motion of viscous fluids established by Navier and Stokes (1840). The same relationship that Poiseuille found experimentally was obtained. The constant K was evaluated as:

$$K = \frac{\pi}{128\mu} \quad \text{where } \mu = \text{viscosity}$$

OR:

$$Q = \frac{\pi R^4}{\mu} \cdot \frac{1}{8} \cdot \frac{P}{L} \quad \begin{array}{l} \text{where } R = \text{tube radius} \\ \mu = \text{blood viscosity} \end{array}$$

In the course of this derivation, it was shown that the velocity profile of the flow was parabolic in shape. This was supported by Poiseuille's earlier microscopical observation that red cells in the middle of the blood stream appeared to move with a faster velocity than those on either side.

Certain conditions have to be fulfilled in the application of Poiseuille's 'law'. (1) The diameter of the tube must be constant, and not change with change in pressure; (2) the flow must

be laminar and not turbulent; (3) the flow rate must be steady, neither accelerating nor decelerating; and (4) the viscosity must not change for different rates of shear, (that is, the fluid must be 'Newtonian').

Whilst it is difficult to apply the law which Poiseuille described in a quantitative fashion to the study of the circulation, it is still of interest to see if it encompasses all the factors concerned with the resistance to blood flow through vessels.

(a) The anomalous viscous properties of blood:

It has long been realized that blood is a heterogeneous fluid containing suspended particles (red cells) and that, on this account, it might have anomalous viscous properties. DENNING and WATSON (1906) were the first to note the apparent decrease in viscosity when blood flowed through tubes of small diameter. This effect is generally named after FAHREUS and LINQUIST (1931) who investigated the phenomenon more extensively and found that the apparent decrease in viscosity occurred when blood flowed through tubes of less than 1 mm in diameter. WHITTAKER and WINTON (1933), using the hind limb of a dog as a viscometer (in which the average diameter of the arterioles was 55μ) were able to confirm this, as were subsequent investigators (HAYNES and BURTON (1959)). It has been suggested (see BURTON 1965) that the effect is related to the

fact that the fluid laminae are not infinitely thin, as they are in a homogenous fluid.

A second phenomenon, first described by HESS (1907), is that the viscosity of blood increases when flowing at very low flow rates. The original explanation of this was that blood behaves as a plastic fluid, requiring a critical yield pressure before it would flow. However, the work of BINGHAM (1944) showed that the pressure-flow curves of blood through rigid tubes did not, in fact, have a yield pressure, and did pass through the origin, although there was a marked inflection of the curve at low flow rates. The work of HAYNES and BURTON (1959), which was an extensive study of the rheological properties of blood, showed that this inflection of the curve at low flow rates was due to an axial accumulation of red cells in the blood stream (an idea long current). Furthermore, they showed that this effect was principally determined by the shearing stress at the wall, and that a critical value of 20 dynes/cm (at which saturation of the effect occurred) was exceeded at all physiologically important flow rates.

Thus the conclusion is reached that blood can be considered, for practical purposes to act as if it were a Newtonian fluid, at normal flow rates. Any deviation from Poiseuille's Law in pressure-flow relationships, except at very low flow rates, is therefore, not due to an anomalous viscous effect.

(β) The behaviour of blood vessels as rigid tubes:

Poiseuille derived his law from experiments performed on glass capillary tubes. He subsequently showed that the rigidity of the vessel wall was an important condition. This is manifestly not true of the larger blood vessels, which expand with each heart beat. However, Poiseuille himself, found in 1828 that there was very little pressure drop across even the smallest of arteries. Therefore, the contribution of these larger vessels to the total resistance across the systemic circulation is quite small. This contribution was defined more exactly by LANDIS (1926), one hundred years later, who was able to cannulate capillaries in the frog mesentery. He found that 70 to 80% of the pressure drop occurred over the 5 mm or so, of muscular arteriole prior to the capillary. In studies on the human nail bed, all but 5 to 10% of the resistance to blood flow occurred in vessels with a diameter of less than 1 mm. Therefore, the principal concern in a study of resistance in the circulation, is with blood flowing through the small vessels.

The problem whether these small vessels act as rigid tubes is not quite so self-evident. As BARD (1960) has commented, on account of the small radii of these vessels, great pressure changes are required to exert significant effects on resistance. The most direct evidence on this point was provided by the paper of NICHOL, BURTON et al. (1951). They subjected the vessels of the frog

mesentery to direct microscopic observation and measured their diameters as the pressure in them was varied. They found that the diameters of these vessels remained remarkably constant with increases in pressure, and reached the conclusion that they did indeed behave as rigid tubes. BAEZ and LAMPORT (1960), in a similar study, drew the same conclusions for arterioles of diameters between 32 and 33 microns. However, as FOLKOW (1952) has pointed out, a 5% increase of the external diameter (supposing a vessel of 60μ external and 40μ internal diameter), can mean a 10% increase in the internal diameter, leading to an increased volume flow of 50%. Thus direct microscopy must be extremely accurate to adequately resolve this question.

Under the usual conditions for determination of pressure flow relations across a vascular bed, flow rates across the small vessels are normally constant. Furthermore, it is generally accepted that blood flow is not turbulent across these vessels (see MacDONALD 1960). In view of the evidence presented above for the Newtonian behaviour of blood, it is most likely that any deviation from Poiseuille's law in the circulation, is due primarily to the small blood vessels acting as distensible rather than rigid tubes. This statement excepts the peculiar circumstance of very low flow rates.

Reference to the equation for Poiseuille's law shows that it is a linear one. Therefore, whenever the law is applicable, a straight line plot between flow and pressure gradient should be obtained. Thus the applicability of the law to the circulatory system can be tested empirically by performing such flow-pressure gradient plots. The results of these have been very varied as the next section will show.

(b) PRESSURE-FLOW RELATIONS IN THE SYSTEMIC CIRCULATION

(a) Pressure-flow relations across various vascular beds

A large number of experiments have been performed to determine pressure-flow relations across various vascular beds. This has involved use of a number of different techniques and preparations. Some of the earliest experiments of this kind used a dog hind-limb preparation which was subjected to a variety of constant pressure infusions. Measurement of the resulting flow rates allowed plotting of the pressure-flow graph. In such an experiment, WHITTAKER and WINTON (1933) found a strictly linear pressure-flow relationship when the hind-limb was perfused with either Ringer's solution, or defibrinated blood. They also found that the plot did not pass through the origin of the graph, but had a positive pressure axis intercept (see later). PAPPENHEIMER and MAES (1942) found a similar kind of linear relationship above pressures of 20 to 100 mm Hg dependent as the level of vascular tone. GREEN et al. (1944) noted that Whittaker and Winton did not ligate the cut ends of the

collateral arteries supplying the hind limb. They postulated that this could give rise to measurement of false flow rates. Green's group found a non-linear relationship between pressure and flow in the dog's hind limb. This related most closely to the expression:

$$F = cP^n \quad \text{where } c = \text{constant}$$

F = flow rate

P = pressure gradient

The value of the exponent 'n' varied between 1 and 3, and most commonly had a value of about 2. With increasing levels of tone, the value of the exponent was found to increase. With maximal vasodilatation, it had a value of 1; that is to say, it became a linear expression. Green's experiments, therefore, suggested that the small resistance vessels did distend with an increase of pressure within them.

DOYLE (1953) used the converse of this technique on the rat hind limb. He subjected the latter to a variety of constant flow infusions and related these to the resultant pressures. He found a linear relationship between pressure and flow at pressures above 40 to 100 mm Hg. A general problem with both the basically similar techniques of Doyle and Green, is that it takes 20 to 45 minutes to complete each pressure-flow curve. If these results are to have any validity, the circulation must remain in a steady state during this time.

A more rapid and ingenious method is that developed by NICHOL et al. (1951). Using a vertical tube of known and constant diameter, they allowed a column of blood to fall under the influence of gravity, and from the rate of fall of the column, they were able to determine the instantaneous flow rate. Thus a pressure-flow curve could be determined in a matter of 3 to 10 minutes. Using this method, Nichol et al. found linear pressure-flow relationships in the rabbit leg, and frog leg, (see Fig. 1). PHILLIPS, BRIND and LEVY (1955) studied the dog hind leg with this method and found a mixture of linear and non-linear curves. Furthermore, they found that increasing the transmural pressure decreased the resistance. LEVY (1958), in another study of this kind in the dog hind leg, found that when the venous pressure was elevated, that there was little change in resistance and that the pressure-flow curves were 'invariably linear'. If, however, the arterial pressure was decreased in a stepwise fashion, pressure-flow curves became curvilinear, with their convexity towards the pressure axis. The pressure-flow curves obtained by GIRLING (1952) on the rabbit ear during stimulation of its sympathetic supply were linear at the lowest levels of tone, but became sigmoid at greater rates of stimulation.

FOLKOW (1952, 1957) has found some interesting results on the denervated cat circulation. He has revived a theory originally proposed by BAYLISS in 1902. The latter noted that there was an

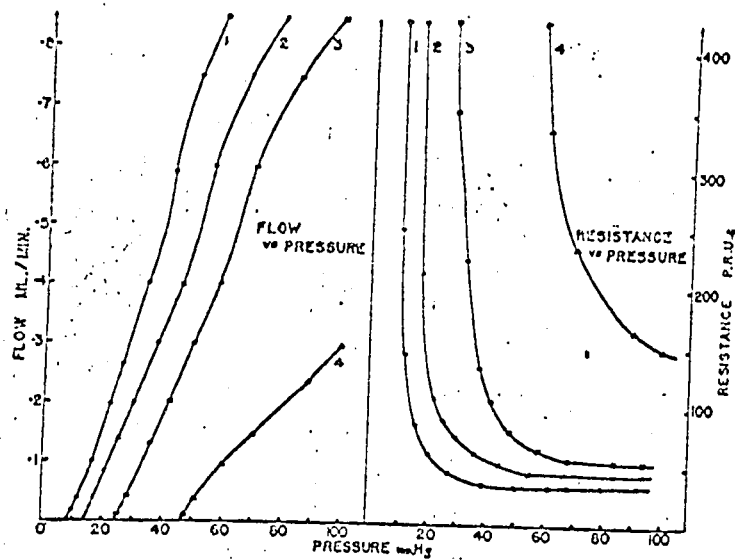


Fig. 9. FLOW AND RESISTANCE vs. pressure. Rabbit leg.

FIGURE 1: Plots of pressure vs flow, and resistance vs pressure, in the rabbit leg (from Nichol et al 1951)

increase in volume of the denervated hind limb after a brief period of hypotension. He suggested that this could result from relaxation of the arterial wall consequent on the diminished pressure within it. He postulated that vascular smooth muscle reacted in a similar way to visceral smooth muscle in its response to stretch. FOLKOW (1952, 1957) re-examined the evidence for this in both the denervated cat hind limb, and the total systemic circulation of the kitten. The spinal cords of the latter were crushed to eliminate vasomotor control. He found that lowering the blood pressure, within one to two minutes, would cause a sustained increase in blood flow - not what would be expected in terms of the passive distensibility of blood vessels.

He described the non-linear pressure-flow curves which he obtained, in a similar mathematical fashion to that used by Green above. He found values of the exponent 'n' to vary from 0.55 to 1.5. The majority of values were below 1 and at no time did he find values of the exponent as great as those found by Green et al. These non-linear pressure-flow plots suggest that as the pressure is increased within the small blood vessels, far from distending in a passive manner, they actually constrict and become smaller. This active response was called a 'myogenic reflex' by Bayliss. It should be noted that Folkow found that this reflex took one or two minutes to manifest itself and was easily abolished by any deterioration in the perfusion fluid. NICOLL and WEBB (1946), in a study

of the small vessels of the living bat wing, noted 'rhythmical active vasomotion' in the arterioles, precapillary sphincters and veins, even after denervation. A sudden increase in pressure caused at first mechanical distension, and then a contraction of great intensity. Thus there is direct microscopical evidence that this phenomenon can occur.

(β) Pressure-flow relations across the whole systemic arterial circulation

There have been very few direct studies on pressure-flow relations across the whole systemic arterial circulation. LEVY, BRIND, BRANDLING and PHILLIPS, (1954) varied the mean pressure of dogs and measured the resulting cardiac outputs by the Fick principle. They found linear pressure-flow relationships, with the line passing through the origin, when the buffer nerves had been sectioned; but a more curvilinear relationship under normal circumstances when these compensatory reflexes were active. In another dog study, REID, KUIDA and JOHNSON (1957) using a technique of total body perfusion by heart-lung machine, found an 'approximately linear' relationship between pressure and flow, with a positive pressure axis intercept of 20 mm of mercury. These are the only two direct studies that this writer has been able to find in the literature.

(c) MEASUREMENT OF TOTAL PERIPHERAL RESISTANCE

Total resistance across the systemic circulation is an important factor in the regulation of blood pressure. Blood pressure itself is an important determinant of flow to the various vascular beds. Therefore, study of this total peripheral resistance is a key factor in understanding the body's reaction to haemorrhage and shock. In spite of this, relatively little work has been performed directly on its measurement.

Measurements of total peripheral resistance have been obtained almost exclusively by the indirect method of measuring cardiac output and mean blood pressure. Two assumptions are made in relating the quotient of these two parameters to 'total peripheral resistance'. The first is that pressure-flow relations across the whole systemic circulation are linear. As has been seen, there is very little direct evidence on this point available in the literature. The second assumption is that the plot passes sufficiently close to the origin of the graph so that the mean blood pressure can be considered to represent the pressure-gradient across the system. There is evidence that this is not so, and this will be considered later. In view of the importance of total peripheral resistance to the understanding of shock mechanisms, it is surprising that more emphasis has not been given to its measurement. An attempt will be described in this thesis to measure total peripheral resistance by a more direct method.

(a) Critical closing pressure

Evidence will be presented in this section that pressure-flow plots across various vascular beds, do not pass close to origins of the graph. There is a positive pressure axis intercept; or, in other words, a certain head of pressure is required before blood will flow through the system. BURTON (1951) has called this the 'critical closing pressure'. It has important implications in the calculation of total peripheral resistance, as will be considered later.

This was recognized by physiologists earlier in the century. As early as 1901, HURTHLE found that the flow across the whole systemic arterial circulation 'increased more than in arithmetical proportion to the rise in pressure'. Similar findings were also noted by FLEISCH (1919), WAGNER (1928) and BAZETT (1927). The experiments of WHITTAKER and WINTON (1933), previously mentioned, showed that their linear pressure-flow plot had a positive pressure axis intercept of about 20 mm Hg. They proposed the following relationship between pressure and flow across the systemic arterial circulation:

$$\bar{P} = (F \cdot R) + 20 \quad \text{where } \bar{P} = \text{mean arterial pressure}$$

$$F = \text{flow rate}$$

$$R = \text{total peripheral resistance}$$

This equation then became adopted for a time. A fixed figure of

20 mm Hg was subtracted from the mean arterial pressure to give the effective pressure gradient across the system. This approach was used in the attempts of BAZETT, COTTON, LAPLACE and SCOTT (1935), and BROEMSER and RANKE (1930) to compute stroke volume from the pressure pulse.

Other investigators studying various vascular beds have found different values than those found by Whittaker and Winton. NICHOL et al. (1951) found values varying from 5 to 50 mm Hg in rabbit hind legs. GOMEZ and VEIL (1936) found that if the blood supply to the hind limb of a dog was occluded (i.e. flow became zero) and allowed to fall, it would reach a steady pressure of 5 to 30 mm Hg. GOMEZ (1937) put forward the idea that there is a 'counterpressure' in the peripheral circulation which must be exceeded before flow begins: by mathematical extrapolation of the diastolic curve (assumed to be exponential) he found a normal value of 74 mm Hg and a range of 34 to 110 mm Hg for 'critical closing pressure' in human beings. STARR (1957) found this value to be too high. In Starr's own studies on human cadavers, he found values between 34 and 45 mm Hg and compared them with the values (16 - 74) found by BURTON and YAMADA (1951) on human fore-arms, using a plethysmography technique.

In the original explanation of this somewhat paradoxical phenomenon, Whittaker and Winton postulated that blood was acting as a plastic fluid, and that this represented a 'yield pressure'.

They drew this conclusion because, unlike the blood perfusion, the pressure-flow plot obtained with Ringer's solution could, it seemed, be extrapolated to pass through the origin. However, more careful study of Ringer perfusion in the low pressure regions (NICHOL et al. 1951), clearly demonstrated that this phenomenon could indeed also occur with Ringer perfusate, so that a peculiar viscosity of the blood could not be the explanation.

The explanation which has received widest acceptance is that due to BURTON (1951). From a relationship established by Laplace in the nineteenth century, he has pointed out that, for a cylindrical vessel in equilibrium, the tension in the wall (T) is exactly balanced by the product of the net pressure within the vessel (P) and its radius (R). Thus:

$$T = P.R.$$

If the radius remains constant at differing pressures (that is to say, the vessel is rigid), then this is a stable relationship limited only by the tensile strength of the material in the vessel wall. If, however, all three parameters are variable (as in a distensible vessel with active tone in its wall), then it can become a very unstable relationship i.e.:

$$T = P.R. \quad \text{or} \quad T \neq P.R.$$

If, for example, the only force opposing expansion of the vessel is active tension (which varies in an adverse manner with any increase in radius), then any momentary disequilibrium in

* ie: more tension is required with an increase in radius.

favor of the forces of expansion (i.e.: $P > \frac{T}{R}$) will result in an infinite amplification of these expansile forces, until another counteracting force is met. In normal blood vessels, this counteracting force is due to the elastic element, which is rapidly recruited, allowing a new equilibrium to occur. This elastic element can be considered as a reserve force, able to buffer the primary disequilibrium.

Similarly, when the only force opposing constriction of the vessel is the pressure within its lumen (which again varies in an adverse fashion with any decrease in the radius), momentary disequilibrium in favor of the forces of constriction (i.e.: $\frac{T}{R} > P$), will again result in infinite amplification and closure of the vessel, unless another force is encountered. The buffer function of the elastic element is again exerted. The total force tending to constrict the vessel is the sum of the active tension (force generated by muscle contraction) and the elastic tension. As the vessel actually constricts, the elastic tension becomes less, so that the total constrictive force becomes less. This allows a new equilibrium, at a lower level of forces, to be reached. When the active tension of the vessel is so great that it exceeds the buffering capacity of the elastic tissue, then complete closure of the vessel will occur. At any one particular level of vascular tone, the buffering capacity of the elastic tissue will

* ie: more pressure is required with a decrease in radius.

be exceeded at a critical pressure, which Burton has called the 'critical closing pressure'.

ROACH and BURTON (1957) have found that human iliac arteries have suitable elastic diagrams to fulfill this buffering function, and postulated that a similar situation occurs in regard to the elasticity of the smaller vessels. NICHOL et al. (1951) also found a residual critical closing pressure in the frog leg with a mean value of 3.3 cms of saline. This could not be reduced even after perfusion with cyanide solution (which would remove all vestiges of active tension in the vessel), and they reached the conclusion that it was due to an interfacial tension, from incomplete 'wetting' of the vessel wall. This was borne out by the fact that it could be reduced by perfusion with a bile salt solution. NICHOL et al. (1951) also found a positive correlation of 0.86 between the critical closing pressure, and the logarithm of the reciprocal of the reduction in flow. On account of this, Burton has proposed that the critical closing pressure is a useful index of the level of vasomotor tone.

GIRLING (1952) found that the critical closing pressure increased with increasing frequencies of sympathetic nerve stimulation to a level of 30 per second in the rabbit ear. Above this frequency level, the critical closing pressure fell back to its initial value, and an increase in stimulation frequency up to 60 per second failed to augment it, but the slopes of the pressure-

flow curves progressively decreased. He attributed this to refractoriness of the arteriolar muscle at stimulation frequencies higher than 30 per second.

The 'critical closing pressure' concept has not been unanimously accepted. It has been suggested that the positive pressure axis intercept results from plugging of the small capillary vessels by red and white blood cells. However, NICHOL et al. have shown 'back-flow', which, they claim, excludes this possibility. GUYTON, LINDSAY and ARMSTRONG (1956) found that on arresting the heart in dogs, arterial pressure continued to show a steady decline until it reached the level of the rising venous pressure. They suggested that the positive pressure intercept was determined principally by the venous pressure. GIRLING (1952) had earlier examined this possibility in a study on the rabbit leg and found that in no case did the 'critical closing pressure' equal the venous pressure. He found a correlation coefficient of 0.53 - 0.46 between the levels of the venous pressure and the critical closing pressure. He did note, however, that raising the venous pressure had a corresponding effect on the 'critical closing pressure' and he suggested this was due to a vasomotor reflex. The 'critical closing' concept has also not been accepted by FOLKOW and LOFVING (1957) for a different reason.

They point out, first of all, that NICHOL and BURTON have drawn the conclusion, in their 1951 paper, that the small blood

vessels are practically indistensible. This conclusion is based on the linearity of their pressure-flow curves and the evidence of direct microscopy. If this fact is accepted, then it means that at these pressures, the vessels are inelastic and so the elastic lamina cannot exert its key buffering role. Therefore, any tendency for the vessel to constrict at any pressure level (critical closing or no) would always result in infinite amplification and complete closure. This obviously does not occur, and the only way to explain a graded response under these circumstances is that when the vessel constricts, the increase of tone which was the initial cause, becomes reduced to a lower level, as a result of the shortening. Complete closure of the vessel under these circumstances occurs as a gradual, rather than a precipitous, phenomenon.

Folkow and Lofving suggest that the activity of the pre-capillary sphincters, which are well known to undergo intermittent closing, are more important in determining the positive pressure intercept, than any instability of the arterioles.

Whatever the theoretical explanation of 'critical closing pressure', there is a considerable body of evidence to suggest that a significant positive pressure head is required before blood will flow through the system. An attempt will be made in this thesis to confirm the finding across the whole systemic circulation.

Under these circumstances, the pressure gradient across the system (which is the important parameter in calculating total peripheral resistance) is not necessarily represented by the difference between the mean arterial pressure and central venous pressure. This was pointed out by PERMUTT and RILEY (1963).

They noted that the arterioles, capillaries, and veins constitute a potentially collapsible system and this modifies the effective pressure gradient across them. The forces causing collapse may be either active tone in the vessel walls themselves, or the result of extra-vascular tissue pressure. Depending on the magnitude of these forces, collapse will occur at a critical pressure (P_c), where the pressure within the vessel or tube is just exceeded. The pressure in the vessel cannot at any time be less than P_c . Nor can it, at the distal end of the tube, be greater than P_c , if the pressure just beyond the tube (P_{out}) is less than P_c . Therefore, the pressure gradient across a collapsing tube becomes $P_{in} - P_c$ where P_{in} is the pressure at the entrance to the tube: if P_{out} is less than P_c . If P_{out} is greater than P_c , then the pressure gradient is what it would be across a rigid tube, i.e.: $P_{in} - P_{out}$. Thus the pressure gradient across a collapsing tube is dependent upon the circumstances and is determined by

$$P_{in} - P_{out}$$

or

$$P_{in} - P_c$$

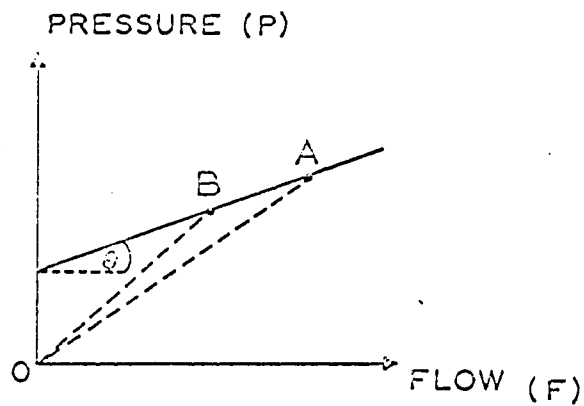
whichever is the smallest. Therefore, the true pressure gradient across the circulation is usually given by the difference between the mean arterial pressure and the 'critical closing pressure'. Only in the rare circumstance that the central venous pressure is greater than the critical closing pressure, is it correct to represent the pressure gradient across the circulation by the difference between mean arterial blood pressure and central venous pressure. Failure to appreciate this point can lead to false interpretation of changes in total peripheral resistance, as the following discussion shows.

(β) Chord and slope resistance

Consider Fig. 2. This shows a linear plot of pressure against flow, with a significant pressure axis intercept. It is analogous to a situation in the circulatory system where a significant pressure head is required before blood will begin to flow.

Consider point A which can be considered to represent a reading of mean arterial blood pressure and cardiac output at any one moment in time. The quotient of the two ('total peripheral resistance') is indicated by the tangent of the angle AOF.

Suppose then that the pressure was dropped to point B by a reduction in cardiac output. The quotient of the mean arterial blood pressure and cardiac output at that particular time would be indicated by the tangent of the angle BOF. As the angle



(a) CHORD RESISTANCE (R_c): at A = $\tan A \text{ of } F$
 at B = $\tan B \text{ of } F$

$\therefore R_c \text{ at A} < R_c \text{ at B}$

(b) SLOPE RESISTANCE (R_s): at A = $\tan \theta$
 at B = $\tan \theta$

$\therefore R_s \text{ at A} = R_s \text{ at B}$

FIGURE 2: Chord resistance and slope resistance

BOF is greater than the angle AOF, the conclusion might be drawn that, as the pressure fell from A to B, there was a compensatory increase in total peripheral resistance. In fact, of course, there was no change in total peripheral resistance. This would have been shown if the true slope of the plot ($\tan \theta$), had been calculated.

If the straight line relationship between pressure and flow had passed close to the origin of the graph, then this ambiguity would not have arisen.

A kindred problem was recognized by HODCKIN and HUXLEY (1952) in the definition of current (I)-voltage (V) relations in the squid axon. Here again, the straight line relationship did not pass close to the origin of the graph. The true slope of the line (dI/dV), they called the slope conductance. The relationship of each point on the line to the origin of the graph (I/V), they called the chord conductance.

In direct analogy with this, similar terms are now proposed to describe pressure-flow relations across the systemic arterial circulation. Thus, slope resistance is defined as dP/dF ; and chord resistance as P/F .

Where possible, resistance will be expressed in terms of slope resistance. However, it should be noted that this is not the common practice. For example, if reference is made back to the study of NICHOL, BURTON, et al. (1951) in Fig. 1, it will be seen

* ie: the usual way to calculate TPR. as the ratio of absolute pressure to absolute flow.

that chord resistances, and not slope resistances have been calculated. This gives a very ambiguous graph of the resistance-pressure relations. The impression is given that resistance has increased greater than four-fold in falling from a pressure of 80 mm Hg to one of 20. Simple inspection of the pressure-flow graph shows that the linear relationship has changed little between these two pressures, and this would be borne out if true slope resistances had been calculated.

This section has considered the physical property of resistance in the systemic arterial circulation. It has been shown to reside principally in the small vessels, as predicted by Poiseuille's law. Most of the conditions for the application of this law are satisfied within a normal range of pressures. There is some conflicting evidence as to whether the small vessels are behaving as rigid tubes, or not. Most experiments on pressure-flow relationships have been performed on various isolated segments of the vascular bed: little direct experimentation has been done across the whole systemic circulation. Because of the evidence that a significant 'critical closing pressure' exists, calculation of the total peripheral resistance has to be modified if ambiguities in interpretation are to be avoided. Calculation of a slope resistance has been proposed.

(ii) COMPLIANCE

The second fundamental physical property of the systemic arterial circulation is that of compliance. This is defined as the ratio of the change in volume (ΔV) to the change in pressure (ΔP). Thus:

$$C = \frac{\Delta V}{\Delta P} \quad \text{Where } C = \text{compliance}$$

It is generally expressed in terms of ml/mm Hg in physiological work, and has the dimensions of $M^{-1} L^4 T^2$. It has the exact equivalence of capacitance in electrical terms.

Stephen Hales used the term 'elasticity', rather than compliance in describing this property of arteries. However, as used now, rigorous physical definition of the term 'elastic' conveys a sense opposite to that of its popular meaning. Strictly applied, wood becomes a more elastic substance than rubber. The term 'elastic' however, in this thesis, will continue to be used in its popular sense i.e.: where rubber is more 'elastic' than wood.

This ambiguity arose out of Young's original definition for an elastic modulus. He defined this as the ratio of longitudinal stress over longitudinal strain. Thus, the modulus (E) becomes:

$$E = \frac{FL}{\Delta LA} \quad \begin{array}{l} \text{Where } F = \text{stress applied} \\ A = \text{cross-sectional area} \\ \Delta L = \text{strain} \\ L = \text{unstrained length} \end{array}$$

Although extensively used in physics, it is difficult to apply this modulus in biology, because materials are generally more heterogenous and it is difficult to find their unstrained length. Furthermore, they rarely obey a simple Hookean type law, where Young's modulus has a single value for a wide variety of stresses and strains. In order to account for these factors, KRAFKA (1939), proposed the term 'incremental elastic modulus'. This is generally written as E_{inc} , and has the same definition as E , except that L is not the unstrained length, but the mean length about which ΔL changes. Thus, even in a material in which E remained the same, E_{inc} would have a different value at every length tested.

The elastic modulus of arteries may be directly expressed in terms of a tension-length relationship (where length refers to the circumference of the vessel). It is often more convenient to express it in terms of a pressure-volume or pressure-diameter relationship. As BURTON (1951) has pointed out, although the circumference of a constant-length vessel is directly proportional to its volume (or diameter), the tension in the wall of a vessel is not directly proportional to its transmural pressure. These latter parameters are related to each other in terms of the Laplace equation, previously discussed (i.e.: $T = PR$). All three parameters are variable, so there is no direct relationship between any two of them. Therefore, tension-length relationships are not directly transposable to pressure-volume ones. If one of these is linear, the other will not be.

Bearing this factor in mind, pressure-volume studies on arteries are also often expressed in terms of an incremental modulus (C_{inc}). Thus:

$$C_{inc} = \frac{\Delta V}{\Delta P \cdot V} \quad \text{Where } V = \text{mean volume about which } \Delta V \text{ occurred.}$$

Note that this is the inverse of the usual stress-strain ratio used in physics. It will be seen that compliance is related to C_{inc} by the expression below:

$$C = C_{inc} \times V \quad \dots\dots\dots (a)$$

BERGEL (1960) has calculated that if C is to remain constant, C_{inc} must vary in inverse proportion to the fourth power of the radius of the vessel. Thus, C_{inc} , whether the system is linear or not, will have a different value for each transmural pressure at which it is measured.

C_{inc} has been referred to as the 'Coefficient of volume distensibility' (REMINGTON 1957), and as the 'Relative volume distensibility' (BURTON 1965). It is one of the most common ways in which to express the elastic properties of blood vessels. In part, its usage has stemmed from the measurement of pulse wave velocity, which is one of the few ways to assess the elastic properties of arteries in the living animals. BRAMWELL and HILL (1922) derived the expression whereby $c = 0.35 \left[\frac{1}{C_{inc}} \right]^{\frac{1}{2}}$: 'c' is the pulse wave velocity (see later). In spite of its convenience in many other ways,

determination of C_{inc} does not provide direct information about the elastic properties of blood vessels. This is illustrated by the results of some experiments on aging.

HALLOCK and BENSON (1937) measured human pulse wave velocities at various ages and found good correlation between these and C_{inc} values measured on excised specimens of thoracic aorta. As C_{inc} values progressively decreased with age, they drew the conclusion that large blood vessels became more rigid and inelastic with age. However, REMINGTON (1948), repeated these experiments and found that in old age, there was a significant increase in the unstretched volume (V) of the aorta. Therefore, the decrease in C_{inc} on aging that Hallock and Benson found, could be due to either an increase in V , or a decrease in C , as reference to equation (a) shows. The conclusion could not really be drawn that C decreases with aging. Indeed, in Remington's experiment, they found that the slope of the tension-length curve, as an index of C , did not show any clear difference with age. This is a common dilemma in the interpretation of C_{inc} values.

Thus expression of the elastic properties of blood vessels in terms of compliance (C), when possible, is the optimum mode. It gives a direct answer to the question that concerns the investigator most i.e.: is there a change in the elastic properties of the vessel wall? Furthermore, it provides a ready value for use in the electrical analogue model.

In spite of the fundamental importance of this parameter of compliance, little success has been achieved in measuring it in the living animal. Two basic approaches in the measurement of the elastic properties of blood vessels have been made. One is direct, but conducted mostly on excised vessels: the other is indirect, but conducted on the intact, living animal. These will now be considered.

(a) Measurement of elastic properties in excised vessels:

Three techniques are commonly applied to the measurement of elastic properties in excised vessels. The most direct is that used by ROY (1880) who cut longitudinal strips of aorta and measured their elongation under various weights. He noted that the wall appeared to be most extensible within the normal physiological range. He also compared the elongation of transversely cut strips with that of longitudinally cut ones, and found that the extensibility of the latter appeared to be greater. This result was confirmed by FENN (1957) in a more sophisticated experiment performed almost 80 years later.

A second technique is that used by HASS (1942), REMINGTON (1948), and others. Rings of aorta are cut and then subjected to circumferential stretch. The presumption is that stretch so applied occurs in a more physiological direction, and length-tension curves and pressure-volume curves can be calculated. The third technique is that used by HALLOCK and BENSON (1937) and ROACH and BURTON (1954), who excised small segments of aorta, or other large vessel and

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performed pressure-volume studies directly on the segment. Hallock and Benson found a sigmoid shape of the pressure-volume curve for human thoracic aorta, with greatest extensibility in the physiological range. Within that physiological range (from 50 to 150 mm Hg) pressure-volume relations were quite linear. GREEN (1963) found pressure-volume relations to be linear for the dog aorta over a range of 0 - 200 mm Hg pressure.

BERGEL (1961) made a definitive study of the static elastic properties of the dog arterial wall. He took a small segment of vessel from various areas, held it at a controlled length, and performed direct pressure-volume studies on it. At the same time, he was also able to measure the radius of the vessel by a sensitive photo-electric method. He found, as Fig. 3 shows, that the length at which the vessel segment was held, was critical in determining the shape of the pressure-volume curve. It was first recorded by FUCHS (1900) that arteries are held under longitudinal tension in the body and that they retract to approximately 60% of their length when excised. Bergel found that if the arterial segment was held at its 'in situ' length (as curve 1 in Fig. 3), pressure-volume relationships were practically linear from 0 to 200 mm Hg. If however, the vessel was held at a shorter length and allowed to lengthen with distension, then the sigmoid curve, 3, would be produced. He suggested that the sigmoid shapes found by Hallock and Benson, and WAGNER and KAPAL (1951), could be accounted for by this length

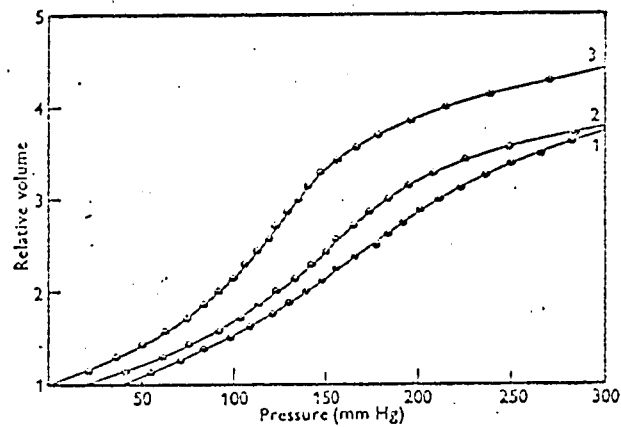


Fig. 2. Three pressure-volume curves for the same thoracic aorta. (For clarity, curves 1 and 2 are displaced horizontally.) 1, slow inflation, held at natural length; 2, fast inflation, held at natural length; 3, slow inflation, free to lengthen. Note the markedly sigmoid form of curve No. 3 which results from the vessel being free to lengthen as it is inflated. This curve also shows the greatest over-all distensibility.

FIGURE 3: Plots of pressure vs volume for the
dog thoracic aorta (from Bergel 1961)

discrepancy.

From these data, Bergel was able to calculate an incremental modulus for the different dog vessels used. He did not use C_{inc} , but used E_{inc} which is defined below.

$$E_{incP_2} = \frac{P_3 - P_1}{R_{O3} - R_{O1}} \cdot \frac{2(1-\sigma^2)R_{i2}^2 R_{O2}}{(R_O^2 - R_i^2)}$$

Where R_O = external radius
of the vessel

R_i = internal radius
of the vessel

σ = Poisson's ratio

Poisson's ratio is defined as the ratio of the lateral strain to the longitudinal strain. It is an index of the volume change of a body on stretching. If the value is 0.5, then there is no volume change on stretching and the substance is said to be isotropic. If the value is less than 0.5, there is an increase in volume on stretching, and the substance is said to be anisotropic.

It should be noted that E_{inc} is a stress-strain ratio, whereas C_{inc} is the inverse i.e.: a strain-stress ratio.

Bergel found that there was a linear increase of E_{inc} with increasing pressure levels, and that for the thoracic aorta, this was compatible with a constant value for C over a range of 0 to 200 mm Hg. In the smaller arteries however, (carotid, femoral), E_{inc} increased at a greater than proportional rate, which meant that with increasing pressure, there was diminution in the value for C . Typical

values for E_{inc} of different vessels at a pressure of 100 mm Hg are shown below.

1. Thoracic aorta 4.3×10^6 dynes/cm²
2. Abdominal aorta 8.9×10^6
3. Carotid artery 6.4×10^6
4. Femoral artery 6.9×10^6

It can therefore be seen that the smaller vessels are less elastic and have a consequently smaller comparative value for C. Thus, in the circulation at large, compliance values decrease as the smaller vessels are reached.

Reference to Fig. 4, obtained from Bergel's experiment also, demonstrates some of the problems generally encountered in assessing elasticity in these excised specimens. The first point to notice is that inflation of the specimen traces a different path to that of deflation. This observation has been made many times by investigators early in the century, but generally was considered to be an artefact of the method. However, there is now no doubt that this hysteresis phenomenon does occur. It is attributed to a viscous element in the vessel wall and becomes more pronounced, the greater the rate of stretch. The area of the hysteresis loop represents the work required to overcome this viscous factor. Measurement of E_{inc} therefore is frequency dependent. This has led to the determination of a dynamic elastic modulus (E_{dyn}) when it is desired to transpose results into the living animal. However, it has been shown that this viscous

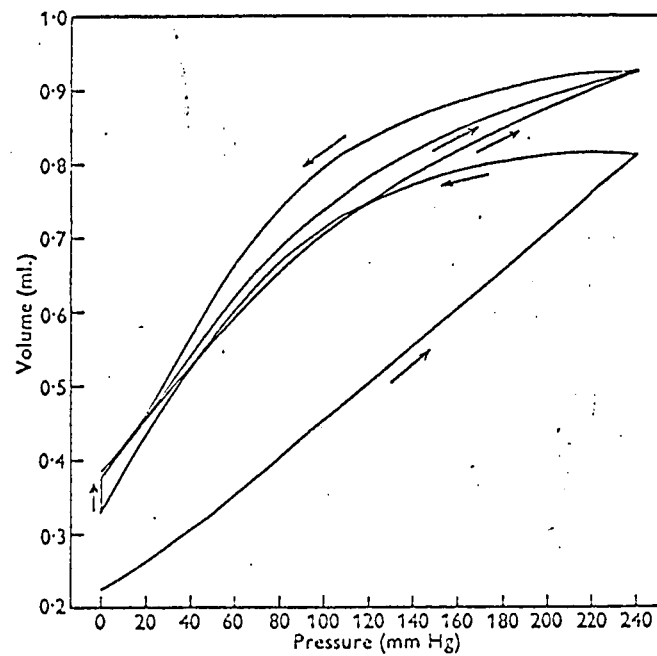


Fig. 3. Three consecutive pressure-volume curves of a femoral artery. The sequence of inflation and deflation is shown by the arrows (the last two deflations followed the same course). The vessel appears to become rather less distensible during the series of inflations (cf. Fig. 4).

FIGURE 4: Consecutive pressure-volume curves of a femoral artery (from Bergel 1961)

factor is relatively small and the ratio of E_{dyn} to E_{inc} at a frequency of 6 cps is 1.1 for the thoracic and abdominal aorta, and 1.3 for the femoral artery (BERGEL 1961a). This correlates with the amount of smooth muscle in the specimen wall. Bergel has suggested that the major contribution of smooth muscle to the functioning of the wall is to affect dynamic behaviour.

The second point to notice in Fig. 4 is that the same segment gives a different value curve each of the 3 times that it is tested. With successive testing the inflation-deflation curve becomes less distensible. This 'time-dependence' is a general feature of many biological materials. An elasticity value obtained from a given tissue may be quite different several minutes later and this appears to be related to the amount of stretching that the tissue undergoes, rather than to any slow deterioration in its biological properties (REMINGTON 1963). A longitudinal strip of vessel that is extended by a weight will quickly reach a relatively stable state, and then slowly elongate further by a process known as 'creep'.

These problems arise from the fact that the vessel walls are not homogenous, but composed of a mixture of elastin, muscle and collagen tissues. Each of these have their own different elastic constants. The internal arrangement may be such that one element is arranged to have a mechanical advantage over the others (BURTON 1954). Attempts have been made to determine elastic constants for each of these tissues. HASS (1942) extracted collagen from the dog thoracic

aorta with a concentrated formic acid solution and measured the Young's modulus of the remaining tissue. This was 3×10^6 dynes/cm² and presumably determined principally by the elastic content of the wall. ROACH and BURTON (1957) compared the properties of the elastin in the wall (as determined by Hass's technique) with the properties of the collagen in the wall. The same type of vessel was subjected to commercial trypsin treatment, which contains the enzyme 'elastase'. This removes the elastin from the wall, but not the collagen. The treatment resulted in a wall about 10 times stiffer than the one containing elastin. A vessel wall composed of such dissimilar elements can thus well account for some of the anomalous elastic properties.

A general question, which is still largely unresolved, is whether smooth muscle contraction can affect the compliance of large arteries. ALEXANDER (1954) studied a short-circuited segment of abdominal aorta in a living dog. He found that adrenalin caused a constriction of the aorta and an increase in its compliance. COPE (1964) found similar results for human aortic compliance values in an experiment to be described below.

On account of these factors, it is difficult to draw conclusions about the elastic behaviour of vessels in the living animal, from experiments performed on excised tissues.

(b) Measurement of elastic properties in living animals.

Various methods have been used to assess elastic properties

in the living animal. LAWTON and GREENE (1956) sewed beads on the outside of the dog abdominal aorta and took cine film of their movements during normal pulsation. From this they were able to calculate a pressure-volume curve for the abdominal aorta. Their results suggested that the vessel was stiffer than the excised studies showed. KATZ et al (1947) used a similar technique by taking rapid X-ray pictures (at 100 msec intervals) of the dog aorta. However, their curves showed a wide scatter of points, and the pressure-volume plots were not well determined.

Franks Windkessel theory (see later) was modified by COPE (1964) in an attempt to measure compliance in the human aorta. Using data obtained by REMINGTON (1948) on rings of excised human aorta, he formed a parabolic expression to describe the shape of the pressure-volume curve. He found that one of the constants describing the parabola was a suitable index of the compliance of the system. This could be calculated from a modification of Franks theory in which the values of the systolic and diastolic pressures and intervals, and cardiac output, were required. Using this technique, he found that compliance values in the living animal were smaller than those found in the excised aorta. Compliance values were decreased in old age.

The most usual way to obtain an index of elastic properties in the living animal is by measurement of the pulse wave velocity (c). This provides a value for C_{inc} and is easy to perform and calculate.

The implications and derivation of this method will now be considered.

Sir Isaac Newton, in Principia Mathematica (1687), published an equation attempting to account for the velocity of sound in air (c). Thus (converting to the symbols used in this discussion):

$$c = \left[\frac{1}{\rho \cdot C_{in}} \right]^{\frac{1}{2}} \quad \text{Where } \rho = \text{density of air}$$

Actual experiment gave a higher value than could be accounted for by this formula, and so began an interest, by a legion of investigators, into the propagation of sound through various media. It became apparent during the course of these studies that the velocity of sound through a liquid was dependent on whether the liquid was bounded or not. If the former was the case, as for water in an elastic tube, then the water would assume an apparent compressibility related to that of the tube.

The versatile English physician, Thomas YOUNG (1812), was the first to comment on the analogy between passage of a sound through liquid in an elastic tube, and the passage of a pressure wave through liquid in an elastic tube. Stated in another fashion, he realized that measurement of the arterial pulse wave velocity should give an index of the elasticity of the elasticity of the blood vessels. In 1878, the first theoretical expression derived for this was published by KORTEWEG. Thus:

$$c = \left[\frac{E \cdot h}{2R \rho} \right]^{1/2}$$

Where E = Young's modulus of wall

h = wall thickness

R = mean radius

ρ = density of blood

In the same year, MOENS found almost this relationship empirically in a series of experiments on elastic tubes. Thus:

$$c = k \left[\frac{E \cdot h}{2R \rho} \right]^{1/2}$$

'k' was a constant which could be empirically found to have a value of 0.9, when the blood was the fluid medium tested.

BRAMWELL and HILL (1922) transformed Korteweg's expression to eliminate the problems of measuring wall thickness and the Young's modulus. Thus, their equivalent expression became:

$$c = \left[\frac{1}{\rho C_{inc}} \right]^{1/2}$$

Solving for 'c' in terms of metres per second, and taking dP in terms of mm Hg and ρ as 1.055 for blood, this becomes:

$$c = 0.357 \left[\frac{1}{C_{inc}} \right]^{1/2} \text{ metres/sec}$$

Like Poiseuille's law, this expression has a number of qualifying conditions. These are: (1) the fluid is assumed to be incompressible, (2) the vessel to be thin-walled, so that there is a low ratio of h to R, and (3) the fluid to have no viscosity.

The first two conditions are satisfied in the normal circulation (LAMBOSSY 1951). The viscosity of the blood, however, does

have a significant effect. MULLER (1951) performed some experiments on the propagation of a pulse wave through rubber tubes filled with fluids of varying viscosity. He found that at wave frequencies of 2 cps there was a 10% decrease of pulse wave velocity over that calculated from the original Korteweg formula. This became progressively greater until a wave frequency of 10 cps was reached, from whence there was no further change. BERGEL (1961a) reached a similar conclusion. Therefore, the equation found by Moens, which contained the empirical constant 'k', is the more valid of the two relationships proposed in 1878. 'k' is thus a reflection in part of this viscous effect.

Further refinements of the theory have been considered by WOMERSLEY (1957a, 1957b). These include modifications for the viscous effect and for the fact that the elastic tube (i.e.: the vessel) is tethered by a connective tissue envelope and not free to move in all directions. In a normal dog vessel, BERGEL (1961a) has found that all these factors account for a discrepancy of approximately 12% over the simple Korteweg formula. Using values for E_{dyn} at different frequencies, he has found good agreement between calculated and experimental pulse wave velocities. In one of the few other studies of this type, REMINGTON (1945), using stretch data from isolated vessel rings, found that the theoretical pulse wave velocities were lower than the experimental ones by 10 to 20 percent.

Pulse wave velocity varies directly with the mean arterial pressure at which it is measured. This is a reflection of the decrease in C_{inc} with increasing pressure and has been documented by REMINGTON (1963). Furthermore, as BAZETT and DREYER (1922) first showed, arterial pulse wave velocity varies according to the site in the body over which it is measured. This is an expression of the decreasing compliance values found in the more peripheral vessels, as discussed earlier. Typical values for pulse wave velocities in the dog arterial tree are: thoracic aorta 4 - 5 m/sec; abdominal aorta 5.5 - 6.5 m/sec; femoral artery, 8 0 10 m/sec (DOW and HAMILTON 1939).

A further complication, in an already complex situation, is that reflected waves occur in the arterial system. These distort the shape of the pressure wave as it is transmitted down the system and so make it difficult to measure true pulse wave velocity. The evidence for reflection of pressure waves is that the amplitude of the flow pulse diminishes as it approaches the distal vascular bed, whereas the amplitude of the pressure pulse increases. This can only be explained by reflection of the pressure waves from a 'closed end'. The reflection coefficient is generally 0.3 to 0.5 (McDONALD 1960). As a result of this, there is no single reference point on the natural pulse wave which can be relied upon to remain in a standard relationship to the rest of the wave, not even, strictly speaking, the foot. This remains, however, the only practical point to use.

Therefore, as an index of the elasticity of blood vessels in the living animal, measurement of the arterial pulse wave velocity is fraught with certain difficulties. The theory on which it is based is complex and measurement of it, in the presence of reflected waves, difficult. But perhaps the largest problem is that it is difficult to interpret the term C_{inc} which is the mode of expression, in terms of primary changes in tissue elasticity, for reasons already discussed.

This section has considered some of the relative merits of the indices commonly used to measure the elastic behaviour of blood vessels. Expression in terms of compliance (C), rather than C_{inc} , was considered to be the optimum mode, because it directly answers the question which the physiologist most wants to know. The difficulties of transposing data obtained on excised tissues to the living animal, because of the inconstant properties of these excised tissues, have been discussed. The only common method of assessing vessel elasticity in the living animal is from measurement of the pulse wave velocity. This results in expression in terms of C_{inc} which can give ambiguous information concerning the elastic properties of the vessels, as the experiment of Remington pointed out.

(iii) INERTANCE

The third fundamental physical property involved when blood flows through the vascular bed is that of inertance. This is defined as the ratio of the change in pressure (P) to the rate of change of flow (dF/dt).

$$\text{Thus: } L = \frac{\Delta P}{dF/dt} \quad \text{Where } L = \text{inertance}$$

It has the dimensions of $M^{-1}L^{-4}T^0$ and has been expressed in the physiological literature in terms of gm.cm.^{-4} . It has the exact electrical equivalence of inductance.

Both resistance and inertance can be expressed in terms of velocity of blood flow (u) rather than volume of blood flow (F). In that case, 'resistance' is expressed as dynes sec cm^{-3} and 'inertance' as gm cm^{-2} . This system will not be used except as noted.

In terms of vessel dimensions:

$$L = \frac{x \rho}{\pi r^2} \quad \begin{array}{l} \text{Where } \rho = \text{density of blood} \\ x = \text{length of effective} \\ \quad \text{mass accelerated} \\ r = \text{radius of vessel} \end{array}$$

Inertance is the most neglected, and in many ways, the least quantitatively important of the three fundamental physical properties of the circulation. However, an understanding of its role is important in making a good model of the circulation.

Otto FRANK (1905) was the first to point out its importance to the complete understanding of physical events in the circulation. At that time, he compared the functioning of the arterial circulation to that of an underdamped manometer. As a result of this, the resonance theory of pulse wave propagation, an idea long current in the 1930's, came into being. Although the concept of inertance is indispensable to any resonance theory, the contribution of this factor to the magnitude of the central arterial pulse contour was rarely taken into account.

A particular difficulty in assessing the inertance factor in a system of elastic tubes is that the effective inertance is not solely determined by the mass of fluid to be accelerated and dimensions of the vessel. The forces involved in determining the parameter of inertance are vectorial and it is only the net axial flow of fluid that is important in determining the inertance. In an elastic system, particularly with a high resistance at its outlet, there is flow of fluid in both axial and radial directions. The amount of radial flow is determined in part by the compliance of the tube. Therefore, in an elastic system of tubes, the compliance factor has an important modifying effect on the effective inertance. If the compliance value is high, then the effective inertance becomes very low.

SPENCER and DENISON (1963) measured the instantaneous flow rates across the ascending aorta in dogs, and found that there is

a phase lag of flow behind the pressure gradient of approximately 90°. This demonstrates that the inertance of the blood is an important factor in the formation of the pressure wave at this point. Furthermore, the experiments of PETERSON (1954), to be described again later, showed that when an artificial pulse is given to the systemic circulation, acceleration causes a very definite and discrete pressure effect. Thus, there is no doubt that inertance is an important factor in the physical description of the circulation.

FRY, NOBLE, and MALLOS (1957) have made use of this fact by designing an ingenious method for measuring instantaneous flow velocities in the ascending aorta. They noted that the blood velocity profile in this region was practically flat. Therefore, flow at this point is governed principally by the laws of inertance, as radial flow and resistance in this region are quite negligible. The following relationship then applies:

$$P(t) = \rho \times du/dt \quad \text{Where } P = \text{pressure difference between 2 points, } x \text{ cm apart}$$

u = velocity of flow

ρ = density of the blood

Measurement of the pressure gradient in the ascending aorta by means of a double lumen catheter thus allows calculation of the instantaneous flow velocity.

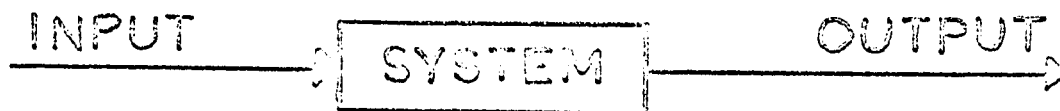
ENGELBERG and DuBOIS (1959), in a study on the pulmonary circulation, have made the only attempt that this writer has been

able to find, to quantitate inertance. Using a 4 Kgm rabbit, they attempted, speculatively as they admit, to calculate the dimensions and acceleration of the total mass of blood in the pulmonary arterial circulation. They discounted any radial flow, and so, in effect, calculated what the inertance would be in a rigid tube of the same dimensions. A value of 8 gm cm^{-4} was obtained. There is thus, an almost complete lack of quantitative information in the literature concerning this parameter.

2. THE COMPOSITE PHYSICAL BEHAVIOUR OF THE SYSTEMIC ARTERIAL CIRCULATION

Part of the knowledge described in the previous section has been obtained with the help of physical scientists. The hand of the latter is even more heavily felt when the circulation is considered as a system in the cybernetic sense. This is a relatively new concept for biologists, but a fundamentally important one if adequate theories of control are to be developed. Reference back to the basic control model on p. 5 shows the importance of understanding the behaviour of the controlled system. Much as many widely different electronic apparata are made from various basic elements, so can other 'systems' differ even though composed of the same fundamental units. It is one of the aims of this thesis to determine the type of common system which most closely resembles in behaviour that of the systemic arterial circulation. It is often helpful in the solution of these problems to attempt to build a model of the unknown system.

The general approach taken by the engineer is to subject the unknown system to a number of standard inputs. From the output response obtained, the basic laws and behaviour of the unknown system can be determined. Thus:

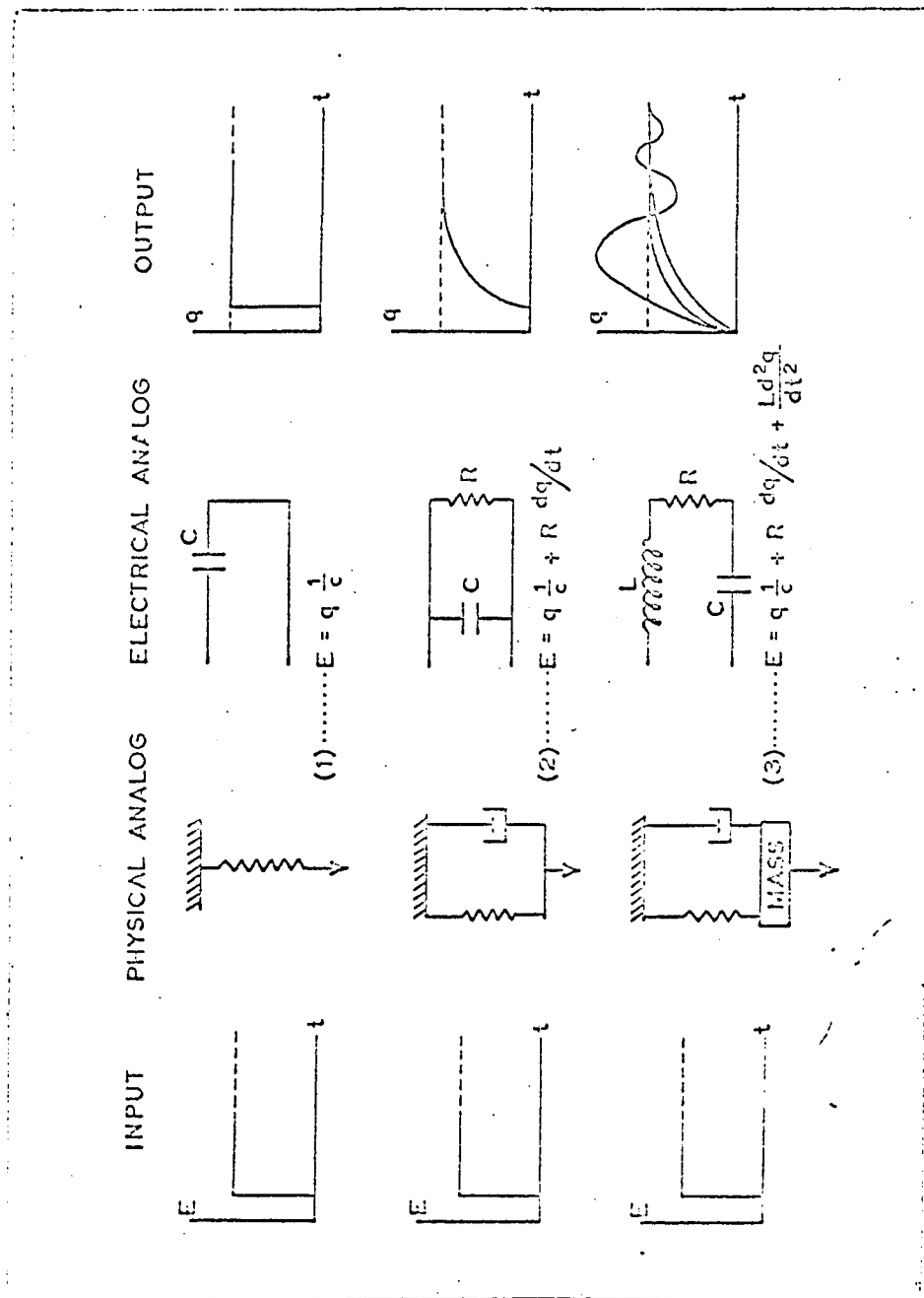


There are two types of input function that are particularly used in the study of linear systems. These are (1) a sinusoidal wave of constant amplitude: and (2), a step function, which is a sudden change of input magnitude from one steady state level to another.

Study of the response to a sinusoidal function is generally called 'frequency analysis'. In any system whose behaviour is described by greater than a zero order differential equation, there is a phase shift between input and output that varies with frequency, and a similar variation in amplitude. Plots of the amplitude and phase shift of the output against the frequency of the input provide a 'frequency response' of the circuit, from which the laws of the system can be determined.

Study of the response to a step function is generally called 'transient analysis'. It is so called because the primary object of interest is the output response during the transient phase i.e.: before it has reached a new steady state level. Linear physical systems are classified as zero order, first order, or second order, according to the class of differential equation which describes their transient response to a step function. The responses of these

FIGURE 5: The responses of linear physical systems to a step function



three types of physical system to a standard step input function are shown in Fig. 5. The second order response (equation (3)) has three alternate pathways depending on the damping coefficient of the system. Complex systems of 3rd order and higher can generally be simplified to combinations of 1st and 2nd order ones.

This, in a highly simplified form, is the general approach taken by the engineer to linear systems analysis (or, if preferred, model building). In the case of non-linear systems, as commonly occur in nature, analysis is considerably more complex and often requires computer simulation techniques (GRODINS 1963). Indeed, scepticism has often been expressed that because of the complex non-linear nature of most biological systems, little progress will be made by these approaches. It is well to remember, however, as GRODINS (1963) has pointed out, that many of the advances in physics have been built on laws for ideal gases, frictionless pulleys, and the like, and it seems not unreasonable to suppose that equivalent advances can be made in biology by making similar approximations.

This type of deliberate approach has rarely been taken in the study of the vascular system. There have been several attempts to describe models of the systemic arterial circulation, and a number of experiments performed that have direct bearing on the problem. These will now be reviewed and considered under the general headings of 'transient analysis' and 'frequency analysis',

although some of them were not consciously performed as either.

(i) TRANSIENT ANALYSIS

Otto FRANK (1899) was the first investigator to describe a model of the systemic arterial circulation. His paper attempted to describe the shape of the arterial pulse wave in terms of the physical forces and parameters of the vascular bed. It was an attempt to describe in mathematical terms the idea that Stephen Hales first put forward concerning the importance of both elastic and resistive elements. Acting in concert, these transform the pulsatile flow of the large arteries, into the more even flow of the peripheral bed. A German translator of Hales book likened this idea to a device used on the fire engines of the day, where a similar transformation was performed (pulsatile flow of the hand-pump, to the more even flow at the end of the hose-pipe). This device was called a 'Wind kessel', and to this day, the hypothesis is known as the 'Windkessel' hypothesis.

Frank proposed, 'in the process of simplification of conditions that is used universally to work out the laws that govern nature', that the systemic arterial circulation could be represented by the behaviour of the two fundamental physical properties of resistance and compliance. He further assumed that relations across both these properties were linear, in the first instance. The following relationships then occur:

$$(1) \dots \dots \frac{dQ}{dP} = C$$

Where C = compliance

Q = volume of Windkessel

P = arterial pressure
gradient

And:

$$(2) \dots \dots \frac{dQ}{dt} = \frac{P}{R}$$

Where R = resistance

On eliminating Q from (1) and (2):

$$(3) \dots \dots \frac{dP}{P} = \frac{-dt}{RC}$$

On integration

$$(4) \dots \dots \log_e P + K = \frac{-t}{RC}$$

Where K = constant of integration

Thus, when $P = P_0$ at $t = 0$, $K = -\log_e P_0$

Therefore

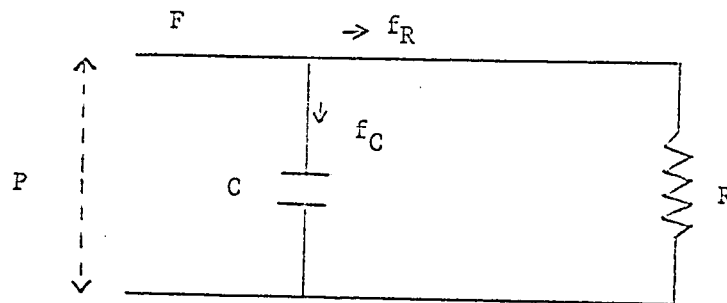
$$(5) \dots \dots \log_e \left[\frac{P}{P_0} \right] = \frac{-t}{RC}$$

Hence,

$$(6) \dots \dots P = P_0 e^{-t/RC}$$

Where P = pressure gradient at any time t.

Frank recognized that this solution is identical to that for the simple linear electrical circuit shown below.



This relationship is perhaps more clearly derived if the above circuit is considered in the following terms. Total flow into the system (F) is composed of the sum of (1) that flowing in an axial direction through the resistance (f_R) and (2) that flowing in a radial direction into the compliance (f_C). Thus:

$$(7) \dots \dots \dots F = f_R + f_C$$

$$\text{Now, } f_R = P \cdot \frac{1}{R} \text{ and } f_C = C \cdot dP/dt$$

Thus the equation of the circuit at any moment in time becomes

$$(8) \dots \dots \dots F = P \cdot \frac{1}{R} + C \cdot dP/dt$$

Thus, this is a first order, linear, differential equation (cf. Fig. 5 eq. (2)). The system is therefore, a first order linear system. If, for a moment, the circulatory system is again considered, it will be seen that when, during diastole, the aortic valve suddenly snaps shut, the input into the system suddenly becomes zero. Thus, in effect, a step function is given which is in

a reverse direction to those shown in Fig. 5. Therefore, continuing with the solution of equation (8) when the aortic valve closes, $F = 0$. Then:

$$(9) \dots\dots\dots P \cdot \frac{1}{R} = -C \cdot dP/dt$$

The solution for P is as before:

$$(6) \dots\dots\dots P = P_{Oe} - t/RC$$

Thus, the transient response of a linear first order system (which, by definition, this analogue becomes) to a step function is exponential in nature. It has a time constant determined by the product of R and C . If this is a correct analogy with the systemic arterial circulation as Frank first postulated, then the fall of the pressure pulse during diastole should be exponential in form. Examination of this curve, therefore provides information about the order of system involved.

Certain assumptions are required in postulating that the systemic arterial circulation behaves in a manner analogous to that of a linear first order system. As these are important to the work of this thesis, they are listed below.

- (1) relations between pressure and flow across the whole systemic arterial circulation must be linear.
- (2) relations between pressure and volume in the systemic arterial circulation must be linear.
- (3) inertance must be relatively unimportant.

- (4) pulse wave propagation must be infinitely fast, so that pressures in the large arteries are everywhere equal.
- (5) the pressure response must not be distorted by wave reflections.
- (6) the controlled system must remain uninfluenced by the controlling system during the time of testing i.e.: the vascular bed must be in a steady state.

Frank examined the diastolic portion of the pressure curve (which he prolonged by vagal nerve stimulation) for evidence of exponentiality. Inspection of equation (3) shows that the ratio of dP/dt to P (that is, the ratio of the rate of change of pressure to the instantaneous pressure at any one moment) should be constant if the pressure response is exponential and the asymptote of the curve is zero. Frank did not find this, and so drew the conclusion that there was a non-linearity in either the pressure-flow, or pressure-volume relations.

COPE (1911) noted that in formulation of pressure-flow relations, as in Frank's equation (2), venous or capillary pressure was usually ignored, so that the absolute aortic pressure came to be taken as the pressure gradient across the arterial circulation. The effective pressure gradient, though, is that between the aortic pressure and the pressure in the

peripheral capillaries (P^+)*. As EADIE and McCRAE (1934) showed, Frank's equation (2) should read:

$$(10) \dots \frac{dQ}{dt} = \frac{(P - P^+)}{R}$$

On substitution of this expression in Frank's theory, integration yields:

$$(11) \dots \log_e \left[\frac{P - P^+}{P_0 - P^+} \right] = -t/RC$$

Or:

$$(12) \dots P = (P_0 - P^+)e^{-t/RC} + P^+$$

Equation (12), on substituting P_{ss}^+ for P^+ , becomes a more general statement of the response of the system to a step function, than does equation (6). It takes account of the step function response that does not begin or end at zero.

Thus:

$$(13) \dots P = (P_0 - P_{ss}^+)e^{-t/RC} + P_{ss}^+$$

P_{ss} denotes the steady state response to any constant input function. It can be seen that equation (13) is the sum of two terms. The first, called the complementary function, is an expression of the transient response of the system. The second (P_{ss}) is called the particular integral, and represents the steady state response of the system.

Under the circumstances of eq. (10), one would not expect

*Symbol changed from the original paper for uniformity of presentation.

a constant quotient of $\frac{P}{dP/dt}$, even if a linear relationship did exist, because of the non-zero intercept (i.e.: equation (3) requires modification to the form, $dP/dt = -(P - P^+)/RC$). Thus Frank's experimental evidence did not really disprove the essence of his simple linear theory.

This Windkessel model of the circulation, introduced at the beginning of the century, acted as a focal point for much of the work in haemodynamics in the 1920's and 1930's. It acted as a stimulus towards the understanding of pulse wave reflections in the circulation, and for a long time, was the source of attempts to calculate stroke volume from the central arterial pulse pressure. The value of expressing ideas, however simple, in definitive mathematical terms (in other words, model-building) was gradually becoming apparent.

The nature of the diastolic pressure curve is of considerable interest to the systems analyst. It represents the response of the circulatory system to a step function. If this response is exponential in form, then the systemic arterial circulation can be classified as a first order linear system, and the first step towards building a model is achieved. A number of investigators have examined the nature of this curve, and their results will now be reviewed.

EADIE and McCRAE (1934), prolonging the interval between heart beats by vagus nerve stimulation, analysed 60 diastolic pressure curves from six open chest dogs. They found that two-thirds of them gave a straight line on semi-log plot of aortic pressure against time. This indicates, as simple inspection of eq. (6) shows, that the curves were exponential, and furthermore, that the aortic pressure did actually represent the pressure gradient across the arterial circulation (i.e.: $P^+ = 0$). In the remaining pressure curves from the open chest dogs, and nearly all the 155 pressure curves from 8 closed chest dogs, P^+ was greater than 0 and varied up to 40 mm Hg. They also noted that P^+ was greatly increased by the use of pressor drugs.

DOW and HAMILTON (1939) occluded the dog aorta at varying levels, using an inflatable balloon, and measured the 'diastolic' pressure curve at the popliteal artery. Occlusion generally lasted from 4 to 10 seconds, and a plot of the rate of fall of pressure (obtained by means of a Richards-Rooke tangent meter) against instantaneous pressure was made, in the analysis of 35 curves from 4 dogs. They found that the plots were linear (therefore, the curves exponential) for the steep pressure fall from 90 to 60 mm Hg, and would have intercepted the pressure axis at 50 mm Hg if extrapolated. However, the plots became curvilinear in the lower pressure regions, so that the actual pressure axis intercept at zero flow was of the order of 20 mm Hg. They point

out, that, in their preparation, collateral channels supplying the occluded bed were not blocked, and that this may have had some influence on the pressure changes.

GOMEZ and VEIL (1936) and GOMEZ (1937), performed similar studies on dogs and humans. They found that the free-falling pressure curve in diastole was exponential in form, and approached an asymptote, which they designated as parameter ' ω '. This represented the 'counter pressure' of the peripheral circulation. It could be calculated from the diastolic pressure curve by the following formula:

$$(14) \dots \dots \dots ' \omega ' = \frac{P_0 P(2) - P(1)^2}{P_0 + P(2) - 2P(1)}$$

Where P_0 = pressure at beginning
of diastole

$P(2)$ = pressure at end of
diastole

$P(1)$ = pressure at a point
equidistant in time
from above values

The derivation of this equation will be considered later. A semi-log plot of aortic diastolic pressure minus ' ω ', against time, gave a straight line. Therefore, (see and compare Eadie and McCrae above) this indicates that the diastolic pressure curve is exponential. Values for ' ω ' (which, in actual fact, are the asymptotes of the curves, P^+) varied from 34 to 110 mm Hg with an average value of 74 mm Hg.

The cardiac impulse has been simulated by STARR (1957) in five human cadavers, by a blow from a heavy pendulum onto the plunger of a syringe placed in the aorta. This produces a rise in pressure in the arterial system, in analogy with natural cardiac ejection. The free-falling pressure in 'diastole' for 43 curves has been analysed for its correspondence to Gomez' data in the living human. These curves were monitored for 5 to 8 seconds, and in no case, did the pressure fall to zero. Those starting from a high or normal level, were still falling slowly when the record was terminated, while those starting from low pressures levelled off if followed 'for long enough time'. Values calculated for ' ω ' had good correspondence with those calculated by Gomez in living subjects. However, it was pointed out that these values (70 mm Hg) were considerably in excess of the asymptotes actually reached (35 mm Hg) and suggested that this discrepancy was due to secondary vibrations at the beginning of the curve. Again, from straight lines obtained on semi-logarithmic plots, Starr drew the conclusion that the curves were 'essentially exponential in form'. In previous investigations, STARR (1953) had demonstrated that the peripheral resistance in these cadaver experiments was comparable with those in the living subject.

These scattered experiments therefore suggest that the diastolic pressure curve is, under certain circumstances, closely exponential in nature, and hence, that the systemic arterial

circulation can be considered as a linear first order system, as Frank first proposed.

The only study to the writer's knowledge, that has attempted to impose a definite function on the vascular system in the manner of an engineer, is that of PETERSON (1952, 1954). He designed an apparatus to deliver a 'square wave' infusion of fluid to the circulatory system. Saline solution was injected into the dog aorta through a cannula connected to a constant pressure head reservoir (with pressures of 25 to 125 p.s.i.). The head of the cannula was closed by a solenoid valve, but this could be rapidly opened at any phase of the cardiac cycle by an electrical signal actuated from the ECG. The speed of opening was such that a constant velocity of injection could be achieved in 6 milliseconds.

By imposition of this square wave input into the systemic arterial circulation, its response to a step function could be further studied. The transient response of a first order linear system to such a square wave function should be exponential, as previously discussed for the diastolic pressure curve. The first 'step' in Peterson's experiments, (a square wave is a combination of two step functions in opposite directions) should give an up-going exponential response as shown in Fig. 5.

The kind of response which Peterson actually obtained when he injected this square wave infusion between normal heart beats

is shown in Fig. 6. It can be seen that there was an initial peak of pressure at the beginning of the infusion, which became greater the lower the blood pressure. This was attributed to the acceleration of the blood and called the 'acceleration transient'. What is seen of the rest of the transient pressure response appears to be roughly linear, rather than exponential, as would be expected from a first order system. However, it was not recorded whether these transient pressure responses were specifically analysed concerning this point.

These results of Peterson, while lacking any quantitative data, further demonstrate that the inertance factor (or 'acceleration transient' as Peterson called it) must be taken into account when considering the formation of the central arterial pressure pulse. It also means, in terms of building a model, that the arterial circulation cannot be completely described in terms of a linear first order system.

(ii) FREQUENCY ANALYSIS

The normal arterial pulse has two phases, systolic and diastolic. It has already been seen in the previous section that the diastolic part, as the aortic valve snaps shut, can be considered to generate a natural step function to the system. Analysis of the diastolic pressure curve thus becomes a 'transient analysis' and furnishes useful information about the composite physical behaviour of the system. The input to the system during the systolic

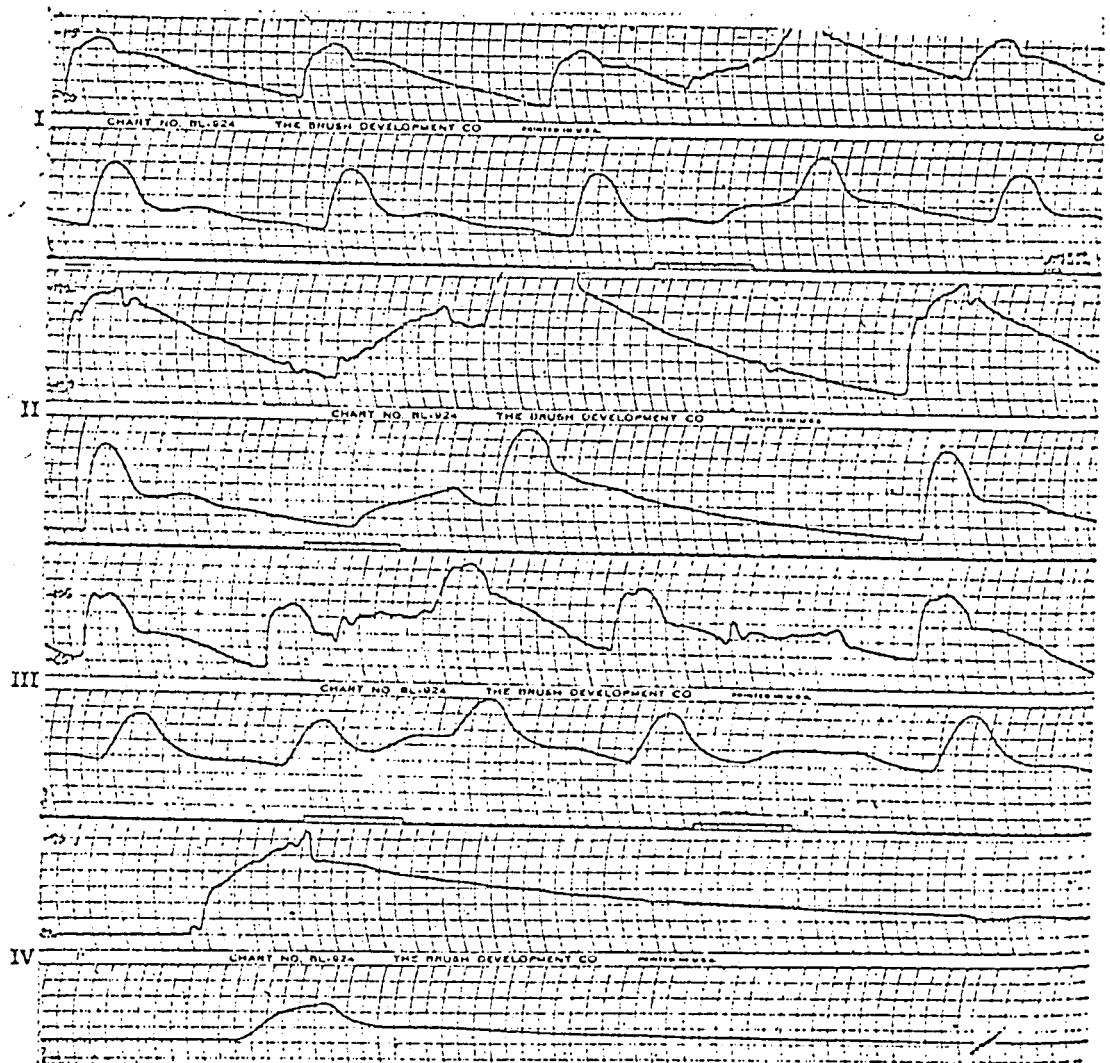


FIG. 9. Four sets of double channel recordings of arterial blood pressure. Upper record in each pair was obtained from the ascending aorta while the lower record was simultaneously recorded from the femoral artery. Vertical lines are 5 mm. apart. Paper speed was 125 mm. per second in all records. Pressure in millimeters Hg is noted on the left margin of each aortic pressure record. Discussion in text.

FIGURE 6: The response of the dog systemic arterial circulation to a step function (from Peterson, 1952)

part of the pulse is more difficult to define exactly, but is broadly in the form of a sinusoidal function. Thus the normal beating of the heart can be considered to generate a sinusoidal input to the system of relatively constant magnitude. Therefore, an opportunity also exists for what engineers call a 'frequency analysis' of the circulation.

This is a current interest in circulatory physiology. Although Otto Frank raised the possibility in two papers in 1905 and 1927, it was not until the late 1950's that this analytical technique began to be explored in any depth. Womersley and MacDonald were the two principal pioneers, and the basis of their approach lay in a proper description of the shape of the pressure pulse by means of a Fourier series.

This is a general mathematical technique whereby any periodic oscillation (such as the normal arterial pulse wave) can be considered as the sum of a number of different sine waves. These sine waves must be at frequencies which are integral multiples of the fundamental frequency of oscillation. In the case of the pressure wave, the fundamental frequency of oscillation is that generated by the heart i.e.: the pulse rate. In general, a Fourier series developed to the level of the fifth harmonic (i.e.: a sine wave at five times the fundamental frequency) will mathematically describe 90% of the shape of the pulse wave.

Womersley realized that, in application of the Fourier series technique, the naturally-occurring pulse wave could thus be considered as the sum of a number of pure sine waves. In 1955, he developed a theoretical expression to correlate a sinusoidal pressure gradient to the corresponding sinusoidal flow, for movement of a viscous fluid through a rigid tube. The expression was developed from Navier and Stokes (1840) general solution for the equation of motion of a viscous fluid. When the frequency of oscillation is zero, it reduces to Poiseuille's expression. It is subject to the same set of conditions as Poiseuille's law (see previous section), except that the pressure gradient is oscillatory, rather than steady. This results in a fluid velocity profile that is flat, rather than parabolic. The expression is reproduced below to give an indication of the characteristics of the relationship.

$$(15) \dots\dots\dots Q = \frac{\pi R^4}{\mu} \cdot \frac{M}{\alpha^2} \cdot M \sin(\omega t - \phi + \Sigma)$$

Where Q = flow ml/sec

M = modulus (amplitude of pressure gradient

ω = frequency of sine wave

ϕ = phase of pressure gradient

$$\text{where } \alpha = R \cdot \frac{2\pi f \rho}{\mu}$$

where R = radius of vessel

f = pulse frequency

μ = viscosity of the blood

ρ = density of the blood

M' and Σ are dependent on the value for α and are calculated from Bessel functions. α is a non-dimensional constant, and when the flow becomes steady, $\frac{(M')}{\alpha^2}$ becomes 1/8. Furthermore, the

value of Σ at steady flow tends to 90°, so the term $M \sin (\omega t - \phi + \Sigma)$ becomes $M \sin (\omega t - \phi + 90^\circ)$, or $M \cos (\omega t - \phi)$. The latter is entirely equivalent to the pressure gradient expressed as

$$\frac{P_1 - P_2}{l}$$

Hence, for constant flow, equation (15) reduces to:

$$(16) \dots \dots \dots Q = \frac{\pi R^4}{\mu} \cdot \frac{1}{8} \cdot \frac{P_1 - P_2}{l}$$

which is Poiseuille's expression.

Equation (15), at any particular frequency is a linear equation i.e.: as in the particular solution for Poiseuille's law, pressure gradient is assumed to be linearly related to flow. The calculation of vessel flow from equation (15) requires the measurement of pressure gradient and radius of the vessel, exactly as does the more specific solution of the equation shown in (16). Womersley's theory also assumes (1) that the tube is rigid, and (2) that the pressure gradient is a function of time only (whereas it is generated

by a pulse wave of finite velocity).

This theory relating sinusoidal pressure gradient and flow can thus be considered to represent an application of Poiseuille's law to an oscillating system. MacDONALD (1955) measured pressure gradients and flow velocity in the dog femoral artery, and compared observed and calculated flow rates. He found agreement, particularly in regard to phase relationships, to be 'reasonable, but far from perfect'. He commented that measurement of pressure gradients (on a differential manometer) was difficult because of the great accuracy required, maximum values being of the order of 3 mm Hg/cm. Furthermore, an error of 0.1 mm in the measurement of the radius of the vessel could give rise to a 30% change in calculated flow.

This 'simple' theory, as noted above, ignores the elasticity of the larger vessels, which undergo a -3 to 4% change of mean radius under physiological conditions (MacDONALD and TAYLOR (1959). WOMERSLEY (1957) has considered the theoretical modification for this, and found it to be negligible, having regard to the accuracy of experimental measurement required for the 'simple' theory.

Much work has been done using this kind of approach, relating oscillating pressure gradient (expressed in terms of a Fourier series) to flow. The obvious analogy is with the electrical

theory of alternating current. Indeed, the electrical practice of relating alternating voltage to alternating current in terms of impedance, is commonly recognized in haemodynamics, by the expression of the analagous relationship (alternating pressure gradient to alternating flow) in terms of impedance also. Under these circumstances, the values of the fundamental physical properties of resistance, compliance, and inertance, all become frequency dependent, and are more conveniently expressed in terms of the phase and modulus of the single output parameter, rather than in discrete terms referable to each of these three physical properties. (cf. the expression of pressure gradient in eq. (15) in terms of modulus and phase, and the expression of pressure gradient in eq. (8) in terms of discrete sums referable to each physical property). Note that strict analogy is with the theory of high frequency alternating currents where the size of the resistor becomes finite. This has the effect of making the value for resistance, frequency dependent also (see the experiments of TAYLOR 1959).

An example of the frequency analysis type of approach is the experiment performed by DICK, KENDRICK, MATSON and RIDEOUT (1968). The linearity of the system in a dog was tested by the imposition of two different sinusoidal pressure frequencies (f_1 and f_2) into the systemic arterial circulation. It is a feature of linear systems, that although the output signal will be altered in terms of amplitude and phase, the basic frequency of the sine wave (f_1 or f_2) input

should be unchanged. DICK, KENDRICK, MATSON and RIDEOUT (1968) found that the dog systemic arterial circulation behaved in a basically linear fashion, with few intermediary frequencies between f_1 and f_2 . When nor-adrenaline, in a dose of 10μ gm/Kgm/min was given, however, these intermediary frequencies increased in number, and the conclusion was drawn that the system had become more non-linear.

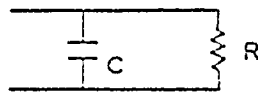
Frequency analysis, by making various plots between the phase, amplitude, and frequency of the response, provides the engineer with information about the stability of a system. Espousing, as it does, the impedance concept, it is well suited to analysis of the complex pressure changes which occur in the vascular bed as a result of wave reflections (McDONALD 1960). Frequency analysis also provides information concerning the 'transfer function' of the system (ie: the laws relating input to output), so that the output response, in terms of phase and amplitude can be predicted from the input. However, frequency analysis does not generally provide information about how the system accomplishes this task in terms of changes in the fundamental physical properties (eg: R, C, and L). And this is the question, rather than the question of stability (which is usually self evident), which most concerns the biologist.

Transient analysis is generally better suited to the solution of this latter problem, because it involves an inductive reasoning process. This can be illustrated by the approach taken to model building in the systemic arterial circulation (see Fig. 7). The first model proposed for the circulation was the simple 'Windkessel' by FRANK (1899). This was generally a theoretical proposition with no experimental data given for the values of resistance and compliance from which it was composed. In 1905, Frank recognised the importance of the inertia of the blood, and added an inertance factor. Further elaboration of the model occurred when LANDES (1949) noted the progressive decrease in compliance as the pulse wave progressed to the periphery. He proposed an analogy between the systemic arterial circulation, and that of an electrical transmission line.

It is today generally accepted that the transmission line hypothesis is a reasonably valid one for the arterial system. However, acceptance of this conceptual framework does not constitute the making of a model. The problem still remains of determining the values of a various resistances, compliances, and inertances involved. Frequency analysis cannot provide the answer to this question because it only deals with the complex wave forms found in the circulatory system in terms of phase and modulus. Attempts have been made to build transmission line models empirically so that their response matches the general frequency response

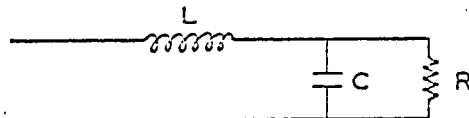
ELECTRICAL ANALOGUES OF THE SYSTEMIC CIRCULATION

1.



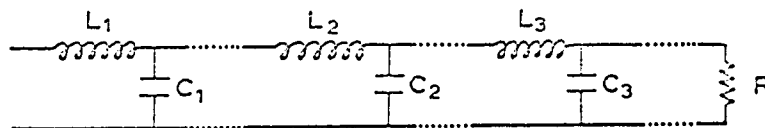
WINDKESSEL MODEL

2.



SERIES RESONANCE CIRCUIT MODEL

3.



TRANSMISSION LINE MODEL

FIGURE 7

of the circulation. Some of these have involved as many as 600 lumped segments (DePater and VAN DEN BERG 1964, VAN TWEEL, 1957). However, these solutions are not unique, and the values used for the physical properties, when not based on biological experiment, must be considered highly presumptive. The technique of transient analysis, at least for simple systems, provides a method whereby the values for R, C, and L can be experimentally determined. This is a better approach to model-building, because it used the process of induction rather than that of deduction.

Frequency analysis and transient analysis are both useful techniques. Frequency analysis is currently much in evidence, but transient analysis has become a rather neglected field. It is proposed to further explore the possibilities of its application to the circulatory system in this thesis.

3. CONCLUSIONS FROM THE LITERATURE REVIEW

This review of the literature has revealed the following issues which still require further investigation or clarification:

- (1) direct pressure-flow relations across the whole systemic arterial circulation (SAC):
 - little evidence is available concerning their linearity, or non-linearity.
- (2) pressure levels across the SAC at zero flow rate (P^+):
 - such evidence that there is, suggests that these are significant, and can lead to ambiguities in the interpretation of pressure-flow data (as, for example, in the study of shock) unless true slope-resistances are measured.
- (3) direct pressure-volume relations across the SAC in living animals:
 - no simple, practical, methods for measuring compliance in living animals are available; expression of elasticity in terms of C_{inc} , which pulse wave velocity measurement provides, can be complex and ambiguous.
- (4) measurement of effective inertance across the SAC:
 - virtually no quantitative measurement.

(5) composite physical behaviour of the SAC as a system:

-much evidence to suggest that it acts mostly as a linear first order system, but the inertance component must also be taken into account.

It is often said that circulatory physiology is an over-worked field, yet this survey of the literature concerning the physical behaviour of the arteries, has suggested that there are many gaps to be filled in fundamental knowledge. Better methods to measure the basic physical properties of arteries are still required.

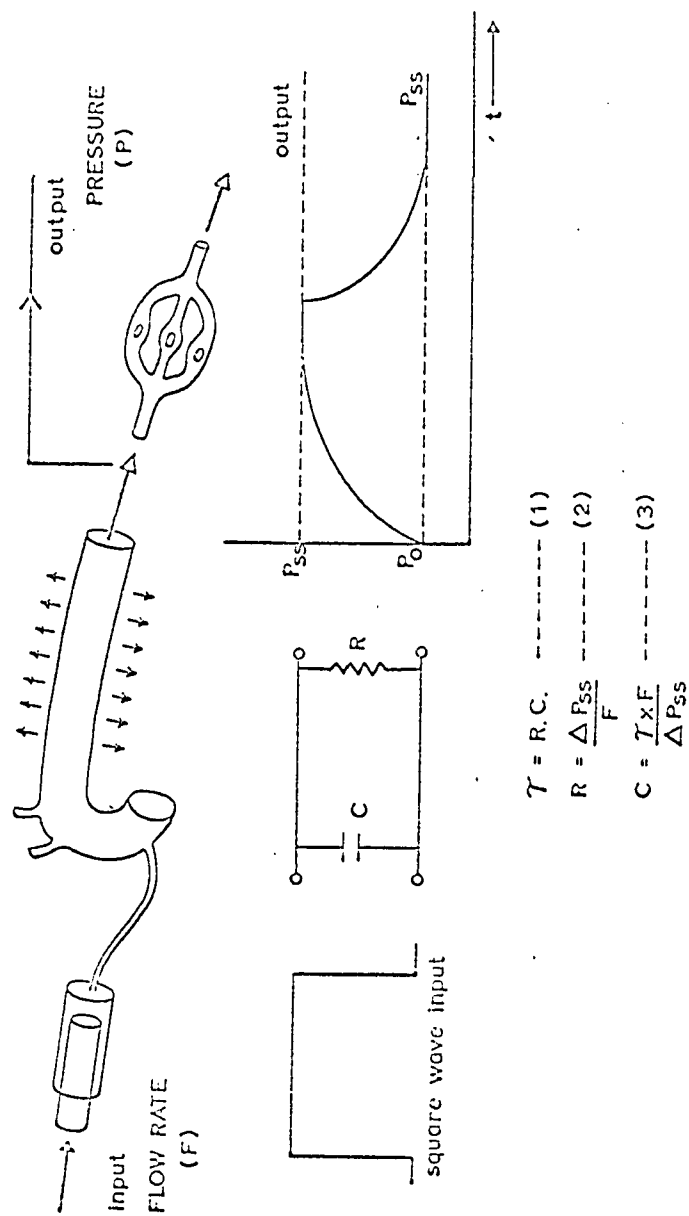
4. INTRODUCTION TO THE PRESENT INVESTIGATION

The original plan of the investigation was to study pressure-flow relationships across the whole systemic circulation. As the experiments progressed, information became available about other physical properties in the circulation. The scope of the investigation then widened to include study of all the physical properties in the systemic circulation that the giving of a square wave infusion allowed. Essentially an engineering approach was adopted. The general objective became to determine if the following simple theory, based on the analysis of transients, could be applied in a practical and useful manner to the study of circulatory problems.

Implicit in the above statement, was development of a technique to impose a square wave function on the systemic circulation in the absence of other disturbing factors, and study of the various parameters that the simple model below allows. In so doing, an attempt would be made to answer most of the questions raised by the literature review, listed on the previous page.

The basic proposition was that the systemic arterial circulation is considered to act primarily as a linear, first order system, as shown in Fig. 8, and as first proposed by FRANK (1899). The small vessels were considered to represent the resistance, and the large elastic vessels the compliance. The equations for such a system have been developed on p. 62, where it was shown that:

FIGURE 8: The systemic arterial circulation considered as a linear first order system



$$F = P \frac{1}{R} + C \cdot dP/dt \dots\dots\dots(8)$$

Consider the pressure response of such a system to a square wave infusion. The square wave begins and ends with a step function. The pressure response to such a step function is exponential in nature, as developed on p. 64, where it was shown that:

$$P = P_0 e^{-t/RC} \dots\dots\dots(6)$$

This exponential pressure has a certain time constant (τ) which, by definition, is numerically equal to the product of R and C -see Fig. 8 eq. (1). The time constant is directly measurable from the pressure tracing.

If the square wave infusion is continued for a sufficiently long period of time (roughly equivalent to four time constants) then the pressure response will reach a steady state where its value is no longer changing. Equation (8) then becomes reduced to:

$$F = P \frac{1}{R} \dots\dots\dots(2)$$

However, it is important to have regard to the modification of this equation suggested by EADIE and McCRAE (1934) to account for the possibility that pressure may not be zero when flow is zero. Under these circumstances, to correctly determine R, it is necessary to know the value of a second steady state pressure. This can be conveniently determined from a single square wave

infusion by measuring the steady state pressure levels reached when the flow is 'x' ml/min and when it is 0 ml/min as shown in Fig. 8. This allows direct calculation of slope resistance from the recording. Thus being able to measure the time constant and slope resistance directly from the recording, it is a simple matter to calculate compliance as in eq. (3) Fig. 8. The application of this theory is dependent on fulfillment of the conditions mentioned on p. 62

Although simple enough in theory, there were many practical problems to be resolved in the pursuit of the above approach. One of the most important of these was to find a suitable method of analysing the exponential pressure response. The following transformation proved, ultimately, to be the most convenient and accurate method of extracting the relevant data.

Consider eq. (9), which represents the response of the system to a step function, as developed on p. , modified to account for the possibility that pressure may not be zero when flow is zero (i.e.: P^+)

$$(P - P^+) \cdot \frac{1}{R} = -C \cdot dP/dt \quad \dots\dots\dots(17)$$

As R , C , and P , are constants at one particular level of tone in the circulation, the ratio of the rate of change of pressure to the instantaneous pressure at any moment will be constant. If

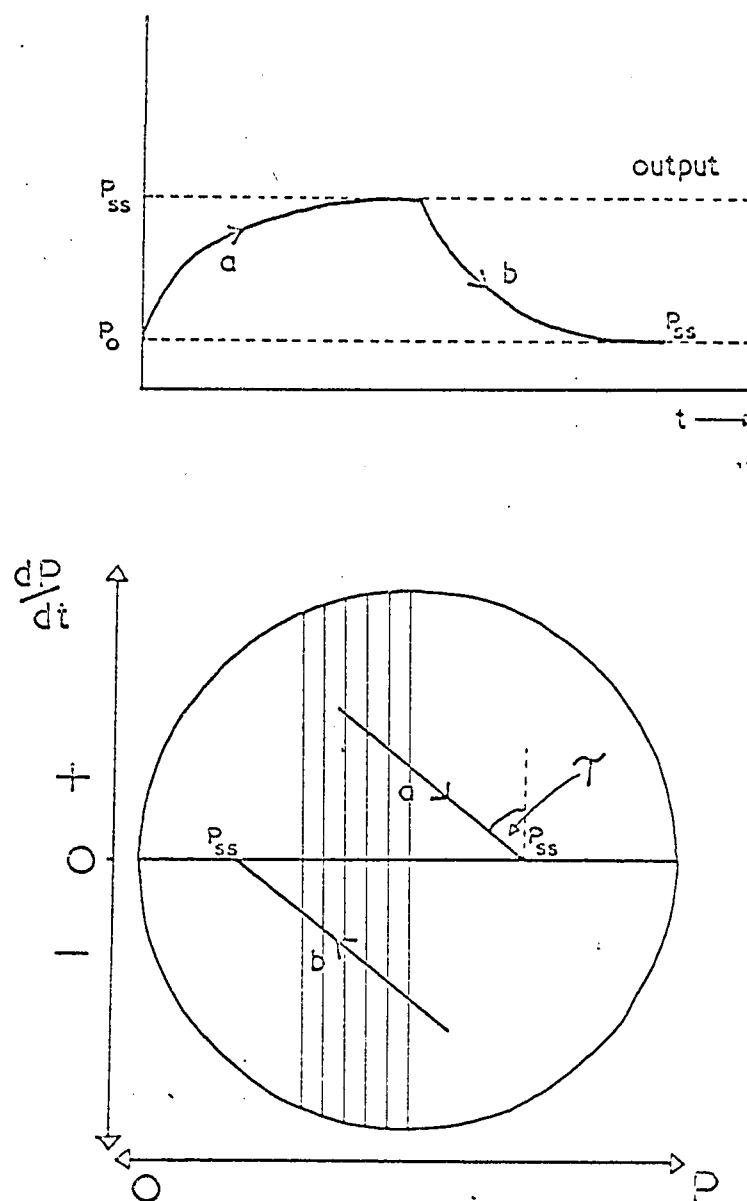


FIGURE 9: Phase-plane transformation, of the pressure response of the system, to a square wave function

these two parameters are plotted against each other, as shown in the lowergraph of Fig. 9, then a straight line should be obtained, whose acute angle of reference to the ordinate should be a function of the time constant (τ) of the system. Such a plot, where a function is plotted against its first derivative, is generally called a phase plane plot.

Modifying eq. (8) to account for P^+ , the equation of the system then becomes:

$$F = (P - P^+) \cdot \frac{1}{R} + C \cdot dP/dt \quad \dots\dots\dots(18)$$

When $dP/dt = 0$, as on the abscissa of a phase plane plot (see Fig. 9), this reduces the expression to:

$$F = (P - P^+) \cdot \frac{1}{R} \quad \dots\dots\dots(19)$$

Therefore, the points where plots 'a' and 'b' intercept the abscissa, represent the two steady state pressure responses. The difference between these two points then gives the steady state pressure gradient (ΔP_{SS}) at any flow rate (F), and so allows slope resistance to be calculated as in eq. (2) of Fig. 8. The linearity of these plots is a good way of assessing whether any particular pressure response is exponential, or not.

As familiarity with this transformation is important, the eye should look primarily at three aspects of the phase plane plot. These are:

- (1) its linearity, as evidence of an exponential response.

- (2) the acute angle which each plot makes with the ordinate as evidence of the time constant of the curve.
- (3) the intercepts of each plot with the abscissa, as an index of the slope resistance of the system. (Further the lower plot, as in 'b', generally occurs when $F = 0$, so its intercept represents the 'critical closing pressure' of the system i.e.: P_{ss}^+).

A technique was developed to perform the transformation electrically and so produce an instantaneous way of measuring these parameters in the system.

Much of the work to be described concerns development and verification of this analytical technique. An attempt was made to correlate the property values obtained with those of independent methods. Application of the technique to determine the effects of some common stresses on the system was also undertaken. Finally, an attempt was made to synthesize all the knowledge obtained and make a simple model of the systemic arterial circulation.

CHAPTER 2

METHOD

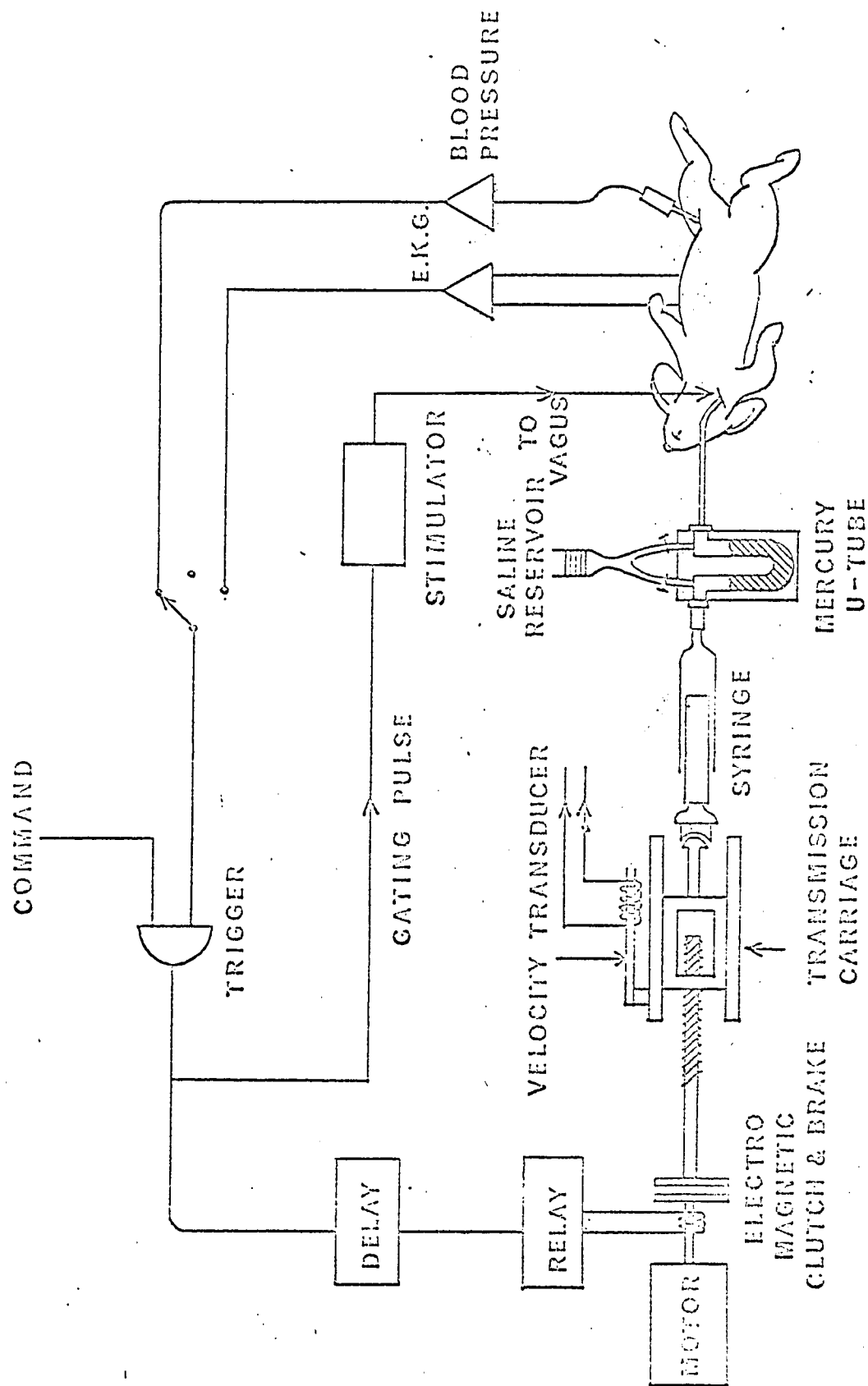
The general aim of this study was to give a square wave infusion of blood to the animal (rabbit) during a period of brief heart stoppage. By recording the pressure response obtained, a 'transient analysis' of the system, along the lines discussed in the previous section, could be made. It was necessary to develop certain techniques, and build pieces of apparatus, both mechanical and electrical, to this end. These will now be described.

1. DEVELOPMENT OF AN APPARATUS TO DELIVER A SQUARE WAVE INFUSION OF BLOOD

No satisfactory commercial piece of apparatus could be found to give a square wave infusion of fluid. Therefore it was necessary to build one, and the principals of the technique finally adopted are shown in Fig. 10.

A large, servo-controlled motor drove a transmission carriage at any desired and constant speed (monitored by the linear velocity transducer attached to it). A glass syringe was attached to the transmission carriage, and therefore infused blood at the same constant speed into the animal, through the intermediary of a mercury U-tube, whose function will be described later. The motor, which was left running continuously, was connected to the

FIGURE 10: Apparatus designed to give a square wave infusion of blood



transmission carriage by an electromagnetic clutch and brake combination. This was capable of causing engagement, or disengagement, of the motor in approximately 25 milliseconds, so that a virtual square wave infusion of blood would be given. The functioning of the clutch-brake combination was controlled by a complex electrical trigger system. Generally, the apparatus would be required to infuse approximately 5 ml of blood over a time period of $1/2$ to $1\frac{1}{2}$ seconds. Because of the short time intervals involved, a high degree of precision was required. The type of function which this system delivered into rigid tubing, is shown in Fig. 11B.

(a) Original Prototype Apparatus:

At the very beginning of the investigation, a commercially available infusion pump was used (Withdrawal-Infusion pump, Model 600-900, Harvard Apparatus Co., Dover, Massachusetts). This drove a 10 ml syringe which was connected to the animal by a cannula in the right carotid artery. The motion of the syringe was monitored by the movement of a steel shaft along a linear resistor.

This system had a number of defects. The build-up time to reach a constant speed was 200 to 400 msec., quite insufficient for most of the purposes of this investigation. The speed of the motor was not really constant enough for precise work. This was not aided by the fact that the carriage sat on only half of the thread.

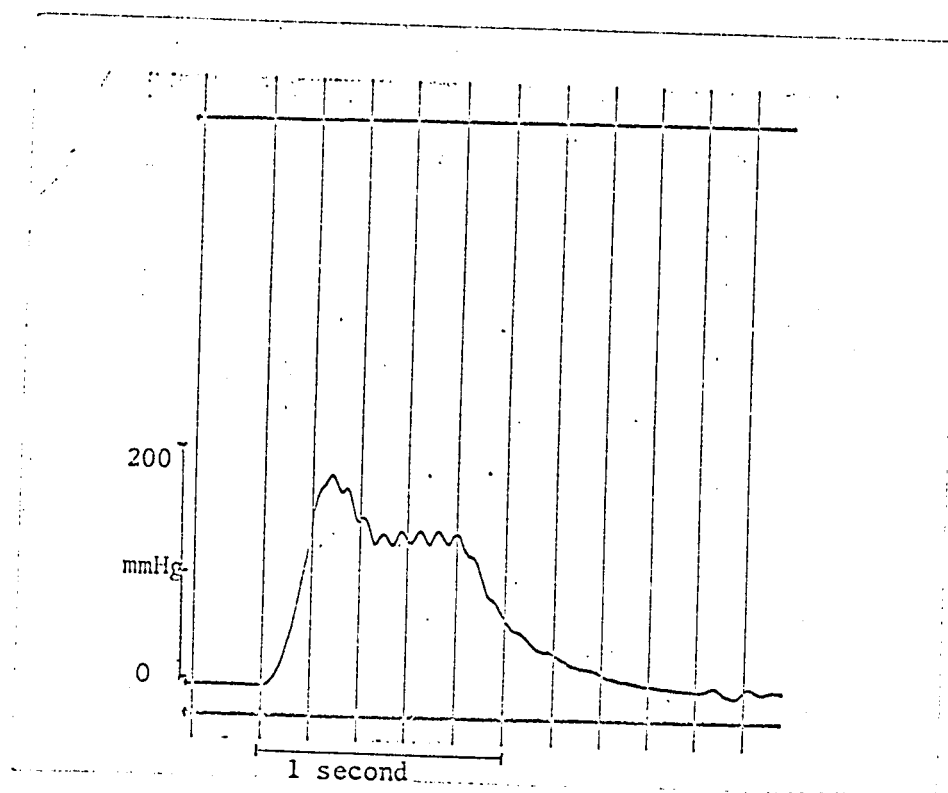


FIGURE 11A: "Square wave" function delivered by the prototype apparatus into rigid tubing

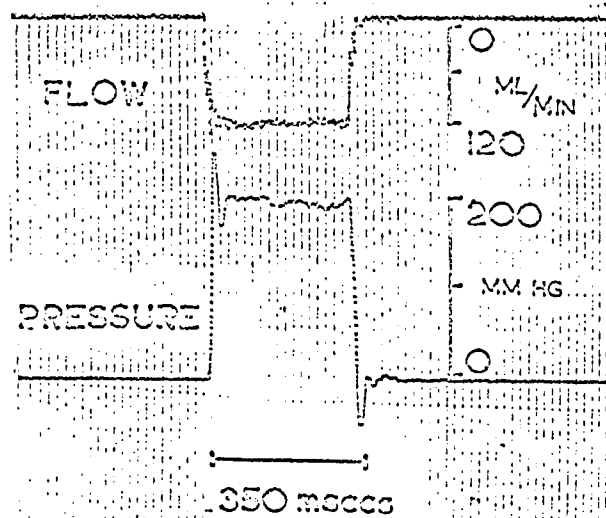


FIGURE 11B: "Square wave" function delivered by the apparatus used throughout most of the experiment,* into rigid tubing

* as in fig.10

Further, the resistor device used to measure the motion of the syringe, was not strictly linear, and gave a step response as the shaft bounced from one turn of the wire to another. (See Fig. 32)

An attempt was made to modify this system. The original motor of the infusion pump was replaced by a 1/16 H. P. motor with a variac control system (Bodine Electric Co., Chicago, U.S.A.). Attempts were made to seat the carriage more securely on the thread by a system of weights, and thrust bearings were added to facilitate smoother movement. These alterations gave a better constant speed response, but the build-up time was still about 200 msec. as can be seen from the type of function which this system delivered into rigid tubing (Fig. 11A). However, it was possible to use this apparatus for the early pilot experiments on rats, where a precise step function was not required.

This prototype apparatus helped to point out some of the problems, before a more sophisticated piece of apparatus was built. The original prototype apparatus was then abandoned and a completely new piece of equipment designed, as shown in Fig. 10.

(b) Apparatus used throughout most of the experiment.

As can be seen from Fig. 11B (where each vertical line represents a time interval of 20 msec.), the build-up and decay times of the infusions pulse in this new system, were less than 30 msec. This was now quite adequate for the purposes of the

investigation, and a considerable advance on that of the prototype system. Much of the improvement was due to the insertion of an electro-magnetic clutch and brake, but an even larger (1/6 h.p.) variac-controlled motor, and a better transmission system, where the carriage sat on a full thread, were also contributory. The problem of keeping blood out of the syringe was resolved by using a mercury U-tube. Trouble was experienced for a while in aligning syringes to the apparatus, but this was eventually solved by using a ball and socket coupling. Once these design problems had been settled, the system worked well with few snags.

(i) The Motor and Motor Speed Control.

The two principal factors in the choice of a motor were (1) that it should be large, so that it could easily handle any load put to it, and (2) that it should rotate at a precisely constant speed for any one setting. This was best accomplished by using a variac motor speed control (Type 1703-A, General Radio Company, West Concord, Massachusetts), designed for use with a 1/6 h.p. D. C. compound wound motor (Type DM Master Electric Division, Reliance Engineering Co., Columbus, Indiana). This motor was reversible and had a speed range from 0 to 1725 rpm. Speed regulation was good for the purposes of the experiment, and the motor required little attention. The Variac Motor Speed Control provided adjustable constant-speed operation of this D. C. motor from A. C. lines. Fluctuations in the line voltage did not affect operation of the control. Generally,

the motor was left running throughout the experiment, and the speed changed when necessary by the dial on the front of the Variac control. It was bolted to the table and connected to the clutch by a Boston FC 12 coupling (Boston Gear Works, Quincy, Massachusetts).

(ii) The Electro-Magnetic Clutch and Brake

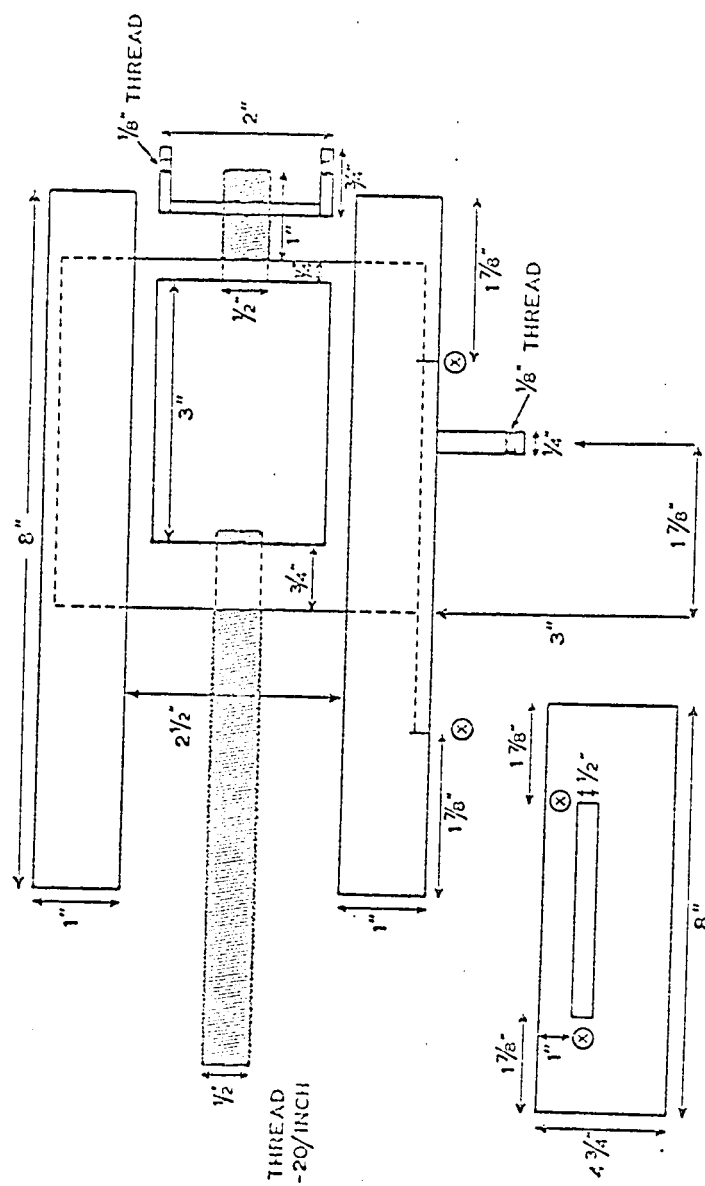
What is sometimes loosely referred to as the 'clutch', was an electromagnetic clutch and brake combination (EP 250 1-25525 Warner Brake and Clutch Co., Beloit, Wisconsin). A.D. C. voltage of 90 volts was supplied to the unit via a transformer obtained from the same company (No. 540024). When such a voltage is applied to the unit, the coil build-up time is 28 msec. (according to the company manual), and the coil decay time 28 msec. If necessary, the build-up and decay times can be further diminished by increasing the voltage applied to them. However, under the conditions of this experiment, it was not found to be necessary. D. C. switching between clutch and brake (which was practically instantaneous) was made an integral part of the trigger circuit. It was found necessary to ground the casing of the clutch-brake combination, because it caused some electrical interference with the recording.

The clutch was also bolted to the table and connected to the 'transmission' system by a Boston universal coupling.

(iii) The Transmission System

It was necessary to design and build a system to transmit the motion of the motor shaft to that of the syringe. The basic principal

FIGURE 13: Top view of the transmission system



was that the motor rotated a long thread, which, in turn, moved a carriage to which the syringe was connected. (See Fig. 10).

Two models were made. The first one, made of stainless steel, had a 'notch' carriage and this was found to be too heavy and not smooth enough. A second system of aluminium, was then made, and the carriage moved on ball bearings. This proved to be quite satisfactory. This is shown in Figures 12 and 13.

A long thread, half an inch in diameter, and with 20 threads per inch, was used to drive the carriage from the clutch shaft (with the intermediary of a universal coupling joint). The long thread was made from brass, and the corresponding female thread on the aluminium carriage was also made from a brass insert. In theory, a harder metal, such as stainless steel, would have been better, but this proved to be quite adequate. The carriage ran between 2 upper and 2 lower rails on ball bearings (8 stainless steel ball bearings on each rail, and 3/8 inch diameter). The ball bearings were spaced by means of a thin plastic cover, with holes bored in it, attached to both the upper and lower sides of the aluminium carriage. The upper rails could be removed to clean or lubricate the ball bearings. Caution had to be taken that these were not screwed back too tightly, as this interfered with the smooth running of the carriage. The total possible excursion for the carriage was 3 inches and an electrical stop-switch, improvised from a relay mechanism,

was placed at its most forward point. Attachments of the syringe and linear velocity transducer will be mentioned later.

A small amount of oil was dropped on the long thread periodically, but care had to be taken not to add too much, as this accumulated dust and interfered with smooth running of the carriage. When this happened, cleaning with 'paint thinner' (Canadian Tire Corporation, Toronto, Canada) was effective.

(iv) The Syringe and its Coupling

The flow rate of the system, in terms of ml/min, was a function of the size of syringe used. The most commonly used syringe size was 10 ml. and this was capable of giving flow rates from 0 to 400 ml/min.

Considerable trouble was experienced in the beginning in aligning and coupling the glass syringes to the carriage transmission system. Unless alignment was perfectly exact, syringes rapidly cracked. Initially, no coupling was used, and the head of the syringe was merely juxtaposed to the transmission carriage. This was not entirely satisfactory (syringes still broke) and further there was no braking effect on the syringe. Various devices were put on the head of the syringe plunger, but none were really successful. Plastic disposable syringes were also tried, but the compliance of their soft rubber ends was too large for them to be of any use.

The only successful solution to this annoying problem was

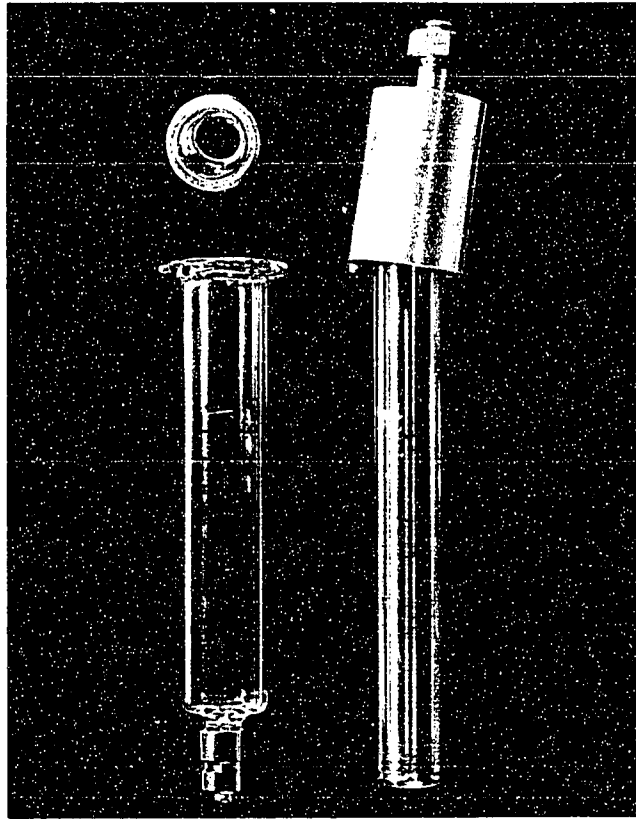


FIGURE 14: Syringe with steel plunger and ball and socket joint at its head.

to make a stainless steel plunger for the syringe, and to put a ball and socket joint at its head, as shown in Fig. 14. This was joined to the transmission carriage by a nut and bolt. In this way, a rigid yet flexible joint was made, the slight play in the ball and socket joint being entirely negligible (tolerance to less than 1 thousandth of an inch). It required a small drop of oil periodically. Having a special steel plunger, meant that only multifit syringes could be used. Ten ml multifit syringes (Becton Dickinson, Clarkson, Ontario) were found entirely satisfactory for this purpose. The scrupulous cleaning of both syringe and plunger in critical detergent (Alconox) each time was necessary to allow smoothest working of the system.

The syringe itself was sandwiched between two layers of plexiglass, (not shown in Fig. 10) with the calibrations held uppermost so that they were visible. The lip on the barrel of the syringe was slightly lower than the hole in the plexiglass, so that it prevented any longitudinal movement of the syringe during infusion. The plexiglass block was also bolted to the table. Care had to be taken not to tighten the upper plexiglass block too hard on the lower one, or else the syringe would crack. A 1/4 inch hole was bored in the centre of the aluminium transmission carriage and the ball and socket joint attached by a nut and bolt. (The device shown with the short thread at the end of the transmission carriage in Fig. 13 was abandoned, along with other devices, in favor of the ball and socket coupling).

(v) The Mercury U-Tube

It was desirable to avoid getting blood in the syringe. Normally, blood would be withdrawn from the animal and then reinfused some minutes later. If this was done at all often into a syringe, the plunger and barrel would soon stick together. Several techniques were tested to overcome this, all of them attempting to find a suitable interface between the saline in the syringe and the blood. A 100 cm length of thickwalled polyethylene tubing was coiled and laid horizontally as an intermediary connection between the syringe and the cannula in the animal. Varying oils, (paraffin and corn oil) were used in different amounts from a 'blob' up, to act as an interface material, between the saline in the syringe and the blood. The usual result however from rapid acceleration was the formation of an emulsion, and soon the blood would trickle back into the syringe. Blobs, or even lengths of up to 10 cms of mercury in this horizontal position were equally ineffective. The only successful solution consisted in enlisting the aid of gravity and making a mercury U-tube.

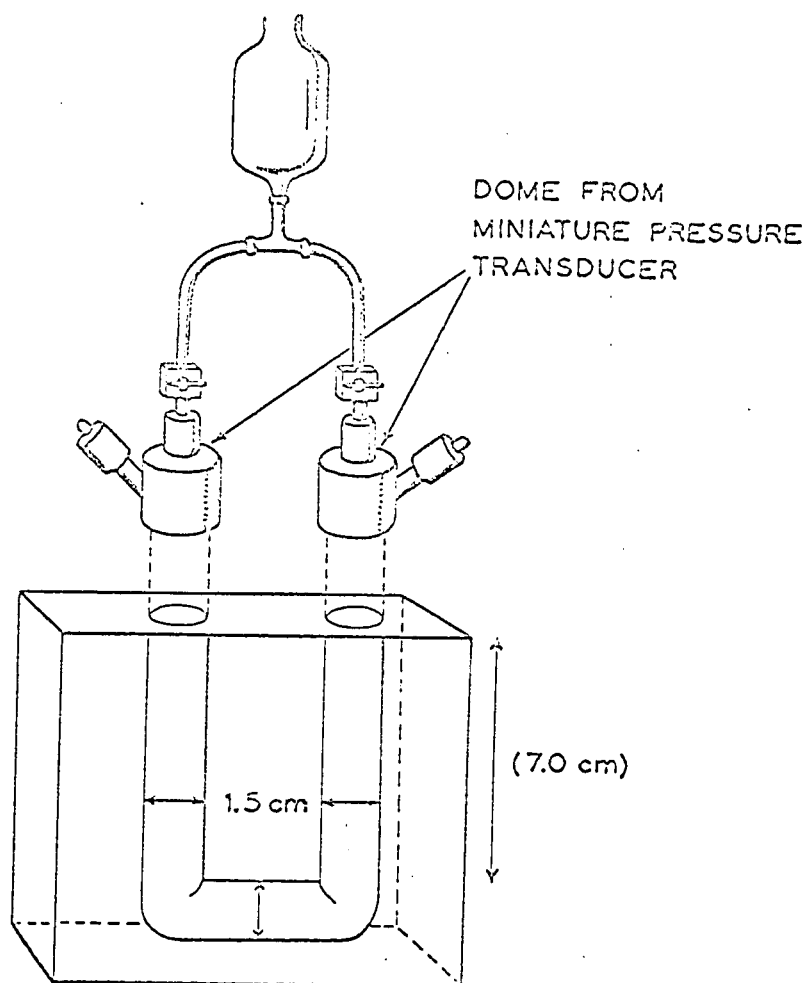
A block of plexiglass had holes drilled in it to produce a U-tube as shown in Fig. 15. It was found that the most efficient connectors for the top of this U-tube were the domes from miniature case size pressure transducers (Statham Laboratories Inc., Hato Rey, Puerto Rico), particularly from the point of view of eliminating bubbles from the system. Two of these pressure domes were used, one to cap each of the limbs of the U-tube. The superior outlet on each

side was connected by a Y piece of tygon tubing to a saline reservoir, and could be closed by a two-way stopcock (Becton Dickinson, Clarkson, Ontario). The oblique lateral outlets of each pressure dome were connected respectively to the syringe (via thick-walled polyethylene tubing) and to the cannula for the animal, again by thick-walled polyethylene tubing (see Fig. 10). The syringe side was filled with saline and the cannula side originally with saline also, soon to be replaced by blood on first withdrawal.

The U-tube was filled with mercury until the level reached halfway up each limb. Thus the volume of fluid, (blood, saline) which could be accommodated in the U-tube without the mercury leaving it, was the whole volume of one limb. This was slightly more than the volume of the syringe used (10 ml). If higher flow rates than 400 ml/min were required, then both a larger syringe and a U-tube would have to be used. A large amount of mercury added inertia to the system, and for this reason, the small 10 ml U-tube was used rather than a bigger one. The motor was quite able to cope with this amount of inertia, as the assembly build-up speed was within 30 msec, which as previously mentioned was entirely adequate for the purposes of this experiment.

In such a short-term experiment, the toxic effects of mercury were considered to be negligible. An attempt was made to substitute a fluorosilicone fluid of density 1.25 (FS. 1265-Dow Corning-Hemlock, Michigan) but this density was not high enough

FIGURE 15: The mercury U-tube



and did not prove satisfactory. It was difficult to clean the U-tube, as the openings were not large enough for the passage of a brush. Particulate matter had to be removed by soaking overnight in Alconox. Provided that all air bubbles were removed, this system was capable of giving a good square wave infusion of fluid.

(vi) Measurement of the Infusion Rate

It was necessary to find a suitable method for measurement of the infusion rate of the syringe. Initially, a steel arm, was attached to the transmission carriage which moved at the same speed as the syringe. This slid along a linear resistor and gave a relatively crude stepwise output whose slope was proportional to the speed of infusion (see Fig. 32). This system was soon discarded in favour of a more refined piece of equipment.

A linear velocity transducer (6LV4N, Sanborn Co., Waltham, Massachusetts) proved to be very satisfactory for this purpose. It is based on the principle that movement of a magnet (attached indirectly to the syringe) through a shielded cylindrical coil will induce a current in the coil, whose magnitude is proportional to the velocity of the magnet (and thus syringe). The circuit provided was used in single ended operation. The signal (after passage through a filter mechanism) was transmitted to the D. C. input of the multi-purpose amplifier on the Electronics for Medicine recorder, via a shielded cable.

Originally, the magnet was mounted onto the transmission carriage by a side-arm (which is shown, 1/4 inch in width, in Fig. 13.). However, pick-up of mechanical vibrations was less marked if the magnet was mounted directly onto the body of the transmission carriage. This was done by simply drilling a threaded hole about half an inch deep towards one side of the transmission carriage. Into this was screwed a steel shaft 1/8th of an inch in diameter and held in place by two locking nuts. At the other end of the steel shaft, the magnet was threaded and this then nestled into the shielded coil which was firmly sandwiched at the correct level between two blocks of plexiglass. The length of the steel shaft was made so that the electrical centres of both the magnet and coil coincided, when the syringe was at the middle of its travel. This ensured that the transducer was working in the linear portion of its range. In this particular case, with the 6LV4N, the steel shaft was approximately 10 cms long.

During the initial part of this investigation, a 6LV3 transducer was used. However, it was found that the working range of 3 inches was not quite adequate as it tended to become non-linear at the extremes of its range. A 6LV4-N with nonbreakable magnet-requiring a recorder sensitivity of 15 cm per volt D.C. was subsequently used. The linear range of this was 4 inches and this was found to be quite adequate. A calibration of the transducer was performed in terms of volume flow, with the particular type of

syringe (10 ml Multifit Becton Dickinson) used throughout the investigation. The height of the deflection produced on the recording was correlated with the rate of observed volume change of the syringe.

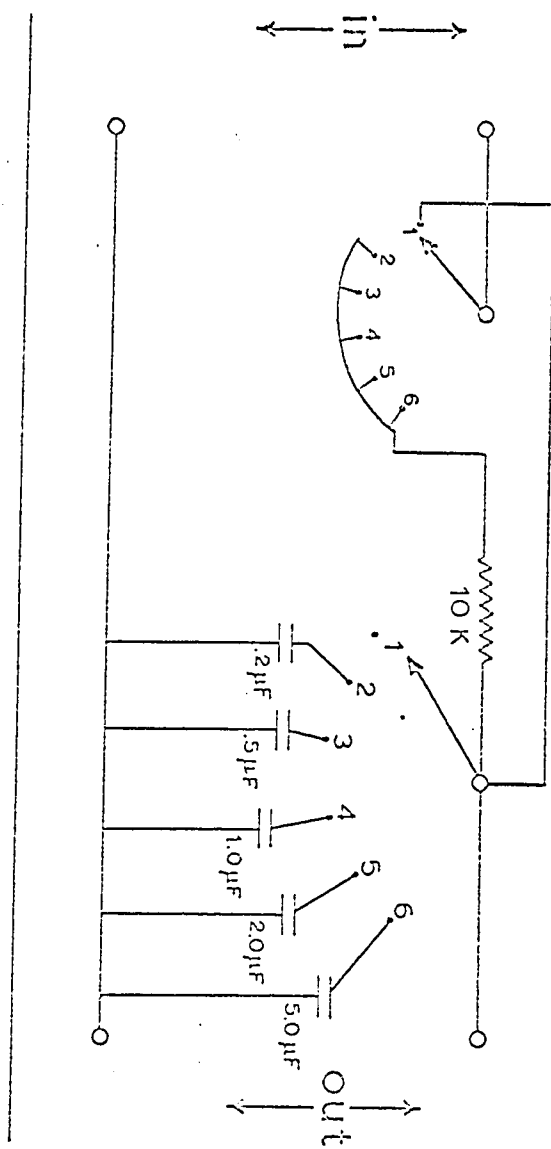
Mechanical vibrations (see next section) of the whole system could not be entirely eliminated and while they did not demonstrably affect the pressure manometers (clamped to a separate table), they did have an effect on the linear velocity transducer. It was decided to filter this signal electrically, in order to render the trace clearer and make the measurement of the mean speed more accurate. Two filter systems were built, the one shown in Fig. 16 eventually being used throughout the investigation.

Position 3 was used throughout most of the investigation, and this filtered most of the 'noise'. It also had the effect of making the input look slightly less square than it really was. Filtering at this level still gave, however, a true representation of the velocity of the syringe.

(vii) Vibrations

The motor, clutch, 'transmission', syringe and linear velocity transducer were all bolted to the same table. The motor inevitably generated some mechanical vibrations and these were picked up by the very sensitive linear velocity transducer. Ideally, it would have been best to locate the motor on a separate table, but once the final alignments had been made this was not really practicable. The whole assembly was mounted on three foam rubber pads, each one

FIGURE 16: Electrical filter system used with the linear velocity transducer



cm thick. This helped considerably in damping the vibrations. The U-tube and animal were located on a separate table, so that no vibrations were transmitted to them.

The only further comments to be made about the functioning of this square wave infusion system, are that (1) it required to be well lubricated and the plunger and barrel of the syringe kept scrupulously clean; (2) all air bubbles required to be eliminated from the system, particularly from the syringe and the mercury U-tube; and (3) rigid, non-compliant transparent tubing (for which thick-walled polyethylene tubing was ideal (Clay-Adams, Inc., New York) - see later) was required throughout.

2. RECORDING TECHNIQUES

The square wave infusion of blood given to the animal (usually through the right carotid artery) represented the 'input' to the system. The 'output' of the system was the pressure response, mostly measured from the right femoral artery. Accessory pressure measurements were made from time to time from other peripheral arteries and measurement of central venous pressure by a jugular venous catheter became an important adjunct to the technique.

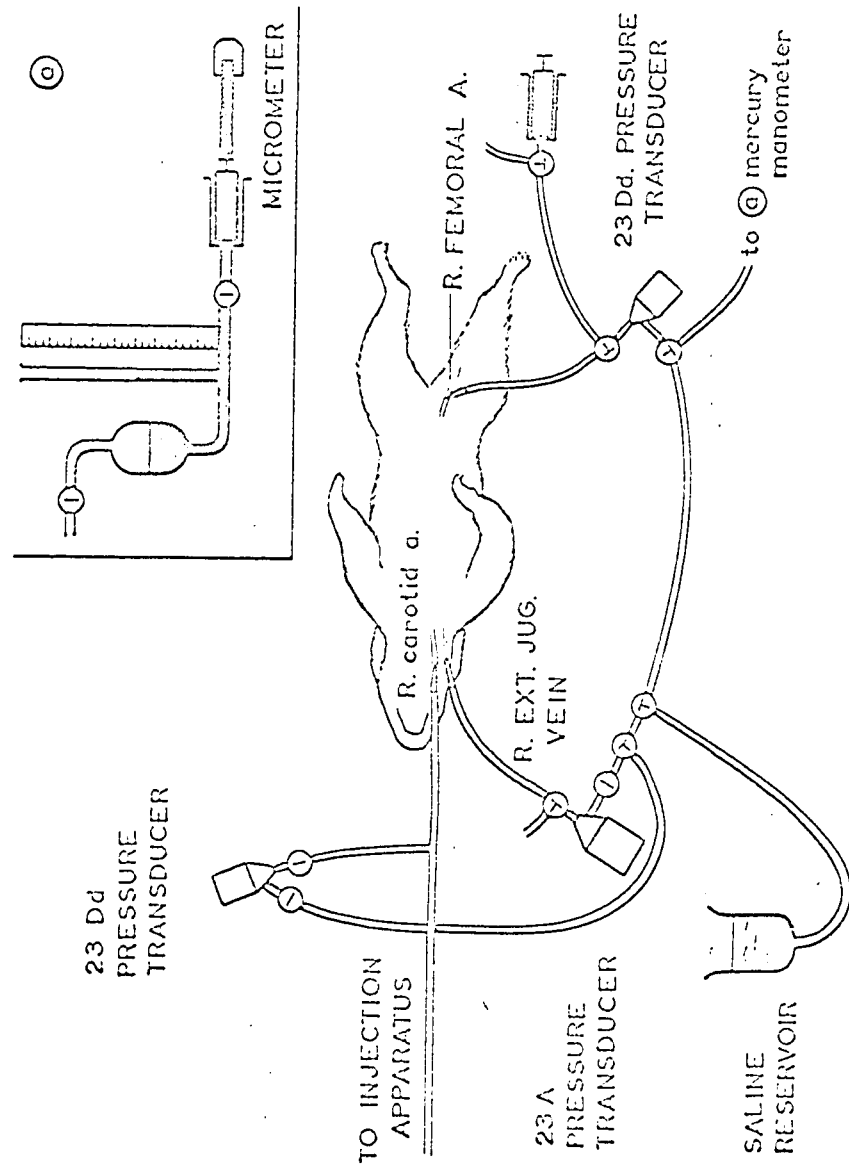
Two principal recording apparatuses were available. One was the Electronics for Medicine (White Plains, New York) Research Recorder Model PR-6. The other was The Grass (Quincy, Massachusetts) penwriting recorder, Model 7PCPA.

The Electronics for Medicine recorder had three pressure preamplifiers, one ECG preamplifier and a multipurpose preamplifier. Varying combinations of these channels were used, but in the latter part of the investigation, the multipurpose preamplifier was used to record the signals from the linear velocity transducer, and the three pressure channels to record two arterial and one venous pressures. The ECG channel was not used at that stage.

This was a single beam multitrace oscilloscope recorder suitable for the accurate recording of rapid phenomena. Nearly all calculations were performed on the recordings taken from this machine. The photographic paper was run at its fastest speed (75 mm/sec) and this was found to be rapid enough, for the phenomena under study. Time lines were marked across the paper at 20 msec intervals. The drawback with this recorder was that it did not have an ultraviolet light source, so that development of the photographic paper had to wait until the end of the experiment. As it was not uncommon to have to develop 50 to 75 feet of paper, a special bath was made which incorporated two spindles, and this considerably speeded up the development process.

The Grass pen recorder was essential because there was no direct read out from the Electronics for Medicine recorder. An immediate record of the system response to the square wave infusion was essential to the conduct of the experiment. It was also useful for general monitoring of blood pressure and heart rate response,

FIGURE 17: The general arrangement of cannulae and pressure transducers



and for marking comments on the paper throughout the course of the experiment. This record was provided by feeding the signal from the pressure pre-amplifier output jacks of the Electronics for Medicine recorder (to which the Statham pressure transducers were attached) to the driver amplifier input jacks on the Grass recorder. The paper was generally run at a speed of 2.5 mm/sec for continuous monitoring purposes, but this speed was increased to 25 mm/sec for the period of the square wave infusion. Only simple calculations were performed from this recorder, because of the relatively poor frequency response that all pen recorders have.

Fig. 17 shows the general arrangement of cannulae and pressure transducers used. The cannula in the right femoral artery (which was the principal site for measurement of the 'output' pressure response) was made from a 3 cm length of blunted needle (21G Yale hypodermic needle-Becton Dickinson, Rutherford, New Jersey). It was connected to the pressure transducer by a 7 cm length of rigid, thick-walled polyethylene tubing. In joining the cannula to the rigid tubing, an intermediate size of soft polyethylene tubing was used, but care was taken to see that this was completely 'sandwiched' between the cannula and the rigid tubing, so that it would not alter the response of the system. The central venous pressure was measured from a long thin-walled polyethylene catheter passed a marked distance of 6 cms down the right external jugular vein. A T-tube connection was placed on the infusion line leading to the right carotid

artery. Central arterial pressure, for the purposes of measurement of pulse wave velocity, could be measured from this point, when required.

Rigid, transparent tubing was used throughout the system wherever arterial pressures were recorded. This was the same type of tubing as used in the square wave infusion apparatus and was thick-walled polyethylene tubing of internal diameter 0.2 cm (Clay-Adams Inc., New York). The compliance of this tubing was tested by using the general apparatus shown in Fig. 29, except that a 30 cm length of tubing was substituted for the aorta. A typical result is shown in Fig 11B. From this it can be seen that the compliance of the tubing was quite negligible. The tubing could be molded by the heat of a match, and conveniently joined to the tubing adapters (Clay-Adams Inc., New York) used throughout. The only disadvantage to this tubing lay in the fact that it was not very flexible, and so it was sometimes difficult to cannulate the vessels when in awkward positions. This problem was largely resolved by using clamps with a ball joint at one end (C.F. Palmer Co., London, England). These held the pressure transducers and attached cannulae, which, thus could be pointed in any direction.

The system was filled with 0.9% saline solution, made each time from freshly boiled water, and strict attention was given to eliminating bubbles. Zero reference point for the system was the mid-thoracic level of the animal. This could be obtained by opening

the stopcock on the syringe used to periodically flush the cannula in the right femoral artery (see Fig. 17). The small vertical side arm at this point contained a column of water whose level was equal to that of the reference point on the animal.

Statham strain gauge pressure transducers were used throughout (Statham Laboratories, Inc., Hato Rey, Puerto Rico). Arterial pressures were measured with a .23 Dd transducer, which has a specified volume displacement of 0.02 ml/100 mm Hg. Central venous pressure was recorded from the larger P23A model, which has a volume displacement of 0.8 ml/100 mm Hg.

The static and dynamic properties of this whole pressure measuring system were tested. A mercury column with fine adjustment provided by a micrometer gauge (see insert of Fig. 17) was built. The static response of the system to steps of pressure from 0 to 300 mm Hg was found to be quite linear for all combinations of pressure transducer and preamplifier used. The dynamic properties of the system were tested by the "pop" method (HANSEN 1950). Each pressure transducer and its hydraulic connections were held rigidly in a vertical position. The cannula was inserted through a rubber bung into a plexiglass tube that was sealed at the other end with an elastic membrane. Through a side connection, pressure was raised in the system by the introduction of extra air. The membrane was then "popped", and so a step function produced. From

the amplitude and frequency of the transient oscillations so produced, the dynamic response of the system could be calculated. The natural frequency of the system was greater than 150 cps: the period of oscillation could not be exactly determined because the paper speed was not rapid enough. The dynamic characteristics of the recording system were relatively unimportant in this investigation as the primary object of interest was an exponential pressure curve with a time constant of 500 msec or more. Under these circumstances the driving 'frequency' is such a small fraction of the natural frequency, that virtually whatever the dynamic characteristic of the system, no significant distortion in amplitude or phase will occur.

3. DEVELOPMENT OF A TECHNIQUE TO CONTROL THE TIMING OF THE SQUARE WAVE INFUSION.

The usual duration of the square wave infusion was half, to one and a half seconds. It was desirable to control the exact duration of this infusion, and its relationship to the cardiac and respiratory cycles. On occasion, repetitive infusions were also required.

As the motor was left running continuously, the timing of the infusion was a function of the engagement and disengagement, of the clutch and brake combination. This clutch-brake was electrically controlled, and had a response time of approximately 30 msec. By varying the duration, of the 90 V DC signal required to activate the clutch mechanism, infusions of any duration, from 30 msec up, could be given. The timing of these infusions in relationship to physiological events (heart beat, respiratory movement, etc.,) could be controlled by reference to E.C.G., pressure, or respiratory stethograph signals.

A number of different electrical systems were built. As shown in Fig. 18, the principal elements in these circuits were combinations of A.C. and D.C. relay mechanisms (Potter and Brumfeld, Guelph, Ont.) and pulse and waveform generators (161 and 162, Tetronix Inc., Portland, Oregon). It was found useful to connect neon bulbs at strategic points in these circuits to assist in troubleshooting.

FIGURE 18: Electrical system to control the timing of the square wave infusion.

FIGURE 19: Part of a second electrical system to control the timing of the square wave infusion (i).

FIGURE 20: Part of a second electrical system to control the timing of the square wave infusion (ii).

FIGURE 18

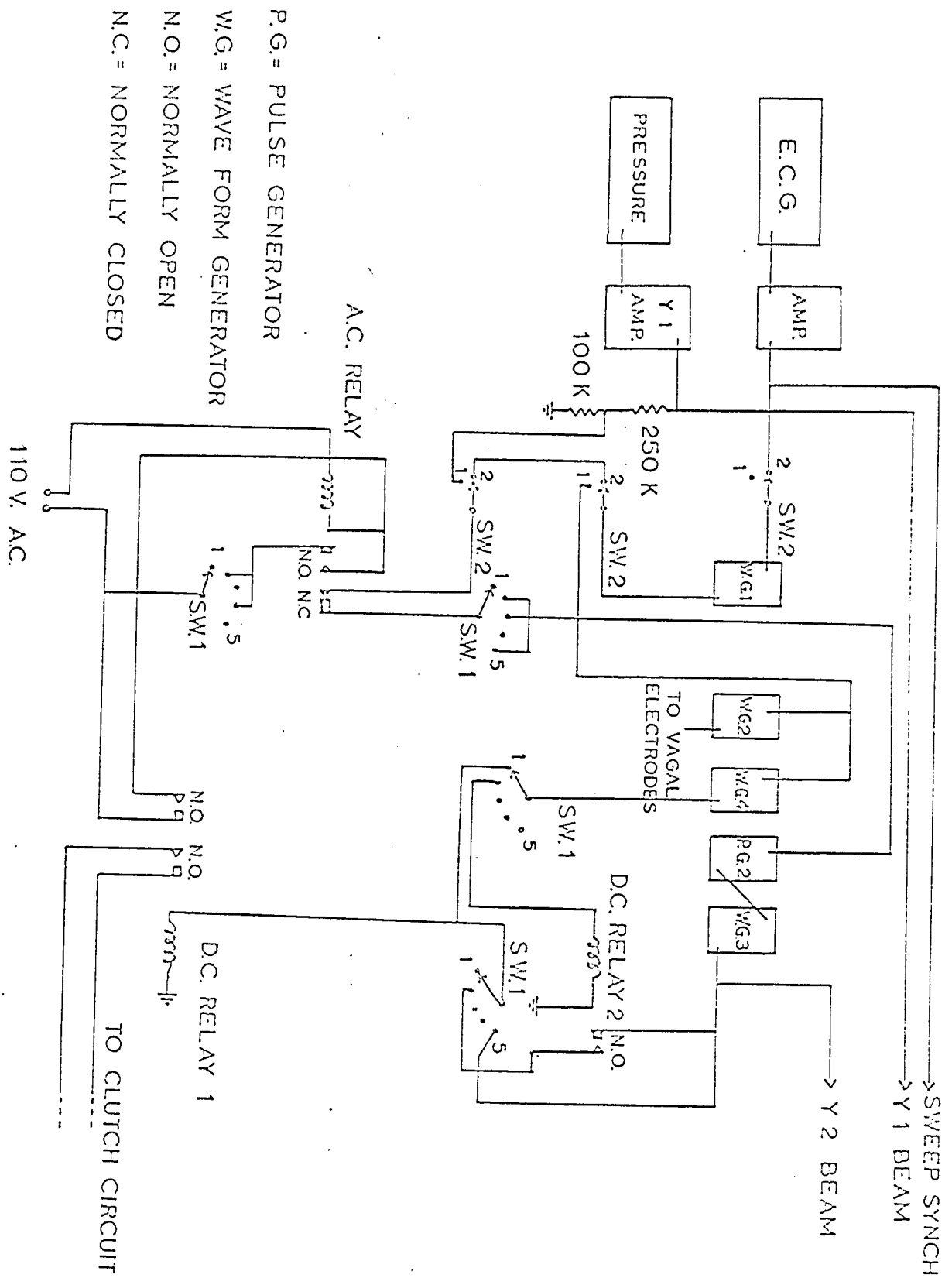


FIGURE 19

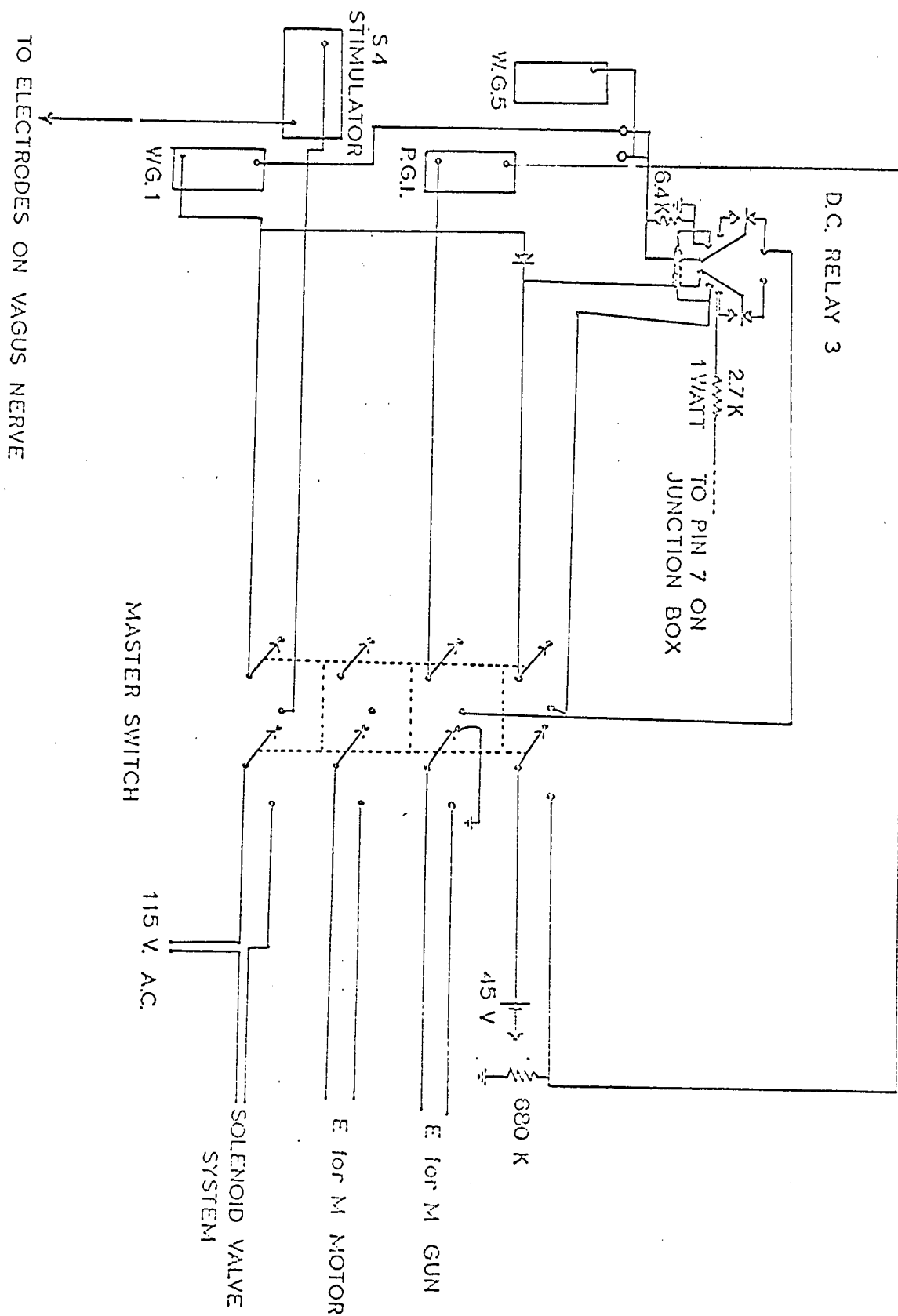
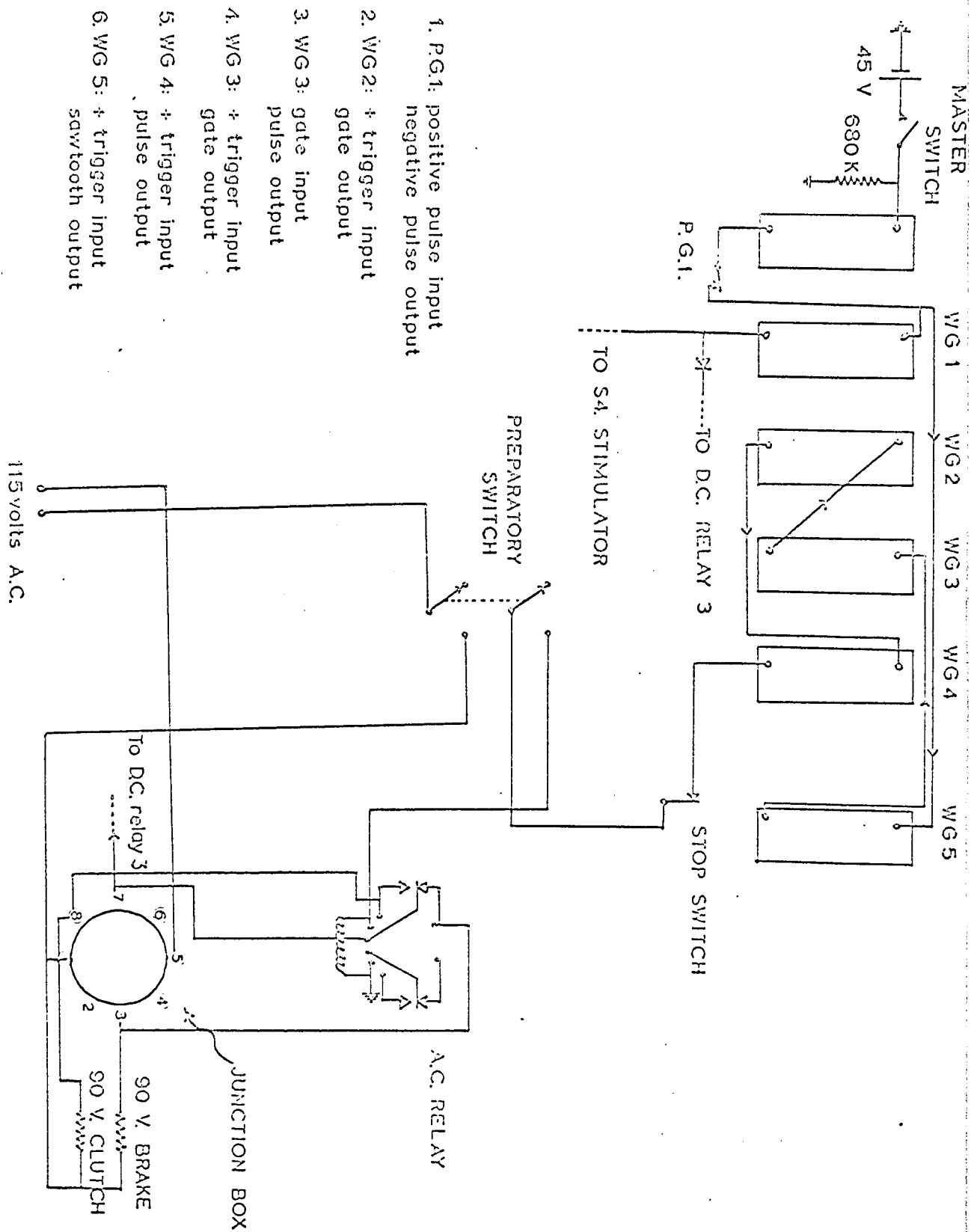


FIGURE 20



The final common output of these systems was a square wave of variable duration produced from a waveform generator. This closed a D C relay which allowed the clutch mechanism to become activated for the duration of the signal. The square wave infusion was thus given to the animal during this time.

As regards the initial triggering of the system and its relationship to physiological events, two basic approaches were used in the circuit shown in Fig. 18. When switch SW 2 was in position (2), the system was triggered by the R wave of an E.C.G. signal. The infusion could be given at a variable time after this, according to the setting on waveform generator WG 1. When switch SW 2 was in position (1), the system was triggered by a particular pressure level in the animal. The signal from the Statham pressure transducer was monitored on the Electronics for Medicine recorder preamplifier. The signal from this was suitably amplified (Y1 amp) and again monitored on a dual beam Cossor oscilloscope (Model 1049, Cossor Instruments, London, England). It was then fed to the input of a pulse generator (P G 2), whose input selector was turned to the 'negative waveform' position. With correct amplification, the diastolic part of the arterial pressure can be considered as a negative waveform. The PG2 pulse generator, in this position, will only be triggered when the incoming voltage (pressure) of the negative waveform precisely matches some preset reference level.

This level (and, in fact, the final duration and timing of the infusion) was monitored on the second beam of the Cossor oscilloscope (Y2). Thus the arterial pressure wave was continuously monitored on the Y1 beam of the Cossor oscilloscope, and the projected infusion pulse on the Y2 beam. This allowed assessment of the timing and duration of the square wave infusion in relationship to the normal heart beat. The infusion would only actually be given when switch SW. 1 was in positions 1,2, or 5.

The remainder of the circuit shown in Fig. 18, was concerned (1) with the problems of not giving unwanted repetitive infusions, and (2) with coordinating stimulation of the vagus nerve of the animal to this general sequence. It was found that the most effective way of causing transient stoppage of the heart so that a square wave infusion could be given, was by stimulation of the vagus nerve anywhere from 100 msec prior to the start of the infusion. Electrodes were placed on the vagus nerve, and a repetitive 15 volt pulse at a frequency of generally 90 cps was delivered to it from an S4 stimulator (Grass Instrument Co., Quincy, Massachusetts). This was kept turned 'on' so that a 'gate' input through the 'mod in' socket would determine the total duration of stimulation. The 'gate' input to the S4 stimulator was from the waveform generator WG2 of Fig. 18, and the total duration of the 'gate' adjusted at this point. It was also found necessary, on occasion, to interpolate a Stimulus Isolation Unit (Model

S10-4B, Grass Instrument Co.) between the S4 stimulator and the vagal electrodes, because of E.C.G. interference problems.

This trigger circuit was generally used in the earlier part of the investigation. In practice, the pressure trigger circuit worked reasonably well, although it was difficult to regulate it very precisely, and the sweep mechanism on the Cossor oscilloscope gave occasional irregularities which could trigger unsolicited infusions. The E.C.G. trigger circuit worked slightly better, once the problem of keeping a stable baseline had been solved. The filters on an A.C. preamplifier (Grass Instrument Co.) were very useful for this purpose.

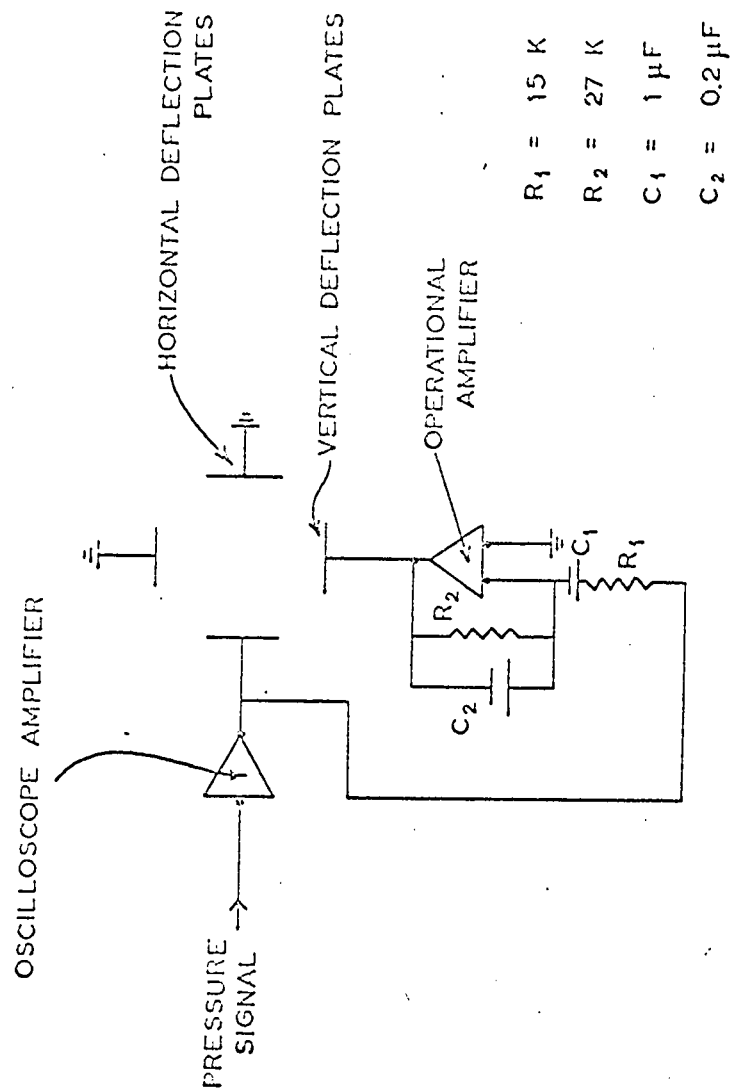
The systems shown in Fig. 19 and 20, represent a single circuit that was built for later use as the experimental design changed. Initial triggering of the circuit was not by E.C.G. or pressure levels, but by the entirely arbitrary manual manoeuvre of turning a 'master switch' (see Fig. 20). This then set a whole chain of coordinated events in motion, the chief of which were that the square wave infusion followed the beginning of vagal stimulation by some preset time interval (e.g.: 500 msec). The remainder of the circuit was designed so that (1) suspension of respiratory activity (see later) by the solenoid valve system (see Fig. 19 and 28) was coordinated to the period of vagal stimulation and square wave infusion, and (2) that recording by the camera on the Electronics for Medicine machine was coordinated to this period

also (see E for M motor, Fig. 19). Both these latter functions were achieved by making them part of the master switch, which was one of two basic switching procedures required to set the circuit in action. The other was the 'preparatory switch', seen in Fig. 20. This connected basic power circuits to the clutch mechanism, but did not actually activate it. Indeed, it activated, not the clutch, but the brake.

Waveform generator WG1 controlled the duration of vagus nerve stimulation. Waveform generator WG5 controlled the delay between the start of vagus nerve stimulation and the giving of the square wave infusion. The duration of the latter was controlled by waveform generator WG4. Waveform generators WG2 and WG3 controlled the interval between infusions (if more than one was given in rapid succession), and the number of repetitive infusions, respectively.

The general conduct of the experiment was such that all these settings were chosen in advance, and then about 5 ml of blood was slowly withdrawn from the animal by rotating the long thread on the transmission carriage backwards, manually. The 'preparatory' switch was then turned on. The paper speed on the Grass recorder was then increased from 2.5 mm/sec to 25 mm/sec. Finally, the 'master switch' was turned on, which would activate: (1) suspension of respiratory activity, (2) the E for M recording, (3) vagal stimulation, and the giving of a square wave infusion.

FIGURE 21: Circuit designed to perform a phase-plane plot



The master switch was turned off 2 to 3 seconds later, which would reactivate respiration, and stop the high speed E for M recording. The preparatory switch was turned off, which would release the brake. The paper speed on the Grass recorder was then turned down again. This system was used in the latter half of the investigation, and proved to be a useful and effective one for controlling the timing and coordination of the square wave infusion.

4. DEVELOPMENT OF A TECHNIQUE TO ANALYSE THE PRESSURE RESPONSE TO A SQUARE WAVE INFUSION

It was eventually found that the most suitable method for analysing the pressure response to a square wave infusion was by means of the transformation shown in Fig. 9. This plot of rate of change of pressure against instantaneous pressure at any one moment is generally called a 'phase plane plot' by engineers.

The principal of the technique developed to make this transformation electrically is shown in Fig. 21. The signal from the transducer monitoring the right femoral artery pressure was fed into the horizontal plates of a dual beam oscilloscope (Type 502A, Tetronix, Inc., Portland, Oregon). The same signal was also fed into a differentiating circuit built around an operational amplifier. The derivative of the signal (in effect, dP/dt) was then

fed into the vertical plates of the same dual beam oscilloscope. Thus the movement of the beam on the screen of the oscilloscope was the result of the instantaneous ratio of dp/dt against pressure. The abscissa represented the absolute pressure recording, and the ordinate its first derivative, in either a positive or negative direction. A polaroid camera was attached to the oscilloscope, and a picture taken of this phase plane plot, during the time of the square wave infusion (for example, see Fig. 44, and compare with Fig. 9).

A sensitivity of 0.2 V/cm was found to be a suitable gain for both axes on the oscilloscope. Calibration of the pressure axis on the abscissa was performed by means of the calibration step resistors on the E for M recorder. In actual practice, the primary pressure signal to the horizontal plates of the Tetrax oscilloscope was derived from the output jack of the pressure pre-amplifier on the E for M recorder. Therefore, calibration of the pressure axis on the oscilloscope screen was simply a matter of turning the calibration step resistors on this pre-amplifier of the recorder, whilst making sure that the pressure transducer was exposed to atmospheric pressure. Although these calibration step resistors were marked in terms of 0-20-40-80-160 mm Hg, direct calibration from a mercury manometer showed that these were not entirely accurate. Correction factors to the calibration of the pressure axis were applied to account for this.

Calibration of the ordinate (dP/dt) was performed by using essentially the same set of calibration step resistors. On the pressure pre-amplifier channel of the E for M recorder, there is a switch called 'normal-filter-mean' - (a). This normally has the function, in the 'mean' position of converting the arterial pressure wave into a mean pressure. When the switch is in this position, and the calibration step resistor turned, an exponential response is generated (exactly the response of a linear first order system to a step function). The time constant of this response was determined by actual measurement from several recordings, of the ratio of the rate of change of pressure to instantaneous pressure at any moment. It was found to be 625 msec. This signal was used in the routine calibration of the oscilloscope ordinate (dP_{dt}). Knowing the exact calibration of the pressure axis, and the time constant of the calibrating signal, it was a simple matter to calculate the oscilloscope ordinate calibration, from the following relationship (see eq. 3):

$$\frac{dP/dt}{P} = \frac{1}{\tau} \quad \text{where } \tau = \text{R.C.}$$

In actual practice, calibration of both ordinate and abscissa was rapidly achieved by turning switch (a) to the mean position, and moving the calibration resistors slowly through each step. A picture was taken of this calibration procedure. Generally, a pressure of 80 mm Hg was held at the center of the screen.

Whilst the basic principle of this technique is simple, the matter of adequate signal differentiation usually is a more difficult problem in practice. Engineers generally avoid differentiation techniques wherever possible because the slightest amount of noise in the signal will usually dominate the derivative trace. This occurs because differentiating techniques are only sensitive to the rate of change of a signal and this is usually high if any noise is present. Attempts can be made to filter this noise, but then this may lead to distortion of the primary signal. Therefore, a good differentiating technique involves balancing the effects of distortion, and noise.

After a certain amount of experimentation, the differentiating circuit shown in Fig.21, was found to be suitable for the purposes of this particular phase plane plot. It was built around an operational amplifier (D-12, Data Device Corporation, Kicksville, New York). This is essentially a D.C. amplifier of very high gain (order of 10^8). The basic differentiating circuit when this operational amplifier is used, is a combination of C_1 and R_2 , as shown in Fig.21. The basic equation of this circuit then becomes:

$$e_o = -R_2 C_1 \cdot de_1/dt \quad \text{where } e_o = \text{volts out} \\ e_1 = \text{volts in}$$

Before using the operational amplifier, it was necessary to balance it, by shorting both inputs to ground, and adjusting a variable resistor inside the circuit so that the null point

could be found with a balance potentiometer.

As expected, the circuit with R_1 and C_2 alone not prove satisfactory, because of the noise problem. An attempt was made to filter the noise from the signal before it reached the differentiating circuit, but this was not satisfactory either. In the end, addition of the feedback capacitor, C_2 , and the resistor R_1 in the values shown in Fig. 21, were found to give adequate elimination of noise without signal distortion.

The circuit was tested for the fidelity of its response, by using a series of triangular waves of varying frequency, produced from a function generator (Model 2022A, Hewlett Packard, Lexington, Mass.). In Fig. 22 an exponential input with a time constant of 400 msec. was given to the circuit. This is represented by the lower trace. The first derivative of this curve, as determined by the circuit, is shown in the upper trace (which, incidentally was calibrated in terms of 10 mv/sec). It can be seen that the maximum rate of change is of the order of 40 mv/sec. As the input is comparable in terms of voltage and time constant, to the natural response of the animal to a square wave infusion, then 40 mv/sec. is the highest rate of change that the system is required to respond to without further distortion. Reference to Fig. 23, shows the typical response of a circuit very like the one used (note the change in C_2 value- see below) to a triangular wave changing at the rate equivalent to 40 mv/sec. The

DERIVATIVE OF AN EXPONENTIAL CURVE

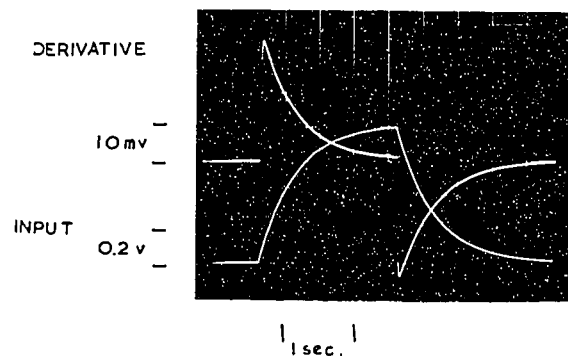
INPUT 4 μ AMP. $R=200K$, $C=2\mu F$ $\tau=0.4$ sec.

FIGURE 22

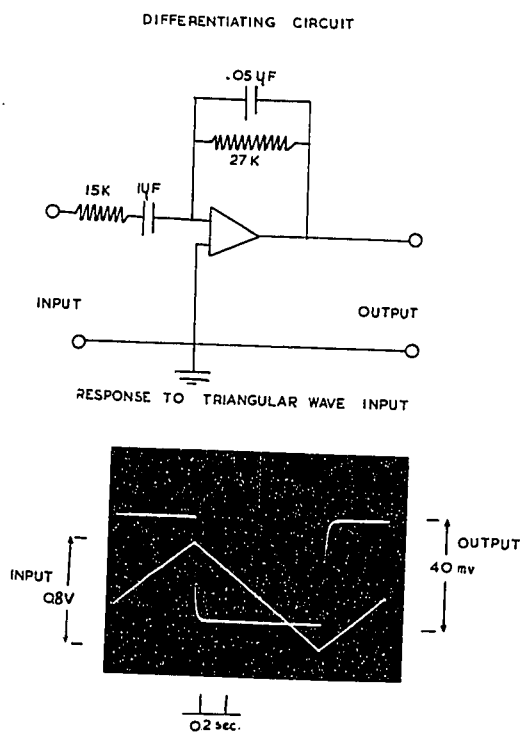


FIGURE 23

AN X-Y PLOT OF A TRIANGULAR WAVE
AGAINST ITS DERIVATIVE

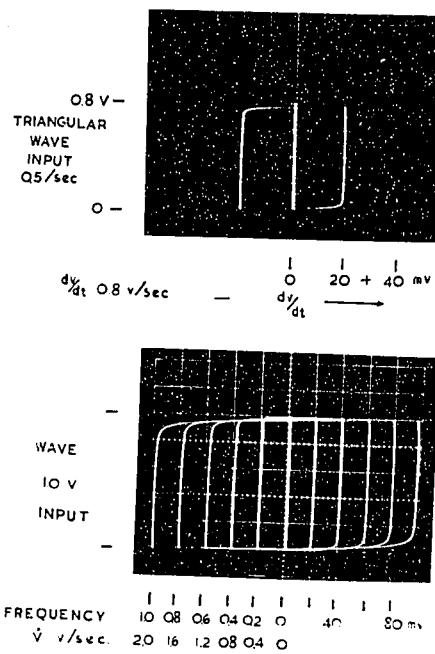
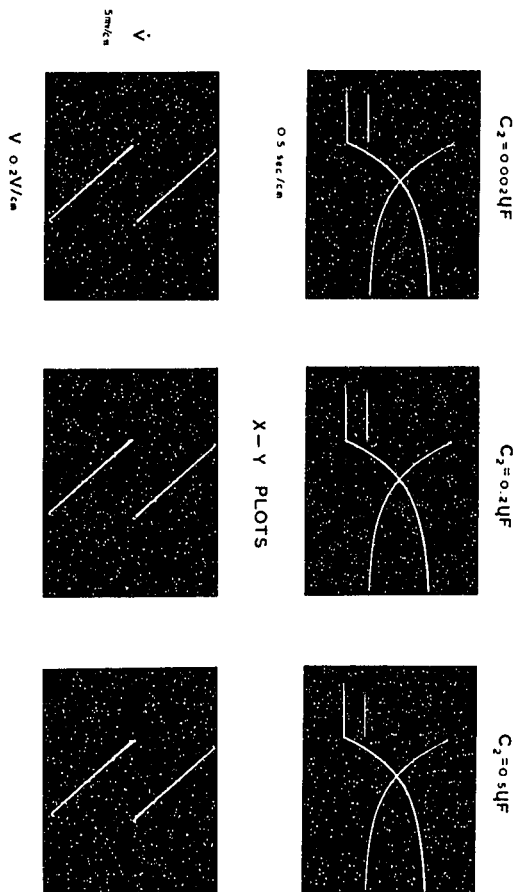
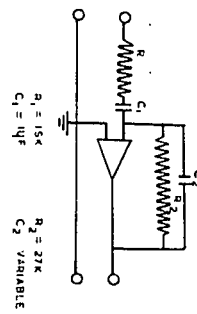


FIGURE 24

FIGURE 25

THE EFFECT OF A FILTERING CAPACITOR ON THE DERIVATIVE OF AN
EXPONENTIAL CURVE



upper trace, which is its first derivative, is virtually in the form of a pure square wave, which indicates a good, non-distorted response to this maximum rate of change. Fig. 24, in which the triangular wave input is plotted on the ordinate, and its first derivative on the abscissa, shows the response of the circuit to rates of change up to 100 mv/sec. The linearity of the system between input and output is shown to be good, although at rates of change greater than 40 mv/sec, there is seen to be some rounding off of the response. Fig. 25 shows that the three different values of filter feedback capacitor (C_2) used, had virtually no effect on the differentiation of the standard input signal.

The differentiating circuit was further tested against phase plane plots hand measured directly from the pressure tracing, as will be mentioned later. This differentiating circuit proved to be very adequate for the transformation of the input signal, and the whole technique a useful way of analysing the pressure response to a square wave infusion.

5. ISOLATION OF THE SYSTEM UNDER INVESTIGATION FROM DISTURBING INFLUENCES DURING THE TIME OF THE SQUARE WAVE INFUSION.

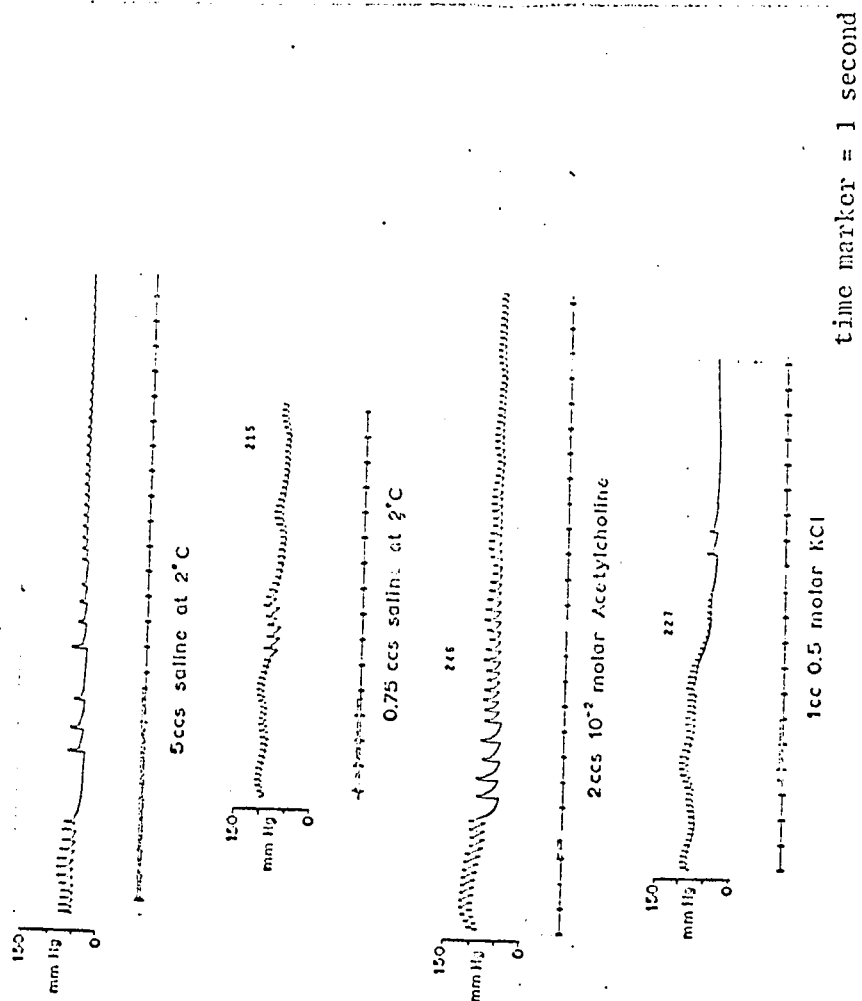
The object of study in this investigation was the controlled system in the systemic arterial circulation. To study this, it was necessary, during the time of the square wave infusion, to isolate it from all disturbing influences. Included amongst these were (1) the normal heart beat which contributed an unknown input

to the system, and only served to confuse the picture; (2) normal respiratory activity, which appeared to have mechanical effects on pressure recording from the systemic arterial circulation; and (3) multitudinous reflex and hormone effects of the controlling system.

(a) Technique to nullify the heart's action:

The first approach to nullify the heart's action during the time of the square wave infusion, was used in the very early part of the investigation, in some pilot experiments on rats. The square wave infusions were given at such high rates that pressures of 200-300 mm Hg were abruptly generated in the system. Under these circumstances, the heart could not generate enough force to open the aortic valve, so that the beats became isovolumic in nature. Whilst this technique had limited application in the present investigation, because it allowed study of pressure-flow relations across the systemic circulation only in a higher than normal range, it did suggest the possibility of coincident testing of the contractility of the heart. Measurement of the intraventricular pressure under these circumstances would allow an assessment of the force-velocity relationship of the cardiac muscle. Intraventricular recordings were monitored from the rabbit heart by passage of a needle (modified after NAPKE 1963) through the thoracic wall into the left ventricular cavity, but the idea was not pursued any further.

FIGURE 26: The effects of various agents on cardiac slowing



The second approach used was the direct one of transiently stopping the heart's action, by vagus nerve stimulation. This was the technique used throughout most of the investigation. Originally it was not felt to be a good idea, because of the possible reflex effects on the circulation during the time of the infusion. However, ultimately faced with no other choice, the effects of various manoeuvres, including vagal nerve stimulation, in causing brief, reversible, cardiac arrest, were investigated.

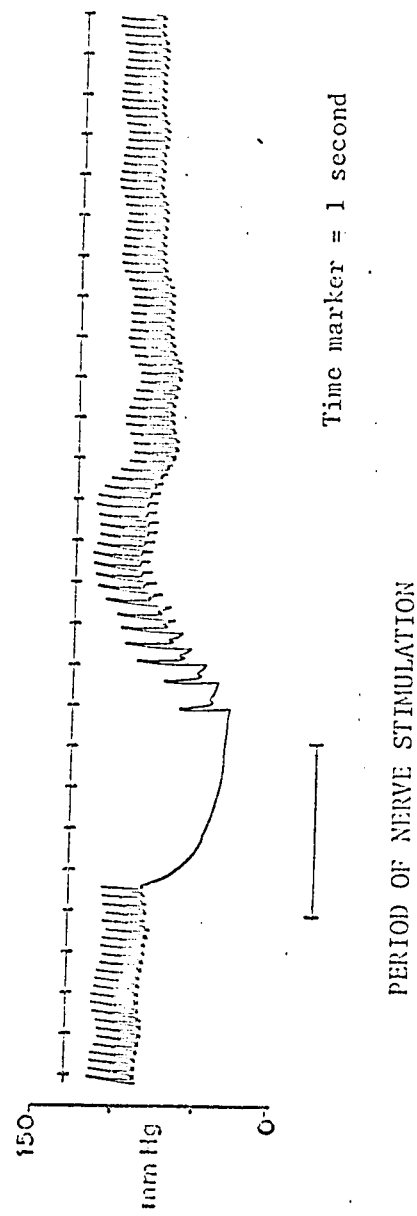
Initially, injection of a number of agents was made into the right atrium of the rabbit, hopefully in close proximity to the SA node. These were acetylcholine, potassium chloride, and cold saline. All but the latter were given through a size P. E. 150 thin-walled polyethylene catheter (Clay Adams Co., New York) passed a marked distance of 6 cms down the right external jugular vein. This is the distance to the proximal right atrium in an average 5 lb. rabbit. Arterial blood pressure was monitored on the Grass pen recorder, and the general results are shown in Fig. 26

Injections of acetylcholine bromide solution, in strengths ranging from 10^{-6} to 10^{-1} molar, were given in volumes between half to 2 ml. Strengths below 10^{-3} molar caused some minor slowing, but in no case was the beat to beat interval extended to more than 500 msec. Injection of 2 ml of a 10^{-2} molar solution produced a beat to beat interval of 1500 msec, but this was followed by poor recovery.

Potassium chloride injections, from 0.1 to 1.0 molar, were also given. The 1.0 molar solution produced irreversible cardiac arrest (1cc). One cc of 0.5 molar KCL also produced irreversible stoppage after 9 seconds, and lower doses gave no appreciable effect. This method was too inconsistent, and moreover, repeated doses would produce a cumulative effect.

Of the injection procedures, the most effective seemed to be the rapid infusion of cold saline ($1 - 2^{\circ}\text{C}$) into the atrium. This produced a beat to beat interval of between 2 to 3 seconds, with rapid injection of 5 ccs from a syringe by hand. The recovery interval varied from one to four minutes, and in the worst instances was followed by prolonged depression of blood pressure. It was decided that further pursuit of this method was worthwhile and a more elaborate injection catheter was constructed. A fine (P.E. 50) tubing with open end, was passed to within one cm of the end of a second larger tubing (P.E. 60) whose end was sealed by a metal tip. As this was the part to come in closest contact with the S.A. node, it was felt to be an advantage to use material such as metal, with a high thermal conductivity. Saline, stored in a thermos bottle and with extra salt added to depress the freezing point, was injected from a syringe into the small inner tubing. A circulation of cold fluid thus passed down the small tubing and out again through the larger tubing. Therefore, the atrium could be cooled without fluid actually being injected into it. Alcohol, cooled to -10°C ,

FIGURE 27: The blood pressure response to stimulation of the right vagus nerve (rabbit)



was also used instead of the saline as injection fluid. Rapid local cooling of the S.A. node ought, theoretically, to be a good method of causing transient cardiac arrest, without circulatory effect. In practice, however, it proved difficult to get this catheter in sufficient proximity to the S.A. node, for it consistently to have effect. This technique was then abandoned, as coincident testing with vagal nerve stimulation appeared to be a more immediately feasible proposition.

The general response of the rabbit to stimulation of the right vagus nerve for a period of 3 seconds is shown in Fig. 27. Complete recovery to the pre-stimulation blood pressure and heart rate normally occurred within a period of 30 secs. The important question whether this procedure had any significant effect on the systemic circulation is more appropriately considered in another section, but the general conclusion is that it did not. It thus provided a good technique for isolating the controlled system from the heart's action during the period of the square wave infusion.

The rabbit was chosen as the experimental animal for this investigation, because of its sensitive response to vagal stimulation. Cats, which in other ways would probably have been ideal, appeared to have a pronounced vagal escape mechanism, and rarely could a beat to beat interval of more than one second be produced. In rabbits, beat to beat intervals of 6 seconds or so could be

produced with good recovery afterwards. It should be noted, however, that as experience was gained in the technique, there was a significant improvement in the number of satisfactory responses obtained from rabbits, and the original assessment of the cat response (which was not repeated later) should be considered in this light.

As suggested by the latter statement, stimulation of the right vagus nerve in the rabbit was not always successful in producing an adequate beat to beat interval. Many experiments, particularly in the beginning, were wasted, because an adequate response to vagal stimulation could not be obtained (even after stimulation of either, or both, left and right, vagus nerves). With experience, though, this failure rate, which was a source of considerable frustration, gradually declined.

The technique used was standard. The right vagus nerve (and if that proved unsuccessful, then the left) was carefully dissected from the carotid sheath, using as long a length as possible. It was transected at the cephalic end and the sympathetic chain, which runs closely along side it, separated from it. It was then carefully placed across two stimulating electrodes, which were held by a micromanipulator (C.F. Palmer, London, England).

The electrodes were connected to the S4 stimulator (see Fig.19). The most generally-effective stimulation pattern was a 15 volt pulse of duration 0.4 msecs, given at a frequency of 90 cps.

The electrodes were made out of silver wires, 6 cms in length. One wire was taken to be the anode, and the other, the cathode. They were supported by a plexiglass block at their top end, and held about 3 mm apart. They were insulated from each other by a sheath of P.E. 50 polyethylene tubing (Clay-Adams, Incl, New York) about each wire. The lower end of each wire, which came into contact with the nerve, was beaten flat to give a good surface area of contact, and turned up into a hook. The nerve was carefully placed across both these hooks, taking care to avoid short-circuiting. A length of the P.E. tubing used to insulate each wire, was placed across both ends of the hook, so that the nerve lay firmly saddled inside it.

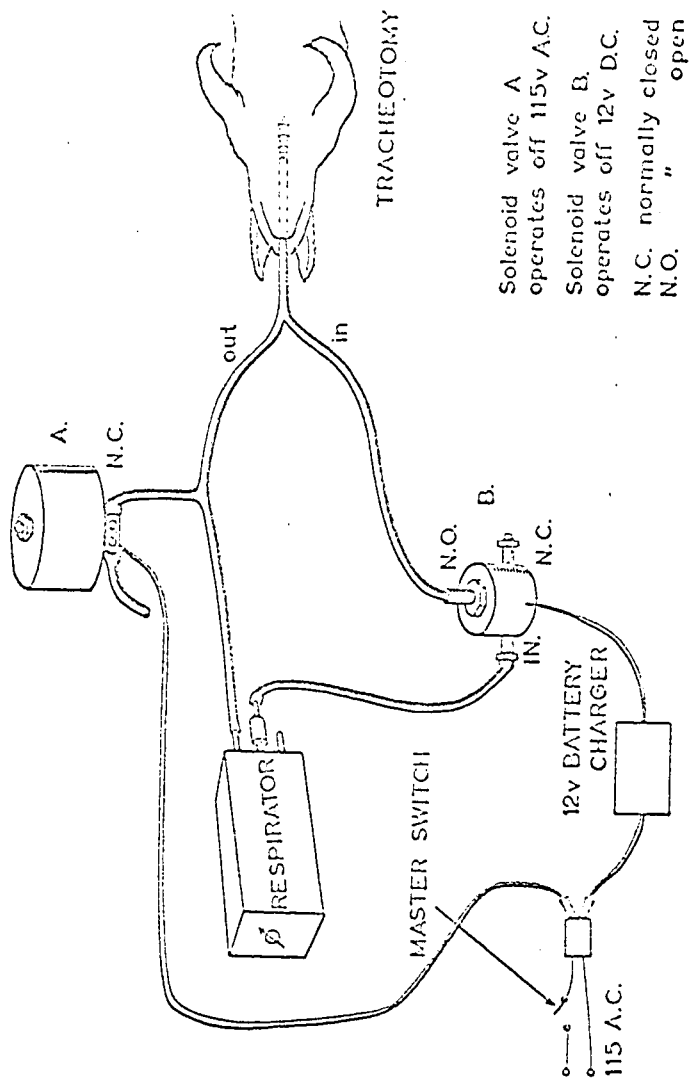
(b) Technique to nullify the effects of normal respiration:

As the investigation progressed, it became obvious that normal respiratory activity affected the pressure response of the systemic arterial circulation to the square wave infusion (see for example, Fig. 46). On account of this it was necessary either (1) to give the infusion at a constant phase of the respiratory cycle, or (2) to suspend respiratory activity completely during the time of the square wave infusion.

Initially, an attempt was made to synchronize the giving of the square wave infusion to a constant phase of the respiratory cycle. The respiratory movement of the animal was monitored by a rubber bellows encircling the thorax which was connected to a volume pressure transducer (Model PTSA, Grass Instrument Co.). The signal from this was fed to a pre-amplifier unit on the Grass pen recorder. The output from plug J7 on the driver amplifier of the same recorder was then increased in voltage by connection to a 45 volt battery in series with it. The signal of the respiratory movement, was oscillatory in nature and at this boosted voltage level, its negative waveform was sufficient to trigger a pulse generator which would then trigger the whole square wave infusion sequence (see PG1 in the circuit of Fig. 20 . The circuit as shown was not set to be triggered by the respiratory cycle, but the modifications required are minor). Thus, by adjustment of the pulse generator, the square wave infusion could be given at any desired phase in the respiratory cycle. This technique was used in some earlier

FIGURE 28

RESPIRATORY CONTROL SYSTEM



experiments, but the respiratory cycle (25 breaths p. min.) was not really long enough for later experiments.

As it was felt that the disturbance which respiratory movement caused was not due to the respiration 'per se', but to pressure effects in the closed thorax, there were two further alternative possibilities: either (a) the thorax and abdomen could be opened, and respiration continued with a positive pressure pump, or (b) all respiratory activity could be suspended during the time of the square wave infusion by turning the respirator off and paralysing the animals own spontaneous respiratory efforts with neuro-muscular blocking drugs.

The latter was the procedure used throughout most of this investigation. The general apparatus used in this approach is shown in Fig. 28 . A small glass cannula was placed in the animals trachea and connected to the positive pressure respirator, as shown. This respirator had adjustable rate and volume controls and these normally set at 25 ml p. min. and 25 ml respectively (Small Animal Respirator. Model 670 Harvard Apparatus Co., Dover, Mass.). An attempt was made to monitor the PCO_2 of the expired air on a Beckman Medical Gas Analyser (Beckman Model LB-1), but the logistics of attending to this and other facets of the experiment at the same time were such that it was not always possible. The respiratory chart prepared by Kleinman and Bradford, of the Harvard Department of Public Health, and distributed by the Grass Company, was a satisfactory guide for normal respiration of the animal.

Solenoid Valve B (Skinner Electric Valve, New Britain, Connecticut) was interposed on the inspiratory line, between the respirator and the animal. This was a three-way miniature valve that was activated from the master switch (see Fig. 19) through the intermediary of a 12 volt D.C. battery charger (Canadian Tire Corporation, Toronto). It was connected so that a channel was normally open between the respirator and the animal. On turning the master switch, however, this channel became closed, so that the respiratory activity was dissipated to the atmosphere, and the animal ceased to be ventilated.

The valvular system within the respirator was such that when the animal ceased to be ventilated, various degrees of positive pressure could remain in the thorax. In order to ensure that intra-thoracic pressure remained at zero during the time of the square wave infusion, a second solenoid valve A (Alco Valve Co., St. Louis) was placed in the expiratory line between the animal and the respirator. When the master switch was turned on, this valve opened a channel between the trachea and the atmosphere. Thus the net effect of this solenoid valve system was that, when the master switch was turned on, the animal ceased to be ventilated and the intra-thoracic pressure remained at zero level. The square wave infusion was then given. When the master switch was turned off again, in three or four seconds, then the lungs once more became ventilated. It was found most useful to ventilate the lungs with a mixture of 100% oxygen. The bore on both

solenoid valves was sufficiently large to prevent the occurrence of any significant respiratory resistance.

The above system, is dependent on the elimination of the animals own respiratory efforts by neuro-muscular blocking drugs. Succinylcholine, in a dose of 0.25 mgms p. Kgm. was initially used, because of its minimal hypotensive effect, (Goodman and Gilman, 1963). However, it was found that the initial depolarising twitch could damage the nerve on the electrodes, or, on occasion, pull the cannula out of the right femoral artery. Thereafter, d-tubo-curare in a dose of 0.12 mgms p. Kgm., was used. In this dosage, which sometimes required supplementation, no ganglion blocking effect was noted, as judged by the blood pressure response.

The above was the technique generally used. However, method (a), which avoids the use of drugs, is worthy of further consideration. It was not generally used because opening the thorax in the mid-line in the rabbit often produced marked reflex hypotension. Merely to touch the exposed area of the sternum could trigger an intense reflex action (which was not a pain response, as analgesia was adequate elsewhere). Furthermore, it was sometimes difficult to avoid cutting the internal mammary artery, and bleeding from this, in a heparinised animal, was difficult to stop. Therefore, because of these two problems, this approach was not generally used. However, towards the end of the investigation, a small self-retaining retractor (Soteria Co., Germany) was placed between the ribs following an incision into the

pleural cavity along the right 4th intercostal space. This held the thoracic cavity widely open to the atmosphere while ventilation was continued in the absence of neuro-muscular blocking drugs. Under these circumstances respiratory activity had no effect on the pressure response to a square wave infusion. Moreover, no reflex hypotensive episodes were noted. Although at that stage it was not possible to change the pattern of the experiments, for any future investigation this would probably be the method of choice.

6. MISCELLANEOUS TECHNIQUES USED DURING THE COURSE OF THE INVESTIGATION.

In the application of a new technique, such as the one described in this thesis, it was necessary to correlate property values obtained with those obtained by existing methods. Standard techniques for measuring cardiac output by the Fick method, serum cholesterol, and pulse wave velocity were used and will now be described. A method for measuring compliance values in the dead rabbit will also be described.

(a) Measurement of cardiac output by the Fick principle method

This requires knowledge of the total volume of O_2 consumed by the animal per minute, (Q_{O_2}), the oxygen concentration of the arterial blood (A_{O_2}) and the oxygen concentration of mixed venous blood (V_{O_2})

in the lungs. The cardiac output (F) per minute then becomes (FICK, 1870):

$$F = \frac{Q_{O_2}}{[A_{O_2}] - [V_{O_2}]}$$

This expression only holds if the circulation remains in a steady-state during the time of testing.

The oxygen consumption of the animal in this investigation was measured by a small animal spirometer. It was connected to the inlet and outlet ports of the respirator, so that it moved up and down with each 'breath' that the animal took. These excursions were recorded on the Grass penrecorder, after the signal from the spirometer was converted to D.C. current by passage through a box containing a selenium rectifier circuit. The spirometer was calibrated volumetrically with a 30 ml syringe at the end of the experiments. The rate of oxygen consumption of the animal was then read directly from the recording.

0.2 ml of arterial blood was sampled via a three-way stopcock on the tubing leading to the cannula in the right carotid artery. This was performed only after allowing some blood to run through to account for the 'dead space'. A similar amount of blood was sampled from the catheter in the right atrium, again after accounting for the 'dead space'. The location of the catheter tip in the right atrium was confirmed at post mortem.

It was most convenient to measure the percent oxygen saturation of these specimens with a micro-oximeter (American Optical Co., Buffalo, N.Y.). The principle of this is that the optical density of the unknown sample is compared to that of one of standard oxygen saturation. As a result of the ratio between the two, a direct reading of the percent oxygen saturation of the unknown sample can be made. The standard provided by the company (79% sat.) is related to human haemoglobin. Rabbit haemoglobin has a slightly different structure, and this alters its light absorbing properties. It was therefore necessary to find this modifying factor before the method could be used.

The percent oxygen saturation of a sample determined against the human standard provided with the micro-oximeter, was compared to the saturation of the same sample determined by the Van Slyke manometric method. The principle of this Van Slyke method is that all the blood gases are evolved in a vacuum (using pot. ferricyanide to liberate that in combination with Hb.), selectively reabsorbed, and then the pressures which they generate measured at a constant volume.

Having first measured the oxygen capacity (by exposing the sample to atmospheric air), then samples were deoxygenated to various degrees by bubbling with nitrogen, or exposing the sample to a vacuum. These results, expressed as a percentage of the oxygen capacity, gave the true percent oxygen saturation of the sample. These values were

then compared with the micro-oximeter readings (which were slightly higher) to give the correction factor between the two.

Haemoglobin concentrations of the samples were measured by using a calibrated spectrophotometer (Bausch and Lomb, Rochester, N.Y.). A 1:200 dilution of the blood sample in a 4 ml Drabkins solution was examined for its optical density at 540 mu. From the standard provided, calculations of haemoglobin concentration were made in the routine way. As 1 gram of haemoglobin combines with 1.34 ml of oxygen, the oxygen concentration of the samples become:

$$[\text{Hb}] \times 1.34 \times \% \text{ oxygen saturation of the sample,}$$

where $[\text{Hb}]$ = haemoglobin concentration in
gms per 100 ml blood

Having determined, in this manner, the oxygen concentrations of the arterial and mixed venous blood, the cardiac output of the animal could be calculated by the application of Fick's equation, above.

(b) Serum cholesterol determinations

The total serum cholesterol of a number of animals was determined by the following method (SEARCY and BERGQUIST, 1960).

Reagents

1. FeSO_4 -Acetic acid reagent: a saturated solution was prepared by adding several grams of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ to 1 litre of reagent grade glacial acetic acid. After mixing, a clear solution was obtained by filtration.

2. Concentrated H_2SO_4 .
3. Acetone - absolute ethanol solution: equal parts.
4. Cholesterol standard (60 mgms/100 ml): 120 mgms of purified cholesterol was dissolved in 200 ml of acetone - ethanol.

0.1 of the serum sample was added to 0.9 ml of the acetone - ethanol solution. This was centrifuged at high speed for several minutes. 0.4 ml of the clear supernatant was placed in a colorimeter tube and diluted with 6.0 ml of the FeSO_4 - acetic acid reagent. Then 2 ml of the H_2SO_4 solution was blown with force into the mixture. The optical density was measured at 490 m μ on a spectrophotometer (Beckman D.U.) using 0.4 ml of the acetone - ethanol solution as a 'blank'. The same procedure was repeated on the cholesterol standard and the ratio of these two readings multiplied by the value of the cholesterol standard provided the total serum cholesterol value for the sample.

(c) Measurement of pulse wave velocity.

Pulse wave velocities of the animal were measured by recording central and peripheral pressure pulses. The time delay between them was measured from the E for M recording, which had time markers at 20 msec. intervals. The distance between the recording sites was measured at post mortem.

The central recording site was either the right carotid artery or the left brachial artery. The peripheral recording site was always

the right femoral artery. The 'foot to foot' transmission time was measured on the recording. The paper speed of the E for M recording was only sufficient to pick up gross changes in this transmission time. The first heart beat following a period of transient cardiac arrest was generally utilised, so that reflections would not distort the pulse wave and a 'true' pulse wave velocity could be determined. It was not always possible to measure all values at the same diastolic pressure level, but this was the primary objective.

(d) Method for determining the static compliance values in the dead animal.

It was necessary to relate the compliance values found in the 'square wave' experiments, with those determined by a more direct method in the dead animal. The only simple way to obtain this information was to perform pressure-volume studies on as long a length as possible of the excised aorta. Generally such studies are performed on relatively short segments such as the thoracic aorta, (see for example the study of NICHOL 1955), because of the problems involved in obtaining a leak-proof specimen. However, as it was necessary to obtain a value for the total compliance of the systemic arterial system, an attempt was made in this investigation to study a length of aorta from the aortic arch to the femoral bifurcation. This involved the ligaturing of close to some 40 branches of the aorta.

Initially, another approach was taken. It had been reported (ENGELBERG and DUBOIS 1959) that injection of a 1% suspension of

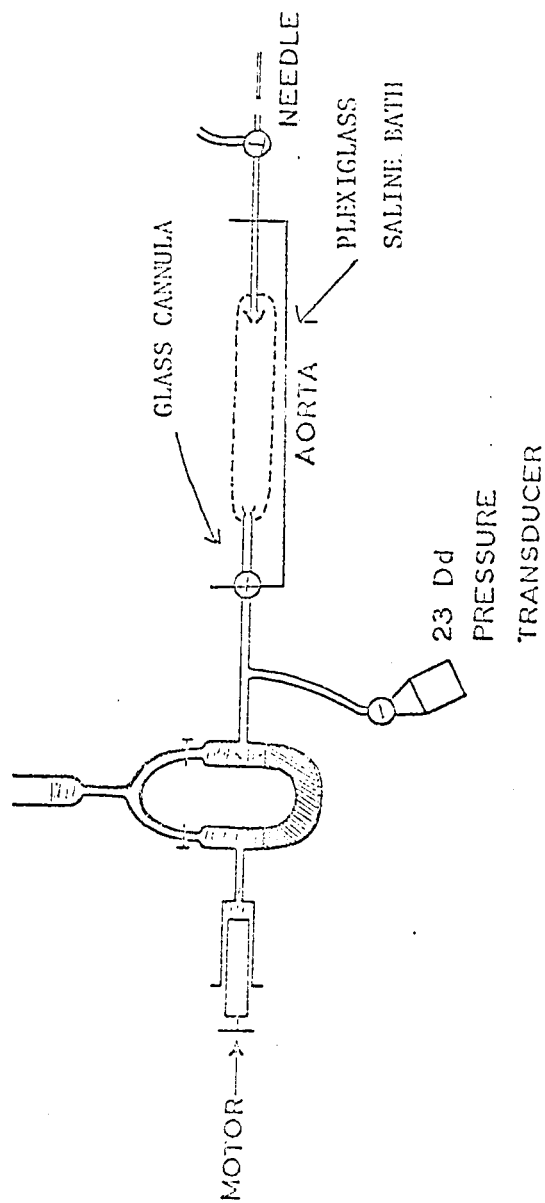
lycopodium powder into the pulmonary circulation eventually blocked all the small pulmonary vessels. This allowed a static compliance study of the pulmonary arterial system to be undertaken.

An attempt was made to adapt this technique to the systemic arterial circulation. A 1% lycopodium suspension was injected through a cannula into the carotid artery of a freshly killed rabbit. However, a sustained pressure rise, as measured from the femoral artery, could not be obtained, and the assumption was made that either there was a leak, or the solution was passing into the small vessels. A suspension of the lycopodium powder in a solution with very high viscosity (1000 centistokes - Medical Fluid 360 Dow-Corning), was then used, but similarly unable to sustain any increased pressure. Indian Ink was added to the solution, and the fluid was observed to pass into the fine vessels of the intercostal muscles. Ion exchange resins of 100 to 200 micron diameter (Amberlite, Rohm & Haas, Philadelphia) were substituted for the lycopodium powder, but again with little effect.

Recourse was then made to the simple, but difficult technique, of ligating all the branches of the thoracic and abdominal aorta. This was best done 'in situ', in a freshly killed animal. A powerful lamp (Photospot D x B General Electric) and suction were useful adjuncts to the dissection and ligation procedure. The surrounding fatty tissue was first separated from the vessel at the level of the diaphragm and then the intercostal branches were systematically tied with No. 6 surgical silk, working proximally. All branches from the arch to the

FIGURE 29

MODEL OF SYSTEMIC ARTERIAL CIRCULATION



femoral bifurcation were eventually ligated, and then the aorta removed from the body and placed in a bath of saline.

As shown in Fig. 29, the aorta was then tied onto a glass cannula (0.4 cm diameter) at one end, and a needle (size 15 Ga) at the other. The glass cannula had a small constriction in it and the needle was fluted, to ensure a tight fit. The glass tubing was joined to the male end of a luerlok stopcock with sealing wax (Pyseal). The luerlok sat in a saddle at the end of the plexiglass saline bath (length 50 cms, width 6 cms), which kept it in a fixed position. The needle was attached to a moveable side arm so that the artery could be stretched to any desired length. A three-way stopcock was attached to the end of the needle to facilitate ejection of air from the system. Originally, the system was attached to a water manometer, but this was abandoned in favour of a strain gauge manometer (Statham 23Dd) because of the problems connected with capillarity and corrections required for water entering the column.

The square wave infusion apparatus was connected to the glass cannula. Controlled amounts of saline were added to the aortic specimen by slow manual rotation of the long thread on the transmission carriage. With the three-way stopcock at the end of the needle turned so that it blocked any exit of saline, static pressure-volume studies could be performed. If a needle of smaller gauge, acting as the equivalent of the peripheral resistance in the animal, was attached to this three-way stopcock, and the latter turned so that it allowed

free passage of saline out of the aorta and through the small needle, then a dynamic study could be performed. In effect, this represented a model of the systemic arterial circulation, and its response to a square wave infusion, should be similar to that of a living animal (see later).

Two problems were generally encountered with this technique. The first involved removal of all air from the system, and was resolved by flushing the attached specimen with saline in the vertical position. The second was that most of the specimens had a slow leak, because of the long length of vessel used. An attempt was made to overcome this problem by flushing the aorta with citrated blood. The outside medium in the bath contained a calcium chloride solution, so that, on reaching the exterior of the vessel, the blood would clot and theoretically seal the leak. It was necessary to use fresh blood (and it was found that that of the investigator himself was generally given with least reluctance). This maneuver had some effect in sealing leaks, but was not entirely able to stop them at high pressures.

7. APPLICATION OF THE SQUARE WAVE INFUSION TECHNIQUE TO THE EXPERIMENTAL ANIMAL

Rabbit was the animal chosen for this investigation. Rats were used in the early pilot experiments, but thereafter rabbits, weighing

approximately five pounds, were used for the following principal reasons: (1) rabbits of any desired weight were readily available, (2) the response to vagus nerve stimulation was sensitive and allowed the heart beat to be stopped for an interval of 2 - 3 seconds without ill-effect, and (3) feeding of a high cholesterol diet readily produced pathological changes in their large arteries (IGNATOWSKY, 1908). A further reason was that it was planned to perform some experiments on the isolated carotid sinus, but these did not materialise. There are, however, as is well known, disadvantages to using rabbits for live experiments of any duration. Chief amongst these is their extremely fickle response to anaesthesia. It was a continuous concern to keep these animals in good condition for the duration of 2 - 4 hours generally required for each experiment. A hypotensive response to positive pressure respiration was not infrequently noted. It was found to be of great value to ventilate the animals with a 100% oxygen mixture on account of their sensitive response to hypoxia. However, in spite of these difficulties, the rabbit proved to be an adequate, if not obliging, experimental animal.

Initially, in terms of anaesthesia, nembutal in a dose of 30 mgms p. Kgm. was used. This was given into the marginal vein of the ear, the site of injection for all parenteral anaesthetic agent subsequently used. Mortality was high using this procedure, so a 2% chloralose solution in a dose of 6 ml p. Kgm was substituted, but

with relatively little improvement. Finally, a 2% chloralose and 20% urethane mixture was used in a dose of 2.3 ml p. Kgm. This gave a relatively light anaesthesia, which would sustain spontaneous breathing for a period of 2 - 3 hours. Initially this was supplemented with subcutaneous injection of 2% procaine solution at the incision points in the neck and other cannulation sites. However, a disadvantage arose when cardiac arrest produced by vagal stimulation was required. The procaine solution sometimes leaked into contact with the vagal nerve and was probably responsible for some of the experiments that failed because the vagal nerve would not stimulate properly. Once this was realized, all 'chloralose-urethane' anaesthetics were supplemented with ether (E.R. Squibb Co., Montreal), administered to the animal with a cotton wool pad. This latter anaesthetic technique with experience worked reasonably well. It was also found useful to starve the animals before the period of experiment.

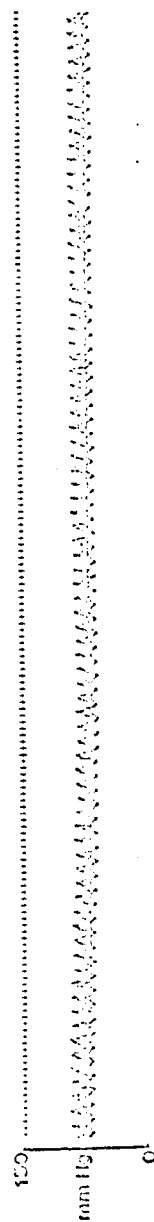
A further point in the general care of these animals, is that tracheostomy was found to be useful as a routine. Stimulation of the peripheral end of the vagus nerve occasionally resulted in violent respiratory movements in animals without tracheostomy. It was probable that these resulted from laryngeal effects (closure of glottis, etc) caused by coincidence stimulation of the recurrent laryngeal nerve. Thereafter, even in the early experiments, tracheostomy was performed as a routine.

Measurement of blood pressure and the repeated reinfusion of blood into the circulation required systemic anticoagulant therapy. This was satisfactorily achieved by an I-V injection of Heparin in a dose of 5 ml.p.Kgm., usually down the catheter in the right external jugular vein. As elimination of all air bubbles from both the infusion apparatus and the recording apparatus was of paramount importance, these systems were filled with 0.9% saline solution made from freshly boiled water.

As previously stated, the fluid used for the square wave infusion was the animal's own blood. The infusion cannula, upon insertion into the right carotid artery was filled with normal saline solution. The long thread on the transmission carriage was then slowly rotated backwards by hand, so that 5 - 8 ml of blood was gently withdrawn from the animal via the right carotid artery. This flowed into the animal side of the mercury U-tube system, which thus became full of a mixture of blood and saline solution. This was then reinfused into the animal and another 5 - 8 ml of blood slowly withdrawn. The proportion of saline on the animal side of the Mercury U-tube then became very small, and the infusion medium was for practical purposes, the animals own blood. This avoided the problems of temperature matching and circulatory overload that might have occurred with repeated infusions of foreign blood. It also has the advantage over 0.9% saline solution infusion, such as PETERSON (1954) used, in that problems arising from the different viscosities of the two solutions,

FIGURE 30

WITHDRAWAL 8 ml BLOOD



THE EFFECTS OF WITHDRAWAL OF 8 ml BLOOD IN A 3 kgm RABBIT

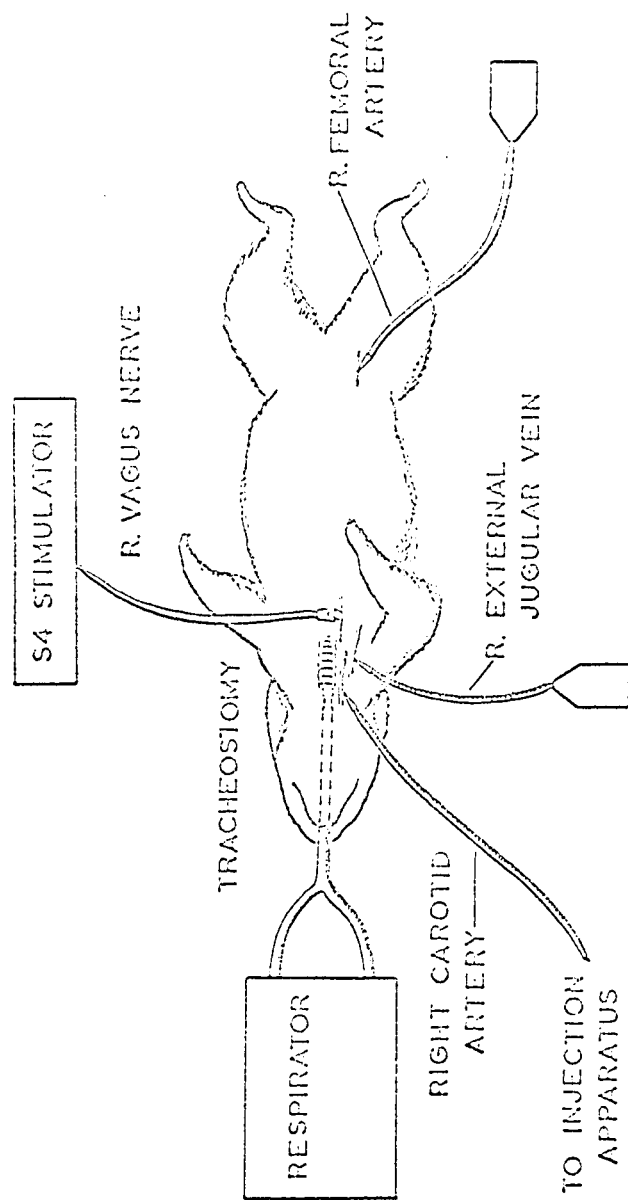
are not encountered.

The general effects on blood pressure of slow withdrawal of 8 ml of blood in a 3 Kgm rabbit are shown in Fig. 30. It can be seen that removal of this quantity has no significant hypotensive effect. Removal of quantities less than this were often entirely adequate. Of course, the response is dependent on the blood volume of the animal at the time of withdrawal, and in some volume depleted rabbits, withdrawal of this quantity did have a significant hypotensive effect. However, if this did occur, it usually occurred immediately and was easily monitored. The average blood volume of the rabbit is 50 mg/Kgm (SJOSTRAND 1962), and so withdrawal of 10 ml in a 3 Kgm rabbit amounts to loss of 6 % of the total blood volume.

The blood was not left withdrawn into the U-tube for much longer than 2 - 3 minutes in order to avoid excessive sedimentation of the red cells. A period of at least 45 seconds or so was waited before reinfusing the blood back into the animal, to allow any disturbance of the steady-state which might have occurred, to settle.

The general plan of a typical experiment towards towards the end of the investigation is that a five pound rabbit was anaesthetised with chloralose-urethane solution. This was supplemented with ether as necessary and the animal prepared for the experiment as shown in Fig. 31. A cannula was placed in the right carotid artery and connected to the square wave infusion apparatus (see Fig. 10). The

FIGURE 31: Dissection and cannulation of the rabbit necessary for the experiment



pressure response of the animal to the square wave infusion was measured through the cannula placed in the right femoral artery. This was connected to a Statham pressure transducer (see Fig. 17) and the E for M recorder. Electrodes were placed on the right vagus nerve to cause brief stoppage of the heart during the time of the infusion. The animal was curarised and given positive pressure ventilation through a glass cannula inserted into its trachea. Central venous pressure was measured from the catheter in the right external tubular vein.

A small amount of blood was slowly withdrawn from the animal into the infusion apparatus. The 'preparatory' switch on the control panel was then turned on and various checking maneuvers performed. The master switch was then turned 'on' and the blood reinfused into the animal in the form of a square wave. During this time, which lasted approximately 2 - 3 seconds, heart beat and the respiratory movement were stopped. On turning the master and preparatory switch to 'off', these normal functions were resumed. During the time of the infusion, a phase plane plot of dp/dt against P , was photographed on the Tetronix oscilloscope with a polaroid camera.

This general plan will now be considered in detail. All recorders were turned on, and a check made to see that all the camera systems were loaded, and that the pens on the pen recorder were not blocked. Two litres of distilled water were boiled to drive off all dissolved gases, cooled, and then a litre of 0.9% saline solution made

from this. This was used to fill the pressure transducer and square wave infusion systems, great care being taken to eliminate all bubbles. Frequently the stopcocks were cleaned and smeared with vacuum grease (Dow-Corning, Midland, Michigan). The pressure transducers were then calibrated from the mercury column manometer at 50, 100 and 150 mm intervals. Zero level was taken at 3 cms from the level of the table top, which corresponds to the mid-thoracic level of the animal. The pressure preamplifiers on the E for M recorder were balanced and the steps of the calibration resistors recorded up to 160 mm Hg. In those experiments in which two pressure recordings of identical sensitivity were required, one preamplifier channel was adjusted to give the same size deflection as the other, by using the fine amplitude control and a standard signal from the mercury column manometer.

The infusion syringe, and its steel plunger were carefully cleaned in Alconox detergent, and then connected and screwed in place on a plexiglas block, taking care to displace all air bubbles. The motor and accompanying apparatus was then switched on. A trial run of the square wave infusion apparatus and its controlling system, was made, without attachment to the animal.

The rabbit was weighed, and injected with the appropriate dose of chloralose-urethane solution through one of the marginal veins of the ear. The rabbits were generally about 5 Kgm in weight. Excess hair was shaved at the neck and right groin region, and the skin incised in these regions, supplementing the anaesthesia with ether.

(held to the mouth over a cotton wool pad) if necessary. The animal was then transferred to the operating table, tied down, and the areas further dissected.

Through midline dissection, the trachea was exposed, encircled with a ligature, and a glass tracheal cannula inserted. Any blood in the trachea was sucked out with a syringe and the table was slightly tilted for a while to discourage drainage into the lungs. The animal was generally allowed to breathe freely on its own, until it was necessary to administer the neuro-muscular blocking agents at a later stage.

The right external jugular vein was then exposed, as it lay between the sternomastoid muscle and the strap muscles of the neck. Cotton ligatures were placed around it distally and proximally, but not tied at this time. The right femoral artery was dissected from its sheath in Hunters canal, and similarly ligatured, but not tied. Finally, the right carotid artery was separated from the carotid sheath and again ligatured, but not tied.

A bulldog clip was then placed at the proximal end of the vein and the distal ligature tied. The external jugular vein was then incised with fine iris scissors, and the polyethylene catheter inserted up to a marked distance of 6 cms. The proximal ligature was tied, but not too tightly over the catheter. The appropriate amount of heparin solution was given to the animal through this catheter, and the Electronics for Medicine recorder checked to see that central venous pressure was being recorded adequately.

The distal ligature on the right femoral artery was then tied, a bulldog clip applied proximally, and the artery incised with fine Iris scissors. Before actually inserting the cannula, fluid was made to flow slowly down it to prevent the possibility of any air entering. The cannula was then inserted into the right femoral artery, the bulldog clip removed, and the proximal ligature tied tightly over the cannula. It was found to be more secure if a second ligature was also tied over this cannula. The cannula was flushed with 0.9% saline solution if the pressure recording became damped.

The right vagus nerve was then gingerly dissected from the carotid sheath, taking care not to incorporate the sympathetic trunk which ran closely alongside it. As long a length as could be carefully freed was then taken and transected at its upper end. A small distinctive ligature was then tied at this upper end. Next, the distal ligature around the carotid artery was tied, a bulldog clip applied at its proximal end, and the cannula inserted into the right carotid artery in exactly the same fashion as in the right femoral artery.

The micromanipulator holding the electrodes for vagal stimulation was then positioned on the table, and the nerve gently laid across the electrodes. Trial stimulation of the nerve without subsequent square wave infusion was then given to see if the heart would stop for a long enough interval. This was accomplished by turning the master switch, but not the 'preparatory' switch, to the 'on'

position (see Fig. 19).

Having completed the preparation of the animal with the square wave infusion apparatus fully attached, and the nerve placed across its electrodes, calibration of the phase plane plot on the tetronix oscilloscope was then made. The right femoral artery cannula was momentarily disconnected from the pressure transducer by a three-way stopcock and the pressure transducer exposed to atmospheric pressure. The filter switch (a) on the pressure preamplifier of the E for M recorder was turned to the 'mean' position, and the calibration resistor switch turned to the 80 mm Hg. position. The position of the beam on the Tetronix oscilloscope was then put at exactly the centre of the screen. The calibration resistor switch was then rotated up to 160 and down to 20 in steps and a Polaroid picture then taken of this calibration procedure. This picture served as the calibrating medium for the phase-plane plot (i.e.: dP/dt against P). The filter switch (a) was then turned back to the 'normal' position, and the three-way stopcock rotated so that the right femoral pressure was recorded once again.

The motor was turned on again, and left running throughout the remainder of the experiment. The infusion rate was a direct function of the motor speed, and this was varied according to the dictates of the experiment. The rabbit was connected to the respirator and a bag containing 100% oxygen was connected to its inlet port. The animal was curarised by injection of the appropriate amount of D-tubo curare solution down the central venous catheter.

Thus the animal was finally 'primed' for the injection of a square wave infusion. This was given, after slow withdrawal of 5 - 8 ml. of the animals own blood into the infusion apparatus. The sequence of events culminating in the square wave infusion that took place after turning the 'preparatory' and 'master' switches on, have already been described. A series of these square wave infusions singly or in duplicate or triplicate, were given at a variety of rates during each experiment. The results obtained will be discussed in the next section. The experiments generally lasted for a period of 2 - 4 hours.

Chapter III

RESULTS

The general objective of the experiments performed, was to see if the simple theory outlined on pp.83-89, could be applied in a practical manner to the circulatory system. The equation of the proposed model for the systemic arterial circulation was:

$$F = (P - P^+) \cdot \frac{1}{R} + C \cdot \frac{dP}{dt} \dots\dots\dots(18)$$

This equation describes the 'transient' behaviour of the system to a step function. When the pressure response no longer continues to vary with time (i.e.: $dP/dt = 0$) the equation is then reduced to the function below, which thus describes the 'steady-state' of the system:

$$F = (P - P^+) \cdot \frac{1}{R} \dots\dots\dots(19)$$

It was necessary to study the steady state response, which is a function of resistance only, before the more complex transient state could be studied. The experiments, which differed in their execution as the investigation progressed, will be described in the chronological order that they were performed.

1. STEADY-STATE RESPONSE OF THE SYSTEMIC CIRCULATION TO A
SQUARE WAVE INFUSION:

The original objective of this investigation, as already mentioned, was to make a direct study of pressure flow relations across the whole systemic circulation. A particular barrier to doing this lay in finding a suitable technique of giving a square wave infusion to the systemic circulation, without the complicating presence of the animal's own heart beat.

The first attempt to solve this problem lay in giving the square wave infusion at such high rates that the heart was unable to eject its contents against the high pressure levels suddenly developed. With this technique, pressure flow relations in a higher than normal range could be studied across the whole systemic arterial circulation. An attempt was next made to study these relations in a more normal range, by giving the square wave infusion between heart beats. However, the time interval of 250 msec. or so, between heart beats in a normal rabbit, proved to be quite insufficient for any steady-state response to be adequately assessed. The final solution to this problem therefore, lay in stopping the heart beat for a period of 2 - 3 seconds and giving the square wave infusion during this time. Using this technique, the steady-state pressure response could easily be established, and pressure flow relations studied over any desired range. These experiments will now be described.

(a) Square wave infusions at high flow rates to cause isovolumic contraction of the heart.

These experiments, which were essentially pilot studies, were performed on rats weighing 400 to 500 grams. Infusion rates three to four times that of the cardiac output, were given to the animal through the right carotid artery. This manoeuvre generated pressures in the systemic circulation of 200 to 300 mm Hg, so that the heart could not generate sufficient force to open the aortic valve. The infusions were continued sufficiently long (generally 1 to 3 seconds) to allow development of the steady-state pressure response.

The rats were anaesthetized with nembutal (50 mgms. per Kgm.), heparinized, and the right and left carotid arteries cannulated. Arterial pressures were measured from both these sites. The infusion apparatus (which at that stage was the crude prototype of Harvard infusion pump and 10 cc. syringe) was connected to the cannula in the right carotid artery, which was constructed in the form of a T-piece. Infusions of saline were then given to the rats at different velocities from this pump until steady-state pressures were reached. The pressures monitored from the right carotid artery were of the order of 100 mm Hg. higher than the ones on the left. This arose from the fact that blood was actively flowing through the cannula on the right at the time of the infusion and therefore generated an extra pressure gradient.

The type of response generally obtained is shown in Fig. 32. The stair case-like tracing in the middle of the figure represents the

TABLE 1

'TOTAL PERIPHERAL RESISTANCE' IN RATS, MEASURED BY THE HIGH INFUSION RATE METHOD

(a) Typical experiment on 390 gm rat:

Mean pressure prior to infusion mm Hg.	62	56	52	50	46	49
Steady state pressure during infusion mm Hg.	178	199	233	219	196	216
Infusion rate ml/min.	210	270	378	348	420	444
'Total peripheral resistance' in P.R.U. _{min.}	0.74	0.73	0.63	0.63	0.46	0.48

(b) Six experiments were performed on rats weighing approximately 400 gm in this manner:

Range of resistance values obtained = 1.5 to 0.44 P.R.U._{min.}

Mean resistance value for whole group = 0.83 P.R.U._{min.}

constant velocity of the infusion pulse (which is proportional to the angle made with the abscissa). The lower tracing, pressure levels recorded from the left carotid artery, and the middle tracing, pressure levels recorded from the right carotid artery. The upper tracing is the ECG of the rat, from which it can be seen that the rate and rhythm of the heart is little changed by this procedure. The rat tolerated these procedures well. Indeed, where hypotension was present, injection of the pulse appeared to improve the situation for a period of one to five minutes, possibly by increasing the coronary flow.

The 'total peripheral resistance' (or chord resistance) could be calculated from the ratio of the steady-state pressure value to the infusion rate as in the simple equation (2). Table I shows the results of total peripheral resistance calculation by this direct method. Actual pressure flow curves constructed from these values showed a very varied and inconsistent pattern.

These pilot experiments helped to define the improvements necessary for the infusion giving apparatus (which was relatively poor at this stage), and demonstrated the efficiency of high infusion rates in causing an isovolumic state of the heart. Repeated saline injections, which would alter the viscosity of the blood, and cannulation of both carotid arteries to monitor pressure, were not used in subsequent experiments.

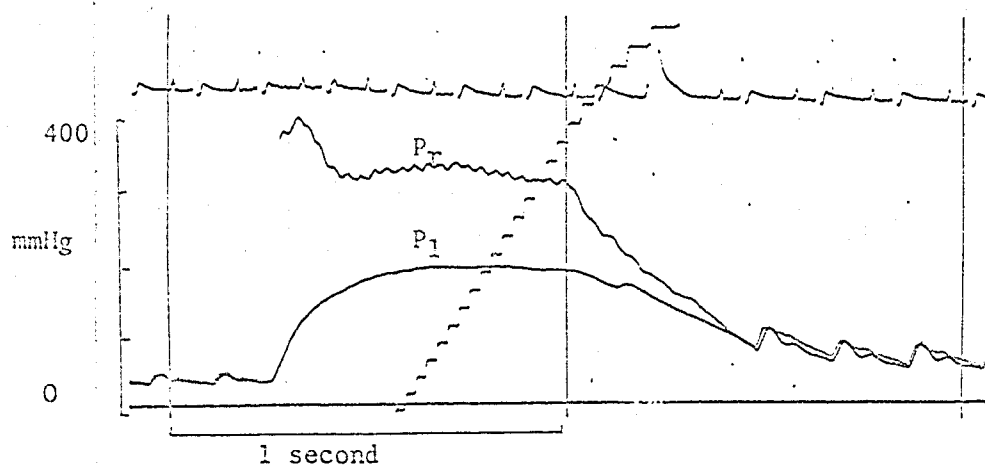


FIGURE 32: Blood pressure response in rats to
square wave infusions at high flow rates
 P_r = pressure monitored from right carotid artery
 P_l = pressure monitored from left carotid artery

(b) Square wave infusions between normal heart beats

This was a considerably more ambitious undertaking. Initially, much time was spent in improving the technique so that a square wave infusion could be given and hopefully, a steady-state pressure response generated within the 250 msec. interval between normal heart beats. It was necessary to choose a larger animal than the rat, because the heart rate of the latter was too rapid at 300 to 400 beats per minute. The rabbit was eventually chosen (heart rate 200 to 300 beats per minute), for reasons already stated. It remained the experimental animal for the remainder of the investigation.

The animal was anaesthetized, heparinized, and the infusion apparatus connected to the right carotid artery. Blood pressure was monitored from the right femoral artery in most cases, but occasionally from the left brachial artery. Blood pressure was no longer measured from the infusion cannula in the right carotid artery because pressure interpretation at this site was difficult on account of the extra flow gradient.

Approximately 5 ml of blood was slowly withdrawn from the rabbit into the mercury U-tube system. The point in the cardiac cycle when this blood was to be infused back into the rabbit was preset, using the monitor on the Cossor oscilloscope. The infusion was triggered by either (1) a particular pressure level or, (2) by a particular interval after the QRS complex if the ECG circuit was used (see Fig. 18). The duration of the infusion was adjusted to be not longer than the interval between

heart beats. A typical response is shown in Fig. 33. The top tracing records the signal from the linear velocity transducer, and thus records the motion of the syringe which can be seen to be in the form of a square wave infusion. The next two tracings represent pressure recordings from the brachial and femoral arteries respectively (distinguished from each other by the fact that the former precedes the latter). The brachial pressure recording almost seems to have reached a steady-state response during the time of infusion. However, it is not possible to assess the infusions effect on the femoral pressure recording, because a prominent reflected wave has become superimposed. This problem was continually encountered and caused the method to be abandoned because the tracings were impossible to interpret, even when the infusion period was extended to cover a series of beats, as in Fig. 34. However, in a species such as Homo Sapiens, in which the interval between heart beats is considerably longer, this may still be a useful method.

--

(c) Square wave infusion during transient cardiac arrest.

This raised the problem of finding a suitable means for causing transient cardiac arrest. The procedures tested have been described in the 'Method' section. Stimulation of the right vagus nerve for a period of three seconds generally proved to be a satisfactory technique. The square wave infusion was given during the time of cardiac arrest and in these early experiments, the object of interest was the steady-state pressure response. By relating this to the various infusion rates given,

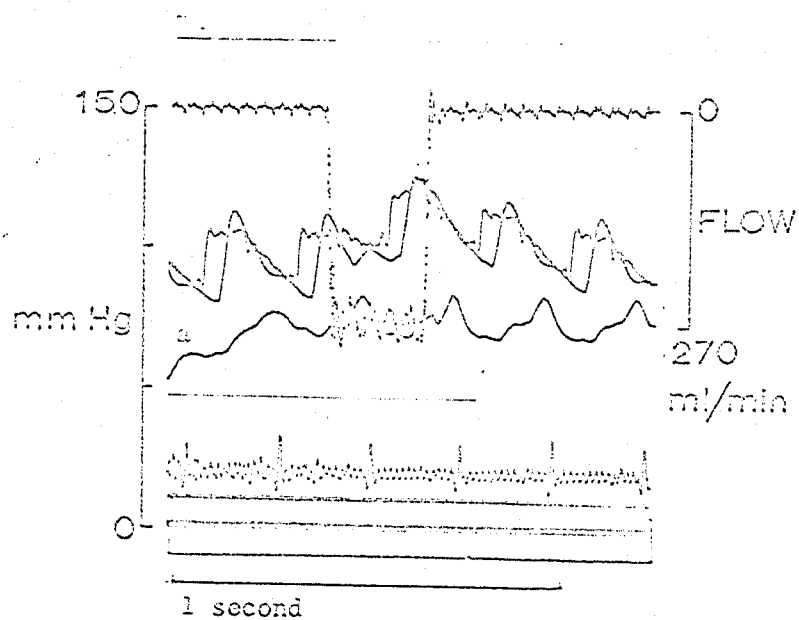


FIGURE 33: Pressure responses resulting from a square wave infusion given between normal heart beats.

a= central venous pressure

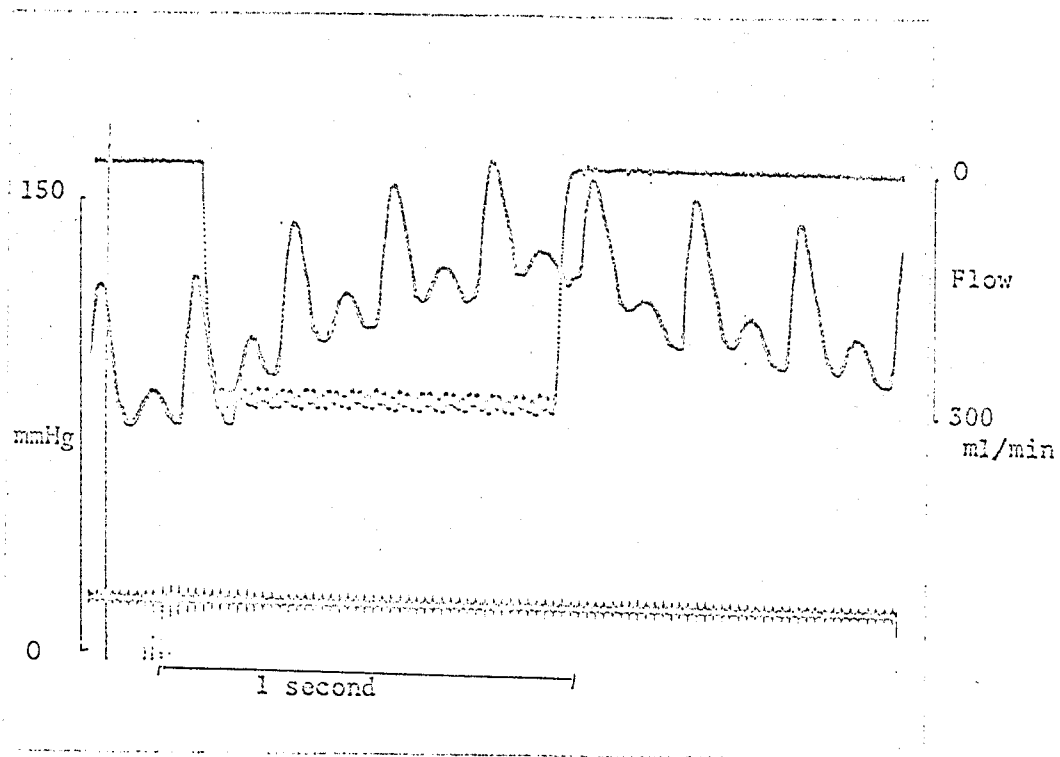
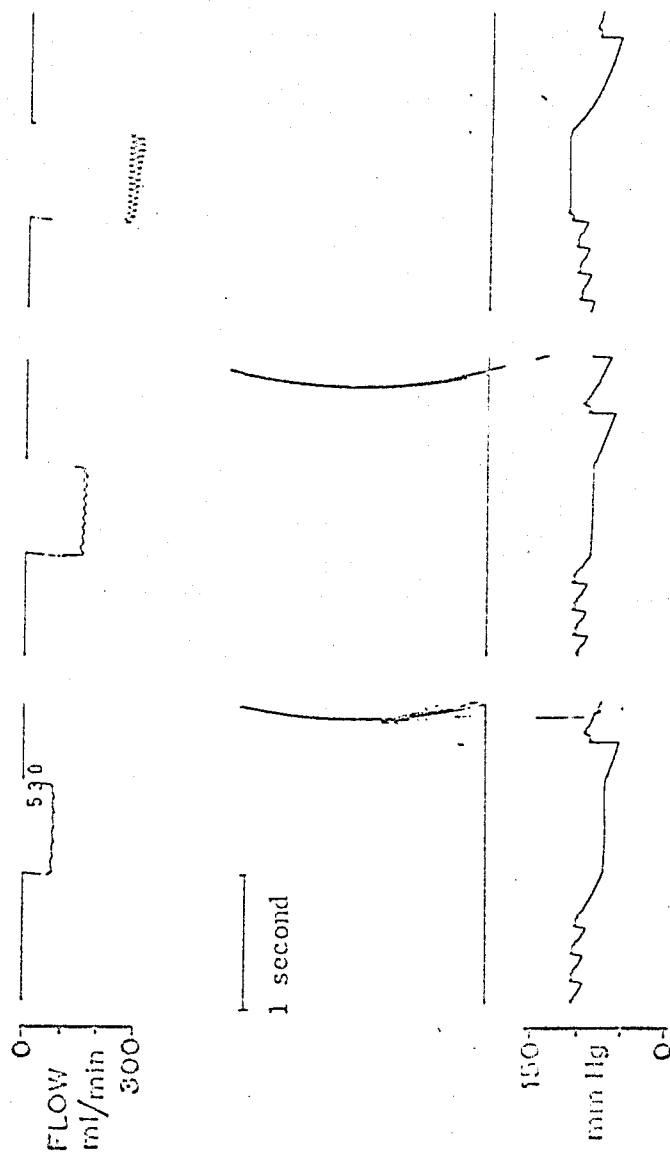


FIGURE 34: Pressure response resulting from a square wave infusion given over several heart beats.

FIGURE 35



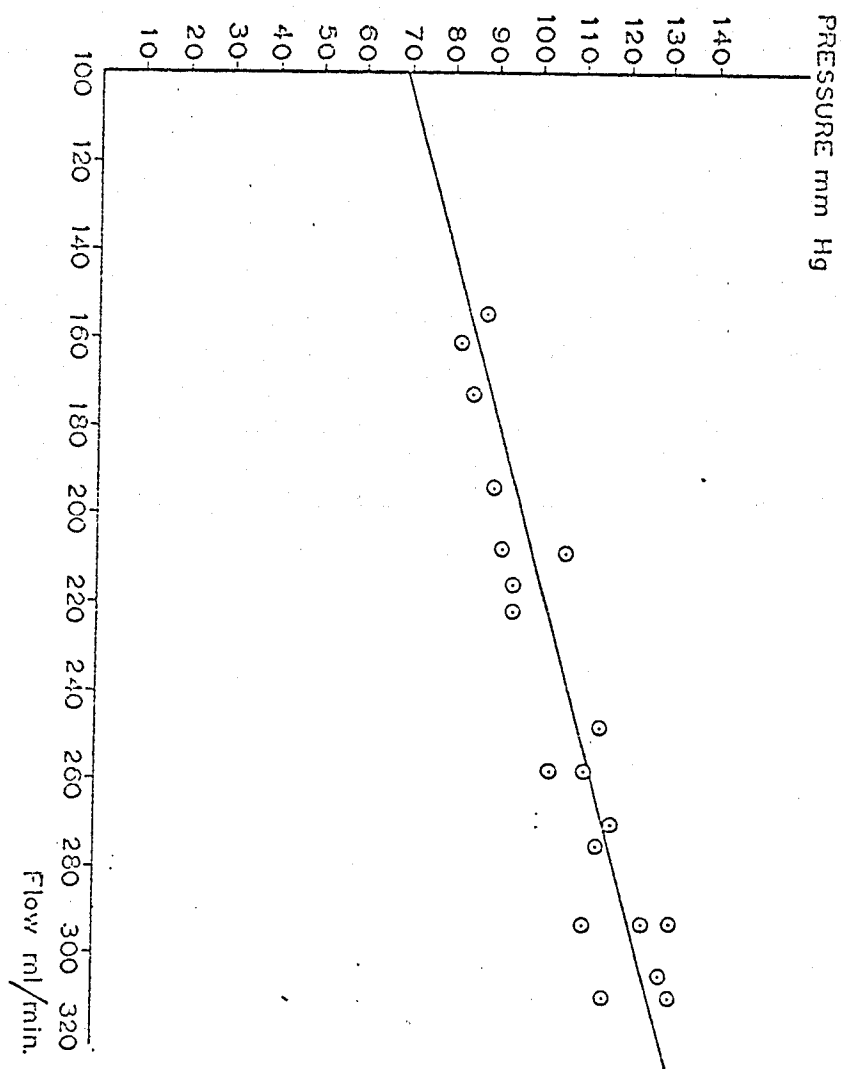
THE STEADY STATE PRESSURE RESPONSE TO A SERIES
OF INFUSIONS AT DIFFERENT FLOW RATES

the simple, linear steady-state expression of the equation (2) could be assessed over any range of pressure and flows.

A typical experiment is shown in Fig. 35. The top tracing represents a series of square wave infusions at increasingly greater flow rates. The bottom tracing represents the pressure response measured from the right femoral artery. The steady-state pressure response during the time of each infusion is represented by the constant pressure level obtained. In three animals, this pressure was also simultaneously measured from the brachial artery but there was no significant difference in the nature of the response. There were several occasions in which the pressure remained at a steady-state value for a relatively long period (2 to 3 seconds), until the square wave infusion was discontinued. This suggested that the circulation was in a steady-state during this time period and that stimulation of the peripheral end of the vagus nerve was having no effect on the circulation, at least for the initial period (see later).

Fig. 36 gives an example of a plot of flow against steady-state pressure across the whole systemic arterial circulation under these circumstances. Each point represents the steady-state response to a single square wave infusion. The example shown has a positive linear correlation coefficient of $r = 0.85$. Furthermore, if this line is extrapolated to the ordinate at the point where flow through the system is 0 ml p. min., there is found to be a positive pressure axis intercept of 15 mm Hg. Table II shows the various values obtained in a

FIGURE 36: Pressure-flow plot determined from the steady-state responses to a series of square wave infusions



MEASUREMENT OF 'TOTAL PERIPHERAL RESISTANCE' IN RABBITS, BY STEADY STATE METHOD

[illegible]

typical experiment on a four pound rabbit.

Table III shows the values obtained in a group of seven rabbits for 'total peripheral resistance' (chord resistance) measured by this direct method. Plots of flow against steady-state pressure across the whole systemic arterial circulation had roughly linear correlations . In each case, at zero flow, there was a positive pressure axis intercept with value varying between 15 to 50 mm Hg., with a mean value of 27 . These values were mostly obtained by extrapolation from higher flow rate recordings, but on one occasion it was possible to give a flow rate of 40 ml p. min. (instead of the normal 200 ml p. min.) and so give experimental justification for the validity of these extrapolations.

All total peripheral resistance values calculated were chord resistances, which ignore the effect of the positive pressure axis intercept. Bearing this in mind, a sudden haemorrhage of 15 ml (in addition to the 5 to 10 ml withdrawn to prime the infusion apparatus) caused an increase in resistance from .39 to .51 P.R.U. within a period of two minutes in a 2 Kgm rabbit. The mean blood pressure fell from 70 to 40 mm Hg. as a result of the rapid blood loss.

A practical point concerning the acquisition of this data for the pressure flow plots is that the controlled system must be in a constant state during this time. The average time taken to obtain 6 points on the plot would be about 15 - 20 minutes. Not every square wave infusion given was satisfactory because it was difficult to judge the

TABLE 3

MEASUREMENT OF 'TOTAL PERIPHERAL RESISTANCE' IN RABBITS BY STEADY STATE METHOD

Resistance values of seven rabbits weighing 4 to 6 lbs determined by the steady state method

Mean resistance value P.R.U. min.	Range of resistance value	Mean, mean pressure of animal mm Hg.
0.57 (15)	.97 to .34	51
0.47 (18)	.68 to .39	92
0.45 (20)	.57 to .38	115
0.33 (16)	.39 to .25	85
0.57 (6)	.48 to .89	72
0.31 (6)	.35 to .28	50
0.21 (5)	.22 to .21	48
Mean resistance value for whole group = 0.42 P.R.U. min. (Figures in brackets refer to number of determinations).		

precise infusion rate required to rapidly reach a steady-state pressure level. Furthermore, it was noted during the course of the experiments, that respiratory activity had a definite effect on the arterial pressure response, during the periods of cardiac arrest. Central venous pressure showed a similar and practically coincident change to that found in the arteries. This effect was more fully investigated later, but it became apparent from these experiments that the square wave infusion had to be given in a particular phase of the respiratory cycle, as well as in the cardiac cycle. Modifications were then made to the circuit controlling the timing of the square wave infusion to account for this factor, as previously discussed under 'Methods'.

These studies on the steady-state pressure response of the whole systemic arterial circulation to a number of square wave infusions at varying rates, thus demonstrated the following points:

- (1) high infusion rates can be made to cause isovolumic contraction of the heart.
- (2) direct pressure flow studies across the whole systemic arterial circulation show a significant positive pressure intercept of 15 - 50 mm Hg. at zero flow rate. This throws the whole question of measurement of 'total peripheral resistance', which is a chord resistance, into doubt.
- (3) In so far as these studies are unavoidably time dependent, direct pressure flow relations across the whole systemic

arterial circulation are roughly linear (see Fig. 36).

(4) Respiratory activity had a definite effect on the arterial blood pressure. During inspiration, there was a decrease in arterial blood pressure, and during expiration there was an increase.

As a result of these steady-state studies, further refinements were made in the technique. The investigation then turned to a study of the combined transient and steady-state response of the vascular bed.

2. TRANSIENT RESPONSE OF THE SYSTEMIC CIRCULATION TO A SQUARE WAVE INFUSION:

Study of the transient response of a system is usually, by implication, a combined study of the transient and steady-state response of the system. In terms of the working hypothesis that the systemic arterial circulation behaves as a simple linear first order system (as first proposed by Frank in 1899), it is a study of that vascular bed in terms of the following equation:

$$F = P \cdot \frac{1}{R} + C \cdot \frac{dP}{dt} \dots\dots\dots (8)$$

The transient pressure response, which precedes establishment of the new steady-state response, is thus a function of both resistance and compliance.

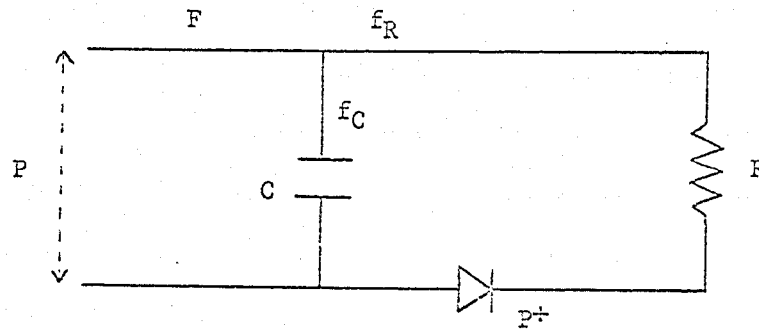
In the first group of experiments performed to analyse the transient pressure response to a square wave infusion, the resistance of the whole systemic arterial circulation remained the primary object of interest.

(1) Transient pressure flow relations across the whole systemic arterial circulation.

*

Consider the electrical analogue of Franks Windkessel model of the systemic arterial circulation (see Fig. 7). Thus :

* modified to account for critical closing pressure



$$\text{Thus } F = f_R + f_C \quad \dots\dots\dots (7)$$

$$\text{Then } f_R = \frac{1}{R} \cdot (P - P^+) \quad \dots\dots\dots (20)$$

$$f_C = C \frac{dP}{dt} \quad \dots\dots\dots (21)$$

Thus equation (7) is an alternate way of considering the transient response of the system to that shown in equation (8).

The resistance of the system, by manipulation of equation (20), becomes:

$$R = \frac{(P - P^+)}{f_R} \quad \dots\dots\dots (20)$$

When the steady-state pressure response is reached, $f_C = 0$, and equation (20) becomes:

$$R = \frac{(P - P^+)}{F} \quad \dots\dots\dots (10)$$

Now F , the total flow rate into the system is measurable, but f_R is not. Eq. (10) only applies when the pressure response has reached

a steady-state level. During the preceding transient state, eq. (20) applies and the value of the unknown f_R changes every moment, as the pressure gradient across the system varies exponentially. It is possible to test the linearity of pressure flow relations across the system as stated in eq. (20) without actually knowing the values of f_R or R , by the following method.

Consider, as in the plot shown in Fig. 38, 2 square wave infusions given at rates of F_1 (for example 160 ml/min) and F_2 (for example 220 ml/min) such that:

$$F_1 = f_{R1} + f_{c1}$$

$$F_2 = f_{R2} + f_{c2}$$

At any time 't' (for example 160 msec) after the beginning of each infusion, the total pressure across the system will have risen to values of P_1 and P_2 , respectively.

Furthermore:

$$\frac{f_{R1}}{F_1} = \frac{f_{R2}}{F_2} \quad \text{Let this ratio be 'a'}$$

Now, if the resistance across the system is linear:

$$\frac{(P_1 - P^+)}{f_{R1}} = \frac{(P_2 - P^+)}{f_{R2}} \dots\dots\dots (22)$$

But f_{R1} and f_{R2} are unmeasurable. However, it has been seen that F_1 is related to f_{R1} by a factor of $\frac{F_2}{f_{R2}} \cdot \frac{f_{R1}}{F_1}$: and F_2 to f_{R2} by

a factor of $\frac{F_1}{f_{R_1}} \cdot f_{R_2}$

Therefore, eq. (22) can be stated:

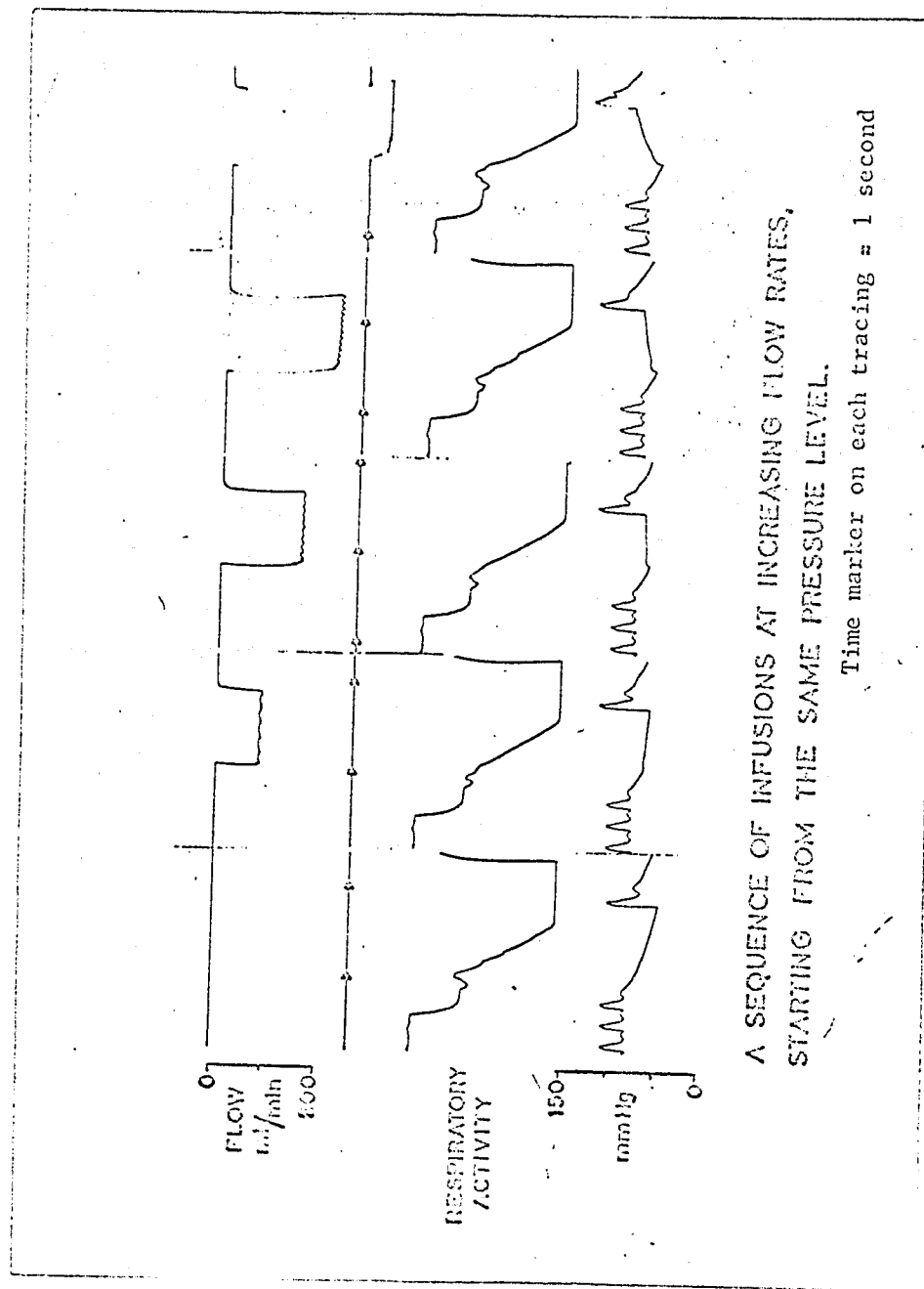
$$\frac{(P_1 - P^+)}{aF_1} = \frac{(P_2 - P^+)}{aF_2} \dots\dots\dots (23)$$

Thus a plot of P_1 and P_2 against F_1 and F_2 at any constant time after the beginning of the square wave infusion (e.g.: 160 msecs, or 300 msecs, etc. ... as shown in Fig. 38) should give a straight line relationship if the resistance (and compliance) across the system is linear. The ratio of P_1^* to F_1 , or P_2^* to F_2 must be modified by the unknown constant 'a' to give the proper value for resistance. The value of 'a' continuously increases from '0' to '1' from the time of the beginning of the square wave infusion until the steady-state response is established. This method requires that all square wave infusions begin from the same pressure level.

Application of this theory was made to study further the linearity of direct pressure-flow relationships across the whole systemic arterial circulation. The same broad technique as used in previous sections was used, in that the square wave infusions were given during a period of transient cardiac arrest. The further refinement was made that the infusions were given at a constant phase of the respiratory cycle (as can be seen from Fig, 37). The top tracing in Fig. 37 shows that a series of square wave infusions of increasing flow rates were given to the rabbit . The bottom tracing, which records

* erratum: all symbols designated with an asterisk require subtraction of P^+ eg: should not read P_1 , but $P_1 - P^+$ etc.

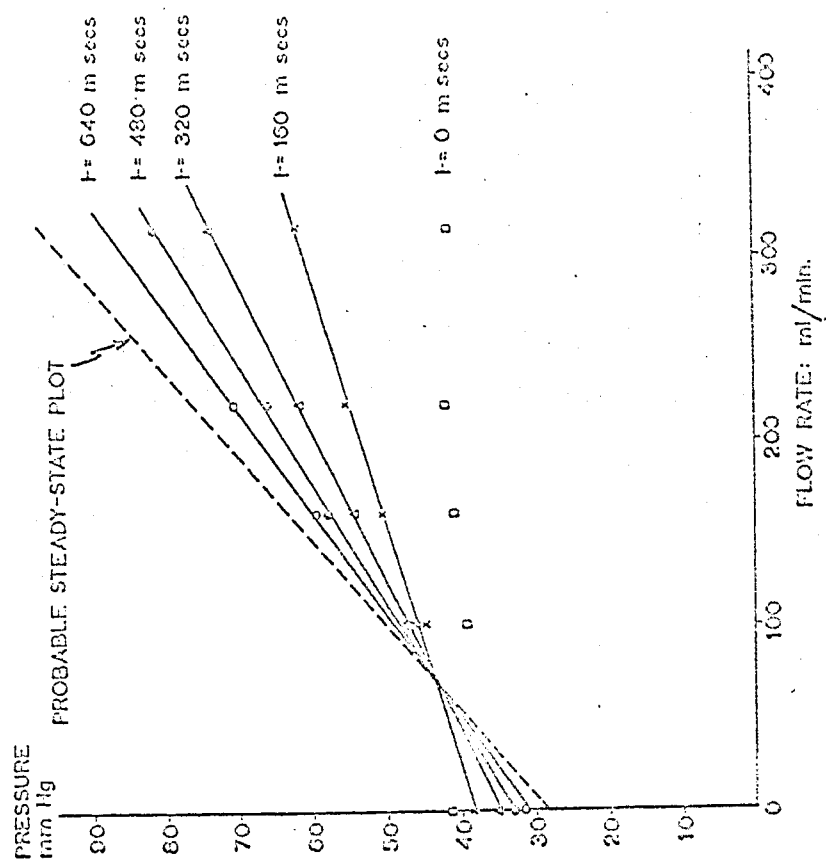
FIGURE 37



A SEQUENCE OF INFUSIONS AT INCREASING FLOW RATES,
STARTING FROM THE SAME PRESSURE LEVEL.

Time marker on each tracing = 1 second

FIGURE 38: Pressure flow plots determined from the transient responses to a series of square wave infusions



the pressure response from the right femoral artery, shows that these infusions were given when the diastolic pressure fell to a critical level. This was achieved by using the pressure trigger in the circuit of Fig.18 and described in the 'Methods' section (it was not possible to trigger the square wave infusions at precisely the same diastolic pressure level (as the points $t = 0$ on Fig.38 show), but a variation of only 2 - 3 mm Hg. in this level was sufficient close to allow the method to be used. The diastolic pressure trigger level ranged between 40 and 60 mm Hg.).

These transient pressure responses to a step function (or square wave infusion), as can be seen, in Fig.37, were roughly exponential in form. They were analysed in the following fashion to give the type of pressure flow plots across the whole systemic arterial circulation as discussed in reference to Fig.38 (which shows a typical example) and eq. (22). At a time of 160 msec after the beginning of the square wave infusion, the pressure responses of the system were plotted against the different flow rates of the infusions. This gave the plot of pressure against flow at $t = 160$ msec. with all points marked as 'x'. The next plot was for the pressure responses of the system at a time of 320 msec. after the beginning of the infusions. This gave the line $t = 320$ msec., with all points marked as 'x'. Subsequent plots were made at time intervals of 480 and 640 msec. after the beginning of the infusion.

Each of these plots at any particular time period after the

beginning of the infusion, gave an index of the linearity of pressure flow relations in accordance with eq. (22). Twelve series of infusions like the one in Fig. 37 were suitable for examination, comprising 50 individual pressure-flow plots. All of these were linear within a range of 90 to 40 mm Hg. At pressures lower than this, either the linearity continued, or the plot became convex to the pressure axis.

These plots were obtained from analysis of the transient response. If each square wave infusion is continued for a sufficiently long time, this transient response merges into the new steady-state response. When the steady-state response is reached, then a plot of P^* against F will give a true numerical value for resistance, as the constant 'a' becomes 1 and eq. (22) becomes the simple expression of eq. 10. If the steady-state pressure level is not actually reached, its value can be predicted from analysis of the transient response.

Let the asymptote of the transient pressure response be P_{ss} . This is unknown and represents the final steady-state pressure level. Measure three absolute pressure levels (P_1 , P_2 and P_3) on the transient response at equal time intervals from each other, (for example, 160 msec, 320 msec and 480 msec on the transient pressure response corresponding to infusion at a rate of 220 ml/min. on Fig. 38).

Consideration of eq. (13) shows that:

$$\frac{P_{ss} - P_2}{P_{ss} - P_1} = \frac{P_{ss} - P_3}{P_{ss} - P_2} = e^{-t/RC}$$

TABLE 4

MEASUREMENT OF CHORD AND SLOPE RESISTANCES IN RABBITS

Wt.	Estimated steady state pressure (mm Hg) at 200 ml/min infusion rate	R _c	p ⁺ mm Hg.	R _s
5.6 lbs	70	.35	32	.18
	70	.35	26	.22
	68	.34	29	.19
	58	.29	25	.16
6.1 lbs	66	.33	40	.13
	65	.32	35	.15
	72	.36	32	.20
6.7 lbs	62	.31	29	.16
	65	.32	31	.17
5.0 lbs	63	.31	29	.17

R_c = chord resistanceR_s = slope resistancep⁺ = positive pressure axis intercept

Mean chord resistance for whole group = 0.33 P.R.U. min.

Mean slope resistance for whole group = 0.17 P.R.U. min.

Solving for P_{ss} :

$$P_{ss} = \frac{P_1 \cdot P_3 - P_2^2}{P_3 + P_1 - 2P_2} \dots\dots\dots (24)$$

Thus the steady-state pressure response of the system to an infusion at 220 ml/min. can be calculated. In a similar fashion, the steady-state pressure responses at other infusion rates can be calculated, and a predicted steady-state response of the system (as shown by the dotted line in Fig.38) drawn. Thus analysis of the transient response of a system can give information about the steady-state response also. In practice, this method is sensitive to the slightest inaccuracy of measurement, particularly of P_2 . However, such calculations allow a reasonable projection of the steady-state response of the system

The transient state plots gave an indication of the linearity of the system, according to eq. (22). The projected steady-state plots allowed the positive pressure axis intercept ('critical closing pressure') across the whole systemic arterial circulation to be determined. This allowed a comparison of chord and slope resistance, as shown in Table 4. All chord resistances were determined at a particular flow rate (200 ml. p. min.) which presents this method of calculation in its best possible light. It can be seen that the chord resistance was approximately twice the magnitude of the true slope resistance. It can also be seen that the chord resistance can vary in the opposite direction to the slope resistance. Greater discrepancies

would be shown between the chord and true slope resistance, if the chord resistances were measured at a variety of flow rates, as is commonly done in calculation of 'total peripheral resistance'.

2. Calculation of compliance values from the transient pressure response data.

Reference to equation (13) shows that the transient pressure response to a square wave infusion is a function of compliance as well as resistance.

$$F = P \cdot \frac{1}{R} + C \cdot \frac{dP}{dt} \dots\dots\dots(18)$$

Two different approaches can be made to calculation of compliance values from the transient pressure response data.

1.

Consider again the electrical analogue of Franks Windkessel model as shown on page and the basic equation where,

$$F = f_R + f_C \dots\dots\dots(7)$$

Now, at $t = 0$,

$$P = 0 \quad \text{therefore} \quad f_R = 0$$

$$\text{therefore} \quad F = f_C$$

Compliance (C) is defined as:

$$C = \frac{\Delta Q}{\Delta P} \quad \text{Where} \quad \Delta Q = \text{change in volume}$$

This can be alternately expresses as:

$$C = \frac{dQ/dt}{dP/dt} = \frac{f_c}{dP/dt}$$

Thus, when $t = 0$,

$$C = \frac{F}{dP/dt} \dots\dots\dots (25)$$

Therefore, experimental determination of the rate or pressure change at the very beginning of the transient response to a square wave infusion enables a value for compliance of the system to be calculated. In practice, the response of the vascular bed to a square wave infusion is complicated by an extra oscillation within the first 160 msec. which can just be made out on Fig. 37, and more clearly seen in Fig. 57. After this time, the curve settles down into a more standard exponential response. The following method of analysis was used to project back to the rate of change of the very beginning of the infusion i.e.: $t = 0$ msec.

Consider eq. (6) which describes the basic exponential nature of the transient pressure response. Thus:

$$P = P_0 e^{-t/RC} \dots\dots\dots (6)$$

On differentiation:

$$dP/dt = -\frac{1}{RC} P_0 e^{-t/RC} \dots\dots\dots (26)$$

Thus a plot of dP/dt against t on semi-logarithmic paper should give a straight line if the response is exponential. By extrapolation of this line back to the point where $t = 0$ msec. the rate of change of

pressure at that time can be determined. A typical plot is shown in Fig. 39 .

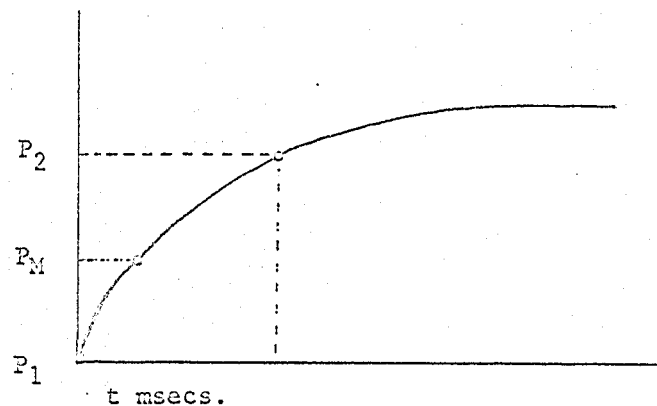
The rate of change of pressure was directly determined from the transient pressure response recording at 100 or 200 msec. intervals. It was then plotted on semi-log. paper as shown, and the best fitting line extrapolated to $t = 0$ msec. The projected rate of change of pressure at $t = 0$ was then divided into the infusion rate to give a value for the compliance of the system, as shown in eq. (25).

It was difficult to get good accuracy after the first few points, because the rate of change became so small. A passive differentiating circuit was built in an attempt to overcome this but the technique (see Method) was not yet sufficiently developed for it to be of any practical advantage.

2.

The second approach to calculation of compliance values from the transient pressure response involves the same analogue. It uses data from the estimated steady-state pressure-flow plot.

Consider the transient pressure response to a square wave infusion of rate F ml/min., as shown below:



From the probable steady-state plot (e.g.: as in Fig. 38) the flow rates through the resistance required to actually sustain these pressures of P_1 , P_2 , and P_M can be determined. Let these be F_1 , F_2 and F_M respectively.

Then the total volume of blood passing through the system as P_1 progresses to P_2 is Q_t ml. and such that:

$$(F_2 - F_1)t = Q_t$$

This is distributed in radial and axial directions. The former represents the volume flowing into the compliance (Q_C) and the latter, the volume flowing in an axial direction across the resistance (Q_R). The relationship between all three is such that:

$$Q_t = Q_C + Q_R \dots\dots\dots (27)$$

Q_R can be roughly determined by considering that the pressure remained at the mean level (P_M), throughout the whole time, t .

$$\text{Then:} \quad Q_R = (F_M - F_1)t$$

$$\begin{aligned} \text{Thus} \quad Q_C &= (F_2 - F_1)t - (F_M - F_1)t \\ &= (F_2 - F_M)t \end{aligned}$$

FIGURE 39: Semi-logarithmic plot of rate of change of pressure vs. time

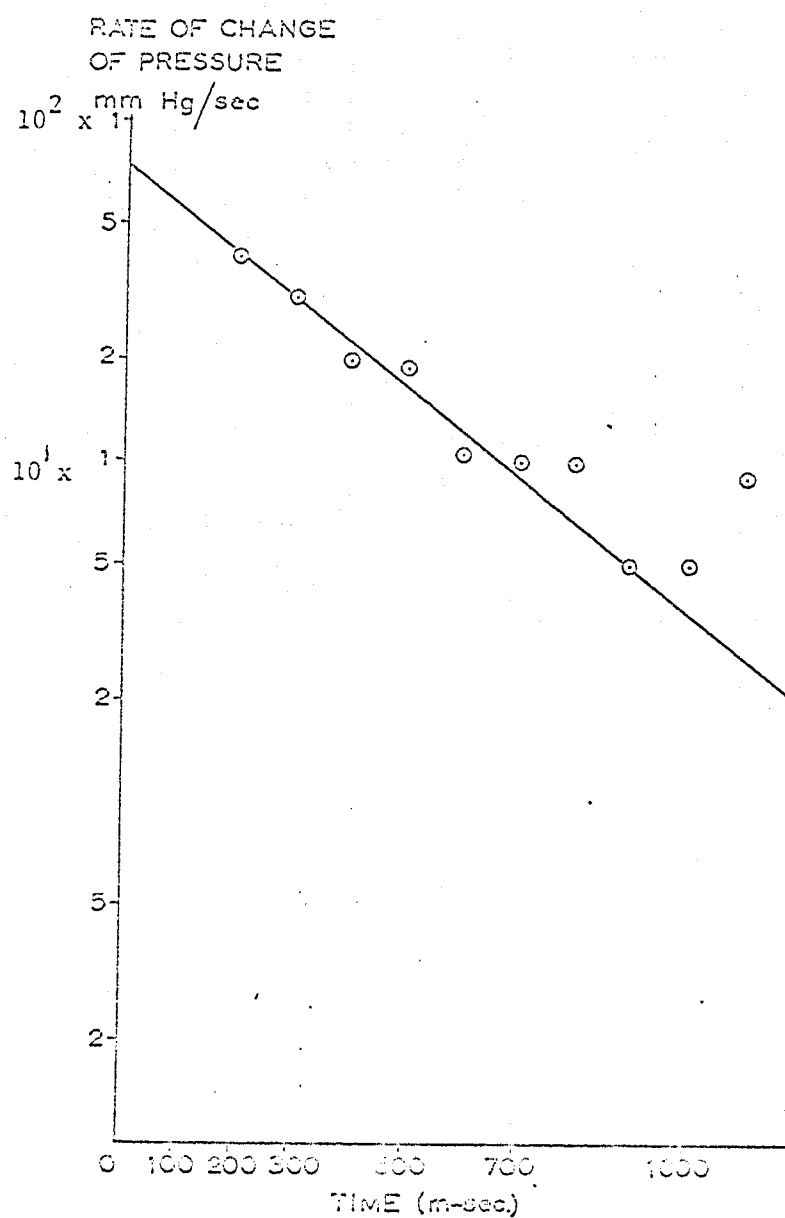


TABLE 5

CALCULATION OF COMPLIANCE VALUES FOR THE RABBIT
SYSTEMIC ARTERIAL CIRCULATION

Wt.	Mean R_s	C_D ml./mm Hg.	C_U ml./mm Hg.
5.6 lbs	.20	-	.027
	.18	-	.027
6.7 lbs	-	-	.028
	.16	.044	-
	.17	.042	-
5.0 lbs	.18	.036	-
	.17	.042	-
5.0 lbs	.18	.046	.020
	.16	.038	.021
	-	-	.031

Mean value of C_U = 0.026 ml./mm Hg.S.E. = $\pm$.002Mean value of C_D = 0.04 ml./mm Hg.S.E. = $\pm$.002 R_s = slope resistance mm H/ml.p.min. C_U = compliance of upgoing pressure curve. C_D = compliance of downgoing pressure curve.

Therefore, the compliance of the system is:

$$C = \frac{Q_C}{P_2 - P_1} = \frac{(P_2 - P_M)t}{P_2 - P_1}$$

The small error introduced by using the arithmetic mean value (P_M) of P_1 and P_2 instead of the more correct geometric mean value (where $G = 2\sqrt{P_2 \times P_1}$), was considered to be negligible.

Calculation of compliance values by either approach should theoretically yield similar results. Table 8 shows compliance values for the system calculated by both methods. It was noted that the values calculated from upgoing pressure curves (e.g.: when the vessel was being inflated as in Fig. 57) were less than those from the down going curves (when the vessel was being deflated as in Fig. 54). This suggested the possibility of a hysteresis phenomenon.

The general results, therefore, obtained from analysis of the transient pressure responses of the whole systemic arterial circulation to a series of square wave infusions starting at the same critical diastolic pressure level, such as shown in Fig. 37 are the following:

- (1) pressure flow relations across the whole systemic arterial circulation are linear in the rate 90 - 40 mm Hg.
- (2) there is a significant positive pressure axis intercept, varying in these experiments from 25 to 40 mm Hg.

- (3) the value of the true slope resistance is approximately half that of the commonly measured chord resistance and can vary in a manner opposite to that of the chord resistance.
- (4) compliance values for the systemic arterial circulation in an approximately 5 lb. rabbit, are 0.026 ml/min. Hg. when measured from an increasing pressure response and 0.041 ml/mm Hg. when measured from a decreasing pressure response. This suggests the possibility of a hysteresis phenomenon.

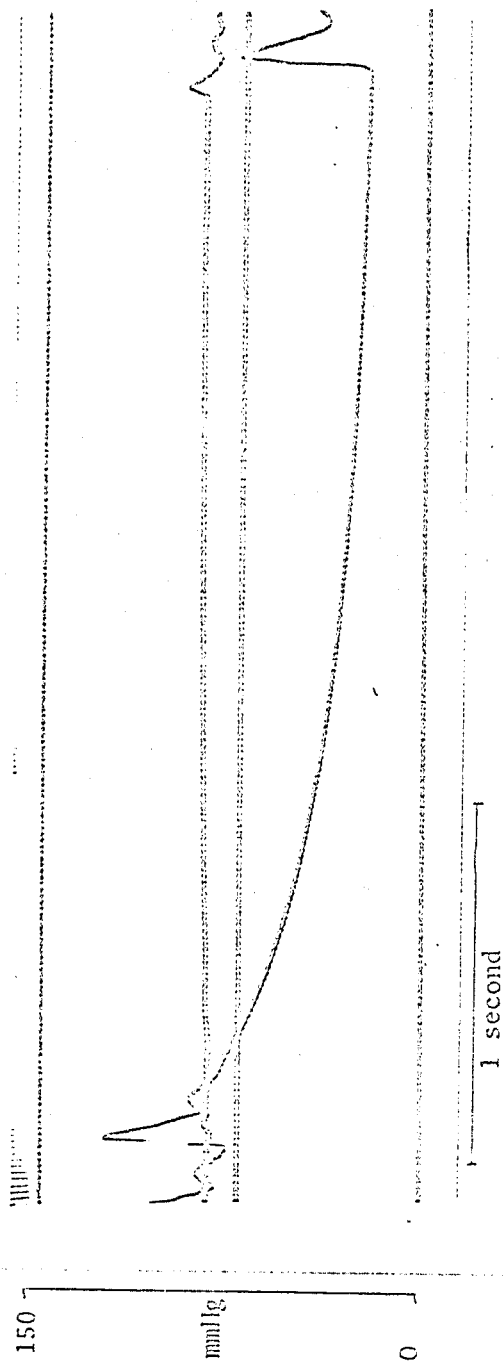
The general problem remained in this type of experiment, that to perform a series of infusions such as shown in Fig. 37, it would take approximately 15 to 20 minutes. Most inferences drawn are dependent on the controlled system remaining in a constant state during this time.

3. The nature of the transient pressure response to a step function

It was the initial working hypothesis of this investigation that the systemic arterial circulation behaved as a linear first order system, as first proposed by Frank. It has been shown that the nature of the transient pressure response to a step function is such a system, should be exponential in nature. This is described by equation (6).

$$P = P_0 e^{-t/RC} \dots\dots\dots (6)$$

FIGURE 40: Diastolic pressure curve prolonged by vagus nerve stimulation



It was modified to the more general solution (13) below, by Eadie and McCrae. This allowed for the situation where pressure is not zero when flow is zero.

$$P = (P_0 - P_{ss})e^{-t/RC} + P_{ss} \dots \dots \dots (13)$$

It has already been noted in the introductory section that when the aortic valve snaps shut, a step function is produced. Therefore, the diastolic pressure curve should be exponential in nature, if this working hypothesis holds true. The nature of the diastolic pressure curve, and other transient responses to step functions were examined in detail.

A typical diastolic pressure curve, prolonged by vagal stimulation and unaffected by respiratory variations, is shown in Fig. 40. Generally, the first 200 msec. or so of the curve were ignored because there were often obvious irregularities until this point. All curves that did not appear smooth to the naked eye, or in whom the central venous pressure did not remain constant, were rejected, as it was realized that the respiratory activity of the animal could have a potent modifying influence on the response. Pressures in the first instance were mostly monitored from the right femoral artery, although this point is dealt with later.

The first approach to analysis of these curves involved a consideration of eq. (13) from which it can be seen that a plot of the log.

of $|P - P_{ss}|$ against t , should produce a straight line. A problem lay in finding the value of P_{ss} which was unknown. This was either (1) estimated by the method previously discussed on p. 198 where:

$$P_{ss} = \frac{P_1 \cdot P_3 - P_2^2}{P_3 + P_1 - 2P_2} \dots\dots\dots (24)$$

for $P_{ss} > P_2$

$$\text{and } P_{ss} = \frac{P_2^2 - P_3 \cdot P_1}{2P_2 - P_1 - P_3} \quad \text{for } P_{ss} < P_2$$

or (2) guessed, where, as for example in Fig. 40, the asymptote (P_{ss}) had almost been reached.

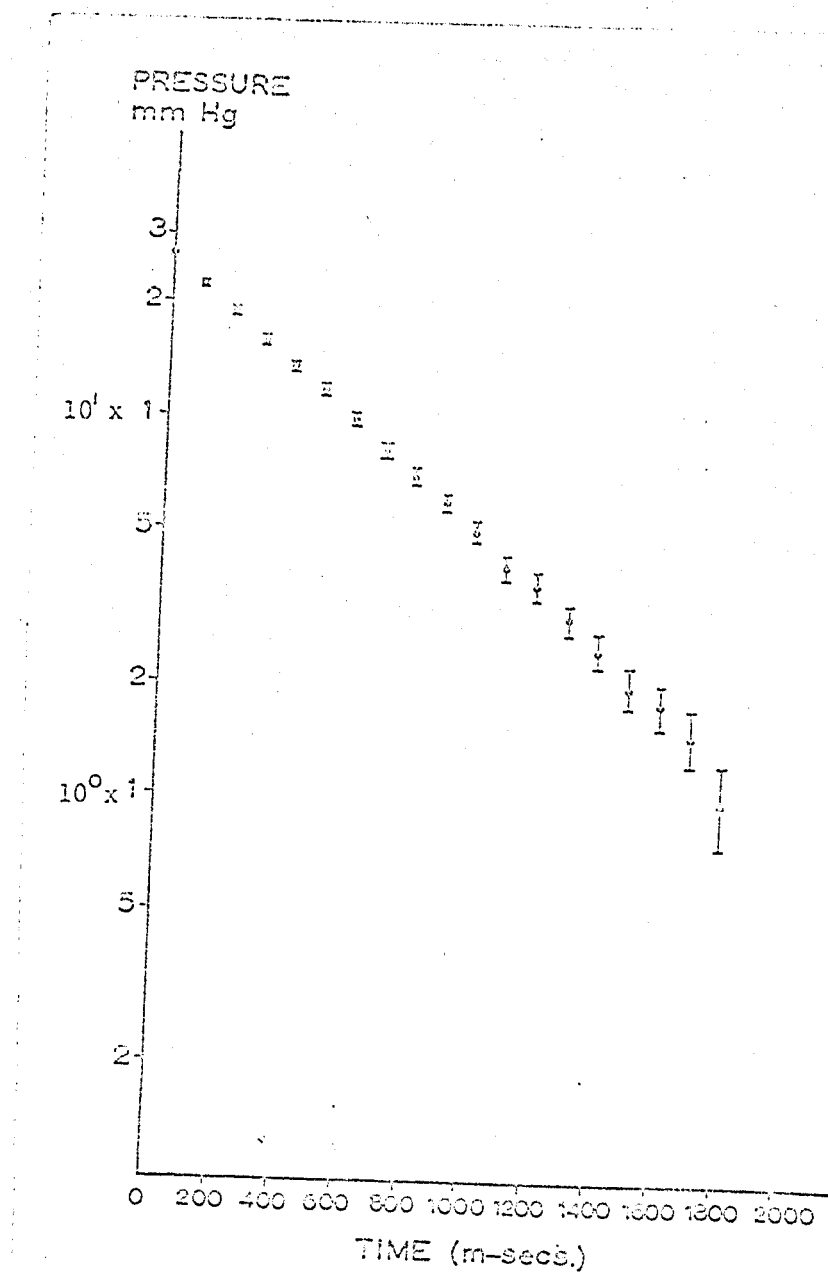
A typical plot of $\log. |P - P_{ss}|$ against t is shown in Fig. 41. The pressure values were measured by hand at the intervals shown, directly from the E for M tracing. The range of possible mensuration error is shown. Thirty-two curves examined in this manner. All curves were examined for a period of at least 800 msec. and some to 1800 msec. All were linear at least for a period of 800 msec., which generally represented a fall of pressure to about 35 mm Hg. In all cases, P_{ss} was above zero, and mostly about 20 mm Hg.

By definition, the time constant (τ) of these curves is such that $\tau = R.C.$ Consideration of eq. (13) showed that:

$$R.C. \log e \left(\frac{P - P_{ss}}{P_0 - P_{ss}} \right) = \tau$$

Thus the particular condition that $R.C. = \tau$, occurs when:

$$\left(\frac{P - P_{ss}}{P_0 - P_{ss}} \right) = 0.367$$

FIGURE 41: Semilogarithmic plot of $[P - P_{ss}]$ vs time

This time constant τ can thus be read directly from the type of plot shown in Fig. 41 . It is the time taken for the pressure $|P_0 - P_{ss}|$ to fall to 36.7% of its initial value. Table 6 shows the time constants of 32 curves from 6 animals determined in this manner. It will be noted that the time constants for the curves where pressure is increasing (i.e.: the vessel is being inflated) are significantly shorter than for curves where the pressure is decreasing, (i.e.: where the vessel is being deflated).

RIGGS (1963) has pointed out, that in fitting data to exponential functions where neither the time constant or asymptote are known, reasonably good fits can be obtained with a number of combinations of time constant and asymptote. In analysis of these curves, a good fit within the mensuration error, could be obtained for asymptotes 3 - 4 mm Hg. different in value.

The second approach to analysis of these curves, was by a phase plane plot, as already discussed in the introduction (see Fig. 8 and 9). The general equation of a linear first order system is again stated below. Thus:

$$F = P \cdot \frac{1}{R} + C \cdot \frac{dP}{dt} \quad \dots\dots\dots (18)$$

Therefore, where F is constant, a plot of dP/dt against P should be linear if this is a proper description of the system. This avoids the problem of guessing, or estimating, the asymptote (P_{ss}) of the curve. On the other hand, it requires accurate measurement to obtain rates of

TABLE 6

Time constants of the transient pressure response to a step function, calculated from plots of $\log. (P_t - P_{ss})$ against time.

Wt. lbs	τ_U msecs	τ_D msecs	P^+ mm Hg
5.0 lbs	240	400	-
	240	480	-
	270	300	22
	250	335	21
	310	420	17
	440		
5.1 lbs	390	440	23
	250	500	23
	460	520	23
	400	490	23
		690	21
		660	24
4 lbs		750	20
		690	23
		740	18
		790	
4.5 lbs		780	20
		870	25
		850	17
		920	20
5.3 lbs		1020	18
5.8 lbs		700	26
		660	30
		480	28

Mean value $\tau_U = 325$

S.E. = ± 28

Mean value $\tau_D = 627$

S.E. = ± 40

Mean P^+ value = 22 mm Hg.

τ_U = time constant of up-going pressure curve.

τ_D = time constant of down-going pressure curve.

P^+ = positive pressure axis intercept.

change of pressure.

Initially, the phase plane plots were measured by hand, directly from the E. for M recording. In the calculation of $\dot{P}$, the pressure difference at 200 msec. intervals was generally used. This was referred to the arithmetic mean pressure of the two points, but the error in not using the more correct geometric mean was negligible. The type of manual phase plane plot produced is shown in Fig. 42 . The deviation of the upper line (which corresponds to an increasing pressure curve, as the plot 'a' in Fig. 9) from linearity in this particular plot is deliberately shown in reference to another matter later. Thirty-six curves were analysed in this manner and results were similar to those found in the first approach. Plots obtained when the arterial pressure was increasing (as 'a' type curves, see Fig. 9) were all linear, (the plot in Fig. 42 is excluded, because the deviation was due to respiratory effect). Those obtained when the curve was decreasing (as 'b' type curves, see Fig. 9) were mostly linear until a pressure of 40 to 60 mm Hg. was reached. Thereafter, the linearity either continued, or was followed by a gentle curving of the plot in such a direction as to increase the time constant. Table 7 shows the time constants of these plots obtained from the ratio $\frac{dP}{dt}$. It can be seen that the time constant of the upgoing pressure curve (type 'a') had a mean value of 714 msec and for the downgoing pressure curve (type 'b') a mean value of 1014 msec.

The measurement of the rate of change of pressure directly from the pressure recording was a slow laborious process, requiring painstaking

FIGURE 42: Manual phase plane plot

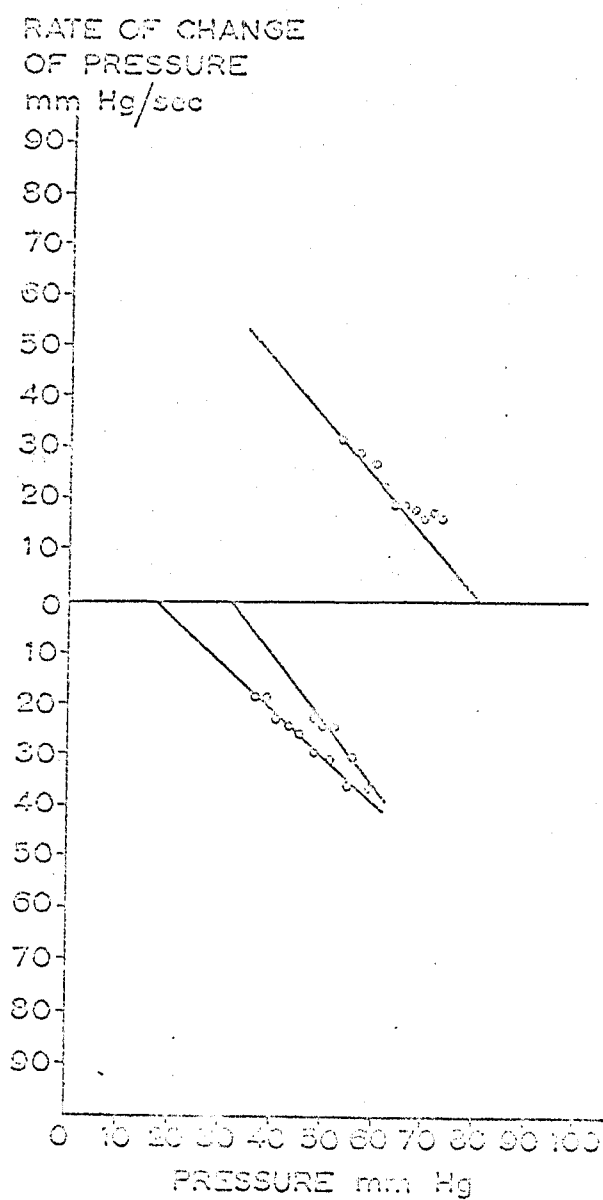


TABLE 7

217.

TIME CONSTANTS OF THE TRANSIENT PRESSURE RESPONSE TO A STEP FUNCTION,
CALCULATED FROM MANUAL PHASE PLANE PLOTS

Wt.	Mean blood pressure mm Hg.	T_u m.secs.	T_D m.secs.	P^+ mm Hg.
6.8 lbs	71	750	1240	18
	71	570	1384	15
	74	1000	1367	18
	68	800	894	26
	70	730	900	25
	72	660	700	26
	70	1000	1000	27
	48	400	1000	20
5.9 lbs	51	500	804	18
	78	-	1110	18
	80	-	1066	18
	78	-	927	22
	80	500	-	
	80	570	875	30
	89	570	1000	25
6.0 lbs	72	800	1000	20
	72	660	833	20
	78	660	882	21
	72	830	1085	20
	78	1140	1200	28

Mean value for T_u = 714 m.secs.

S.E. = ± 48

Mean value for T_D = 1014 m.secs.

S.E. = ± 42

Mean value for P^+ = 22 mm Hg.

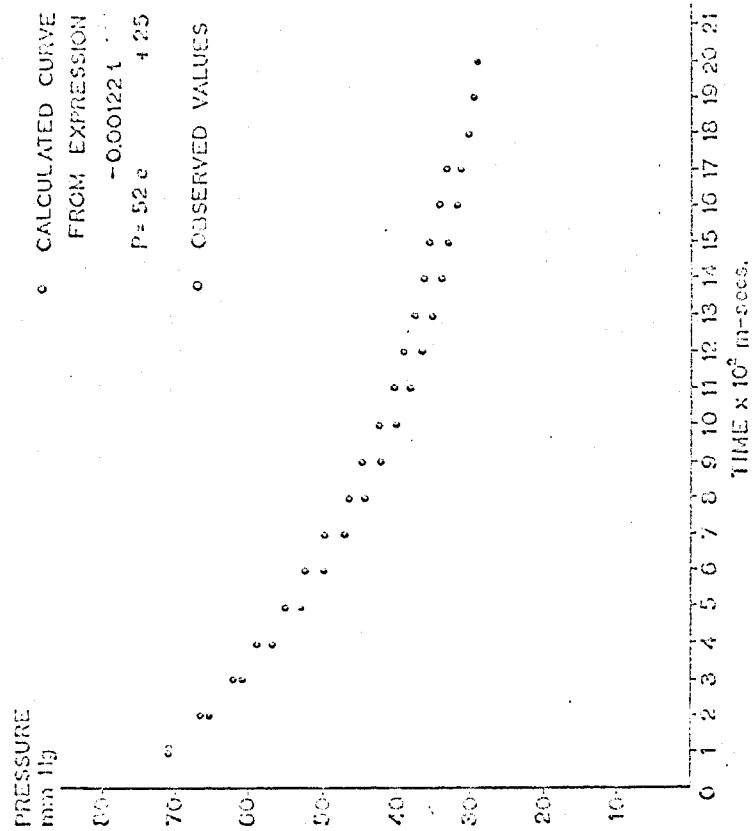
accuracy. Large numbers of curves could not be quickly analysed in this way. Attention was, therefore, directed to the development of a more suitable way to obtain these phase plane plots.

As detailed in the section on 'Methods', an electrical differentiating technique was finally developed. The pressure signal could then be connected to the X axis of an oscilloscope, and its first derivative ($\dot{P}$) to the Y axis. An instantaneous plot of $\dot{P}$ against P was thus produced on the oscilloscope screen, and photographed with a Polaroid camera. This proved to be a very suitable technique for analysing the curves.

As this electrical differentiating technique became an important part in the investigation, its accuracy was tested in two further ways, apart from its response to various triangular waves which have already been discussed in the 'Methods' section. The first approach to clarification of the technique involved extraction from the oscilloscope phase plane plot of (1) the value for the time constant of a particular curve and (2) the value for its asymptote (P_{SS}^+). The method for doing this has already been discussed on p. 86, in reference to Fig. 9. The theoretical expression of the curve, deduced from the oscilloscope phase plane plot, can then be given in terms of eq. (13). Fig. 43 shows an example in which the theoretical equation of the curve, calculated from the oscilloscope plot, is

$$P = 52e^{-0.00122t} + 25$$

FIGURE 43: Comparison of observed and calculated pressure curves



This was then evaluated for various values of t , as shown by the closed circle plot. The actual measurements from the curve on the E for M pressure recording are shown by the open circle plot. Thus Fig.43 demonstrates close correspondence between the actual pressure curve and its theoretical description, obtained from an oscilloscope phase plane plot. Twelve curves were analysed in such a manner. They varied from 800 msec. to 1800 msec. duration. In no case was the deviation of the calculated curve from the actual observed curve, greater than 5 mm Hg.

The second extra approach to verification of the oscilloscope technique was to compare phase plane plots performed manually with those performed electrically. This was done on 10 curves and correspondence was found to be good. The deviation from linearity of the upper plot in Fig.42 performed manually, is also noted in the electrical phase plane plot of the same curve in Fig. 62 .

The final technique used in analysis of the transient pressure response involved the analogue computer. Tape recordings (on an instrument generously lent by the N.R.C.) were made of several transient pressure responses. A digital computer was programmed to find the best fitting polynomial for each curve. A third degree polynomial of the type shown in the example below generally gave a very adequate description of the curve.

$$P = -0.12 - 0.43t + 0.12t^2 - 0.0099t^3$$

Even though described by a polynomial (for easier programing), this was a closely exponential curve, as a phase plane plot showed. There was good correspondence between the analogue computer, the manual phase plane plots, and the oscilloscope phase plane plots.

The oscilloscope phase plane plots became the technique of choice for analysing the transient pressure response to a square wave infusion. A typical example is shown in Fig. 44, which should be compared with the theoretical drawing in Fig. 9. Attention should be particularly paid to the intercept (actual, or projected) of these plots with the abscissa where $dP/dT = 0$. This represents the steady-state pressure response of the system, from which the true slope resistance can be calculated. Note that the lower plot in Fig. 44 is actually a combination of two plots side by side.

Many of these oscilloscope plots were performed during the course of the investigation. A random analysis of the linearity of the curves from 20 animals was performed in the following manner. Only plots which extended over a pressure range of 30 mm Hg, or more, were accepted from the first four oscilloscope plots drawn from the record bag of each animal. They were classified as linear if the plot did not deviate more than 1.5 mm from a ruler's edge. Fifty-three out of 58 plots accepted, were linear by this criterion. Thus, approximately 90% of the phase plane plots of pressure responses that appeared smooth to the naked eye, could be described by a single exponential function. The pressure range over which this was tested was between 80 to 20 mm Hg,

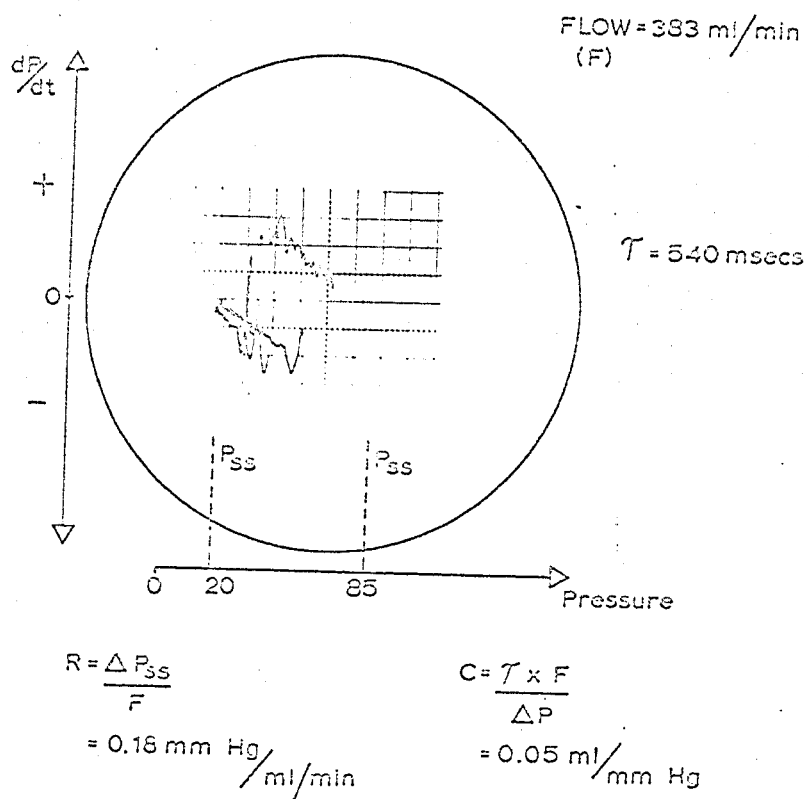


FIGURE 44: Oscilloscope phase plane plot

although some individuals did not have plots higher than 60 mm Hg.

All plots examined had a positive pressure axis intercept at zero flow. This normally had a value of between 20 to 30 mm Hg, and was virtually never less than 15 mm Hg.

This series of experiments has thus shown the following results:

(1) If respiratory activity is controlled during the time of recording, and the first 200 msec. of the curve discounted, then the transient pressure response of the whole systemic arterial circulation to a step function is closely exponential in nature.

(2) An instantaneous plot of $\dot{P}$ against P is the most suitable way of analysing this response. The electrical circuit finally developed to perform this plot gave good correspondence with results obtained by (1) hand measurement from the E for M tracing; and (2) analogue computer analysis from a tape recording of the transient pressure response.

The general conclusion to be drawn is that the controlled system in the systemic arterial circulation does behave, to a reasonable approximation, like a linear first order system. Before applying the analytical technique developed in reference to Fig. 8, however, there are certain caveats to be considered. These mostly concern directly or indirectly, the conditions listed on p. 62.

3. POSSIBLE MODIFYING FACTORS OF THE SYSTEM RESPONSE TO A SQUARE WAVE INFUSION

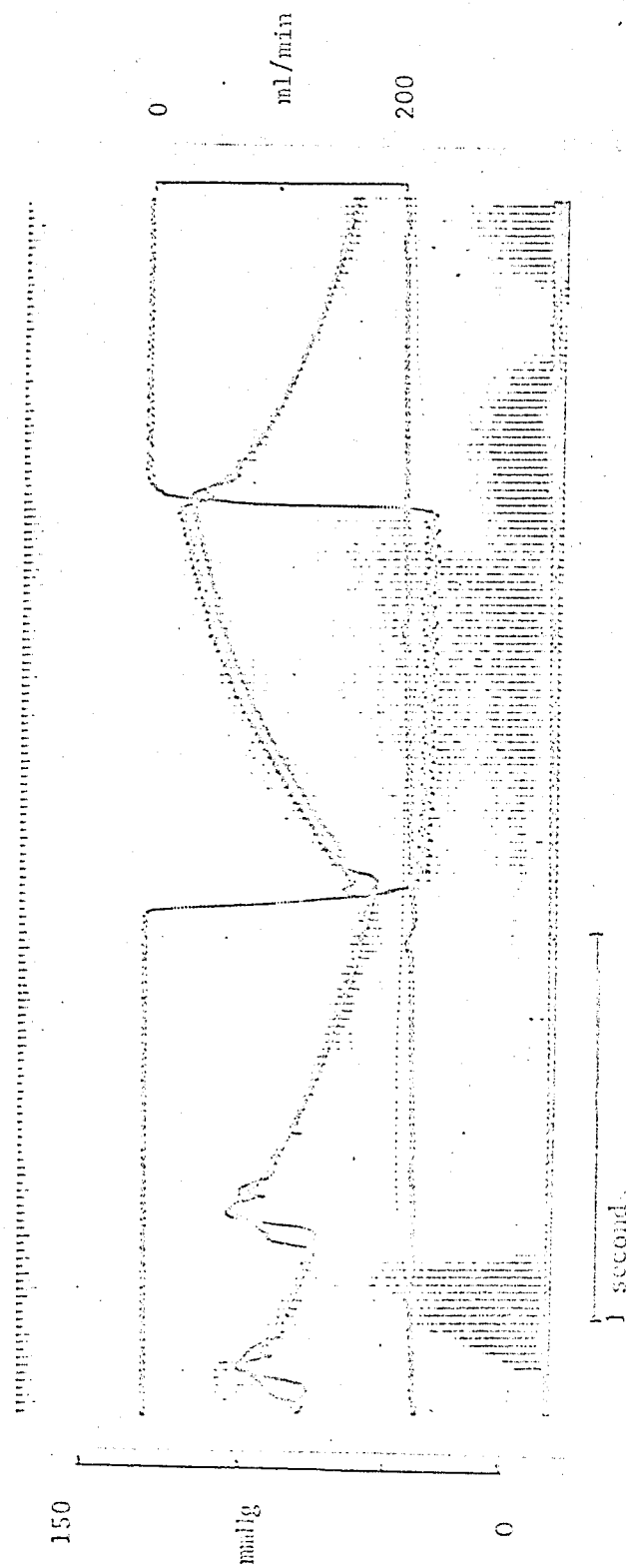
A number of factors capable of modifying the system response to a square wave infusion require consideration. The principal conditions required for the theoretical treatment used in this thesis are (1) that the system is a linear one, both in relations between pressure and flow, and pressure and volume; and (2) that the system is in a steady-state during the time of testing. These will be considered, but a miscellany of equally important factors will be considered first.

(i) Pressure recording from different sites in the system:

All calculations in this investigation were done on pressure recordings obtained from the right femoral artery. However, since the normal pulse wave is changed as it is transmitted through the systemic arterial system, it was considered important to see if the transient pressure response to a square wave infusion was modified in a similar manner.

In a number of experiments, pressures were measured simultaneously from the right femoral artery, and from the left brachial artery, which branches directly off the aorta. This is a slightly smaller vessel than the femoral, but the same sized cannula was used and attached to an identical hydraulic and transducer system. Identical

FIGURE 45: The response to a square wave infusion measured simultaneously from the brachial and femoral arteries



sensitivity of the two recording systems was obtained by subjecting them both to standard pressures from a mercury manometer. The 'fine sensitivity' control on the E for M pre-amplifier was then adjusted to give identical deflections.

A typical result is shown in Fig. ⁴⁻⁵_A. It can be seen that there is little difference between the two pressure tracings. The initial oscillation (see later) is slightly modified as it is transmitted down the system. The brachial artery recording is readily distinguished by the fact that it precedes that from the femoral artery. Central arterial pressure was also measured from a 'T' piece connected to the infusion cannula in the right carotid artery. Because of the very high pressures generated at this site during infusion (as previously discussed), it was only possible to measure the diastolic pressure curves at this site, if damage to the pressure transducer was to be avoided. These diastolic pressure curves showed a similar response to that of the femoral artery recordings. It was therefore, concluded that the recording site made practically little difference to the results obtained. This non-distortion of the pressure wave was attributed mainly to the absence of significant reflected waves.

(ii) The effects of turbulence:

There is no doubt that some turbulence occurs in the larger vessels during the square wave infusion. This must be so from consideration alone of the angle at which the right carotid artery

(through which the infusion is given) meets with the ascending aorta, and the abrupt change of diameter which it undergoes. The curve of the arch of the aorta will have some compensating effect on this. Calculation of a Reynolds number for blood flow through the aorta (radius 0.2 cm) at an infusion rate of 300 ml.p.min. gives a value of 199; the viscosity of the blood is taken at 0.04 poise and the density as 1. At the same infusion rate, flow through a cannula of 0.05 cm radius (the size of the cannula in the right carotid artery), gives a value of 795. The critical value of the Reynolds number above which turbulence occurs is 1000 in straight tubes, but this can be considerably lower at junctions. Some effort was made to assess the turbulence factor further by attempting to take a phonocardiograph recording during the period of the square wave infusion, but there was so much 'noise' on the recording, that this was not of any practical use.

The assumption was made that the contribution of turbulence to the pressure response was of minor concern, particularly in view of the fact that it almost certainly did not occur in the smaller vessels (see McDONALD 1960). Furthermore, it would be a relatively constant factor in all experiments.

(iii) Competence of the aortic valve:

It was important that the aortic valve should be competent during the testing of the system. The theory assumes that all axial

flow occurs in a peripheral direction, and this is obviously dependent on the competence of the aortic valve. Six animals were examined for aortic competence after completion of the experiments. The major branches of the aorta in the dead animal were tied, and a retrograde injection of diluted Indian ink given from a syringe tied into the thoracic aorta. Much of the left ventricle was removed to ensure that the Indian ink could not enter the ventricular cavity by the Thebesian veins. No Indian ink was seen to cross the valve into the heart when the aorta was well distended, and this was considered sufficient evidence to demonstrate the general competency of the valve. No pressure recordings were seen to suggest the 'collapsing' pulse of aortic incompetence.

(iv) The possibility of artefacts in the pressure recording:

The general accuracy and linearity of the whole pressure monitoring apparatus (including the recorder) was satisfactory, as already discussed in the 'Methods' section. Two potentially capable sources of artefacts, however, that were recognised, were (1) any significant compliance in the thick-walled polyethylene tubing used to connect the cannula to the transducer; and (2) the presence of air bubbles anywhere in either the infusion, or recording system.

The compliance of the tubing under (1) was found to be negligible, as already discussed on p. 115. The possibility of air in the system under (2), however, was always present, and some experiments

were discarded because small bubbles could not be eliminated. This possibility was continually guarded against by preparing the saline for each experiment from freshly boiled water, which drove off any dissolved gases. The apparatus was frequently cleaned with detergent (to prevent bubbles sticking to the side) and then rinsed with water. It was carefully inspected for bubbles before the start of each experiment. There was little likelihood under these circumstances that this was an important unrecognised factor.

The pressures measured from the cannula in the right femoral artery are 'end' pressures, and thus also measure the pressure resulting from the conversion of the kinetic energy of the blood (i.e.: the 'kinetic artefact'). At an infusion rate of 300 ml.p.min. the mean velocity (v) in the aorta is 40 cm/sec., and therefore this kinetic energy artefact ($1/2 \rho v^2$) at most amounts to a pressure of 0.6 mm Hg, which is thus quite negligible.

It is unlikely that artefacts have a significant role in determining the transient pressure response to a square wave infusion.

(v) Evidence that the system is in a steady-state during the time of testing:

The pressure response to a square wave infusion, such that it could be adequately analysed, lasted in the order of two seconds. It was important that the system remain in a steady-state during this time.

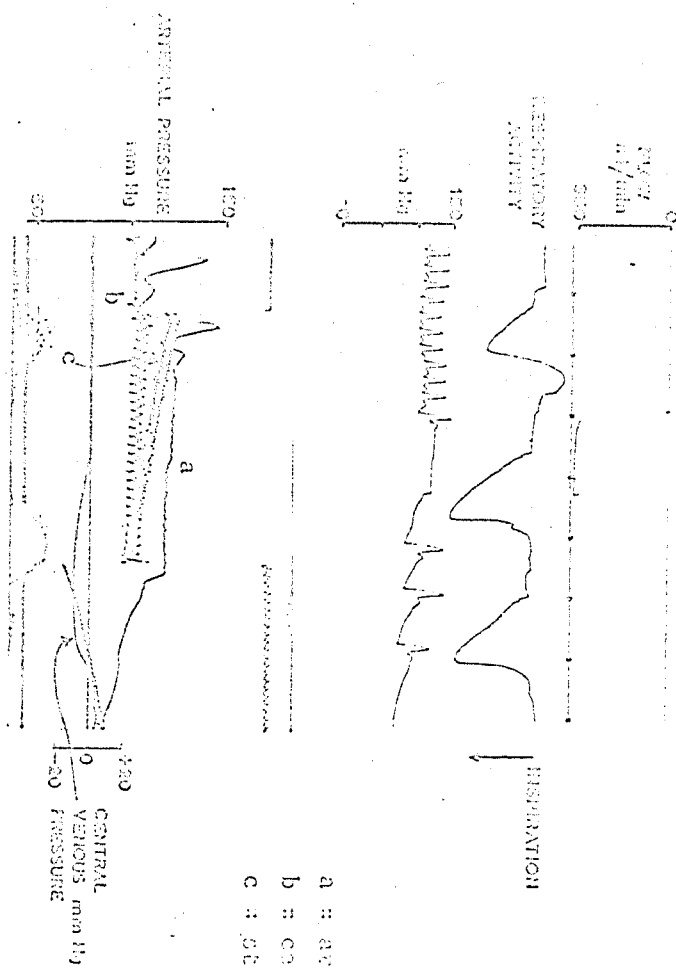
There are several theoretical possibilities why this should not be so. The square wave infusion was given during a time of vagal stimulation. This might have some effect on the peripheral circulatory system as well as on the heart. Stoppage of the heart itself might cause important venous reflex effects. Lowering of the blood pressure during analysis of the diastolic pressure response may cause baroreceptor reflexes to occur. Infusion of the blood may be associated with destruction of red cells, and liberation of vaso-active substances such as ATP, (however, there was no significant change in haematocrit, from beginning to end of the experiment). A further possible disturbing factor, already mentioned, is the effect of the respiratory activity of the animal.

(a) The immediate effects of respiratory activity on the arterial system:

If respiratory activity was not suspended during the giving of the square wave infusion, there was an obvious effect on the pressure response, as shown in Fig. 46. During inspiration, there was a decrease in arterial pressure and during expiration, there was an increase in arterial pressure. These changes were accompanied by a concomitant change in the central venous pressure. This is noted in the lower section of Fig. 46, which is a magnified version (on a different recorder) of the one above it. The association between these arterial and central venous pressure fluctuations with respiratory

FIGURE 46

EFFECT OF RESPIRATORY ACTIVITY ON THE SYSTEMIC BLOOD PRESSURE



Lower section is an enlargement of the upper one, taken on a different recorder.

Time marker on tracing = 1 second

TABLE 8

MAGNITUDES OF THE SIMULTANEOUS CHANGES IN ARTERIAL AND CENTRAL
VENOUS PRESSURE ASSOCIATED WITH RESPIRATORY ACTIVITY.

Rabbit	Δ Central venous pressure mm Hg.	Δ Arterial pressure mm Hg.
1.	7.5	3.0
2.	4.0 5.0 5.0	2.0 2.0 2.5
3.	11.0 8.0 5.0	2.5 2.0 2.5
4.	12.0 7.0	5.0 3.0

activity, or perhaps best seen in reference to Fig.47 . The magnitude of these changes are seen in Table 8 .

While there is a remote possibility that these changes could be due to reflex pathways interacting between lung inflation and the systemic resistance, an interplay of mechanical factors was considered to be the more likely cause, particularly in view of the fact that central venous pressure changed almost instantaneously with the systemic thoracic pressure as measured from the brachial artery. During inspiration, there is an increase in the negative intra-thoracic pressure. This will cause an increase in the effective compliance of the thoracic aorta and so can cause a decrease in arterial blood pressure, such as that shown in Fig. 46 . This effect will be compensated to some extent by the simultaneous increase in positive abdominal pressure. When the thorax was widely opened to the atmosphere, and positive pressure ventilation given, the effect was abolished.

The methods adopted to avoid this disturbing influence of respiratory activity have already been discussed. The technique most generally used was that of paralysing the animal's own respiratory efforts with curare, so that artificial ventilation was required. The latter was then stopped for 2 - 3 seconds during the time of each infusion. Whilst effective for the purpose for which it was designed, this manoeuvre sometimes brought problems in its own wake. Reference to Figs.48 and 49 shows that cessation of ventilation was sometimes associated with marked fluctuations of blood pressure response. If a

FIGURE 47: Correlation of central venous pressure changes due to respiratory movement, with pressure recordings from the Brachial and Femoral arteries

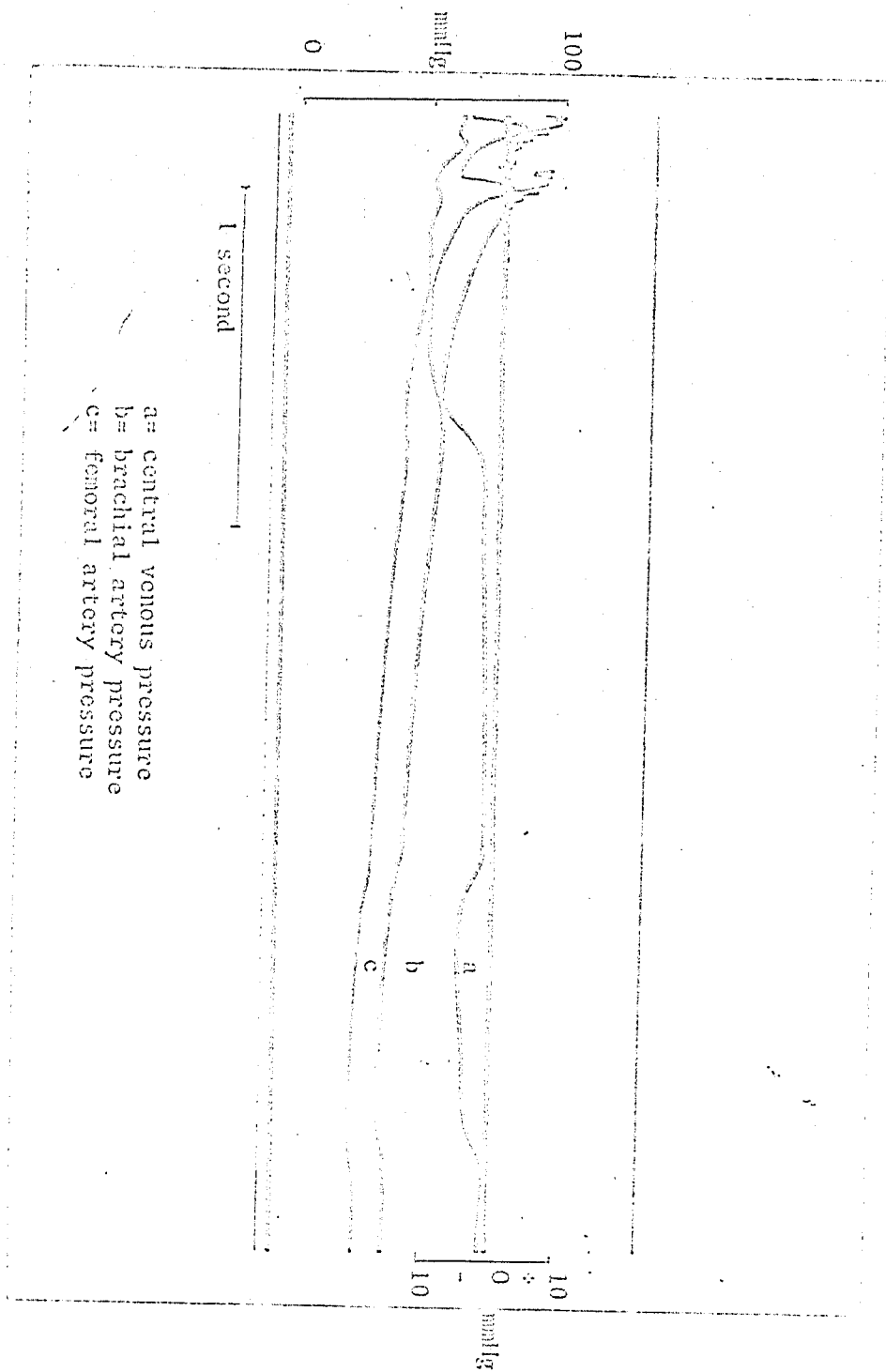
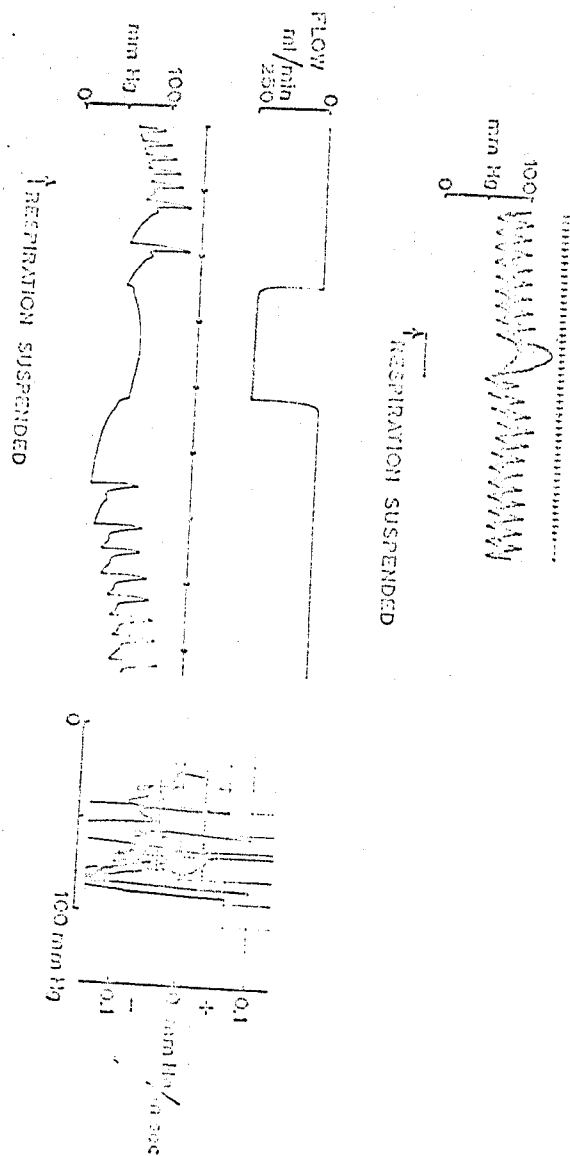


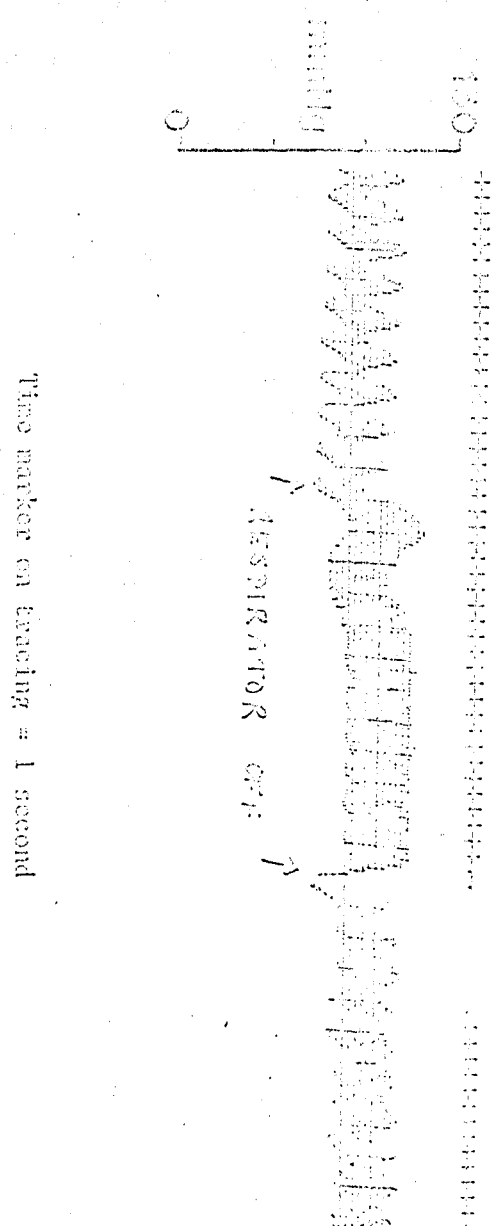
FIGURE 48

THE EFFECTS OF SUSPENDING RESPIRATION ON BLOOD PRESSURE
AND PERIPHERAL RESISTANCE



Time marker on each tracing = 1 second

FIGURE 49: Effect on blood pressure of prolonged ventilatory arrest



square wave infusion was given during the time of these fluctuations (as in the lower section of Fig. 48), the pressure response was affected in such a way as to indicate a change in resistance. This is well shown in the phase plane plot of the pressure response. This type of change did not occur too frequently, but it was important to determine its presence or absence by monitoring the blood pressure when respiratory activity alone was suspended (as in Fig. 49). It could generally be eliminated by minor alterations of the respiratory rate. In any particular experiment, the square wave infusions were given at a chosen time (usually 1 - 3 seconds) after the suspension of respiratory activity. It was generally possible to delay the infusion until the period of fluctuation had passed. Furthermore, any change during the square wave infusion became readily apparent because of the obvious deviation from the normal exponential response.

(b) Other influences tending to alter the arterial system
during the time of the square wave infusion:

These influences include the effects of vagus nerve stimulation on the peripheral circulation, other reflexes and chemical actions. It was not possible, nor necessary, to study each of these effects individually. The possible influence of their actions in disturbing the steady-state of the arterial system during the time of the square wave infusion was assessed in the following three ways.

Fig. 50 shows the response to a square wave infusion given at such a critical rate, that the steady-state pressure response was

rapidly reached. The infusion was then continued for one second, and it can be seen that during this time, there was little change in the steady-state pressure response. This indicates that the resistance of the system was not changing during this time and that the system was probably in a steady-state. (Care should be taken to distinguish between the confusing terms 'steady-state pressure response of the system' and 'steady-state of the system' itself - a small price to have to pay for the marriage of physical and biological disciplines).

A second way of demonstrating this was to give two or three consecutive square wave infusions at identical rates, as shown in Fig. 51. When identical pressure responses were obtained, this was strong evidence that the system was in a steady-state during this time. The input function of the first of the two infusions in Fig. 51 appears less 'abrupt' than normal, but this is only an artifact, due to the linear velocity transducer being extended just beyond its linear range.

The third method of assessing whether the arterial system was in a steady-state during the time of the square wave infusion, was by examination of the phase plane plot. If the system is in a steady-state, then the time constant of two successive diastolic pressure curves should be the same. In this case, their phase plane plots should overlap, as shown in Fig. 44. This was a good way of assessing the steady-state of the system during the time of the square wave infusion.

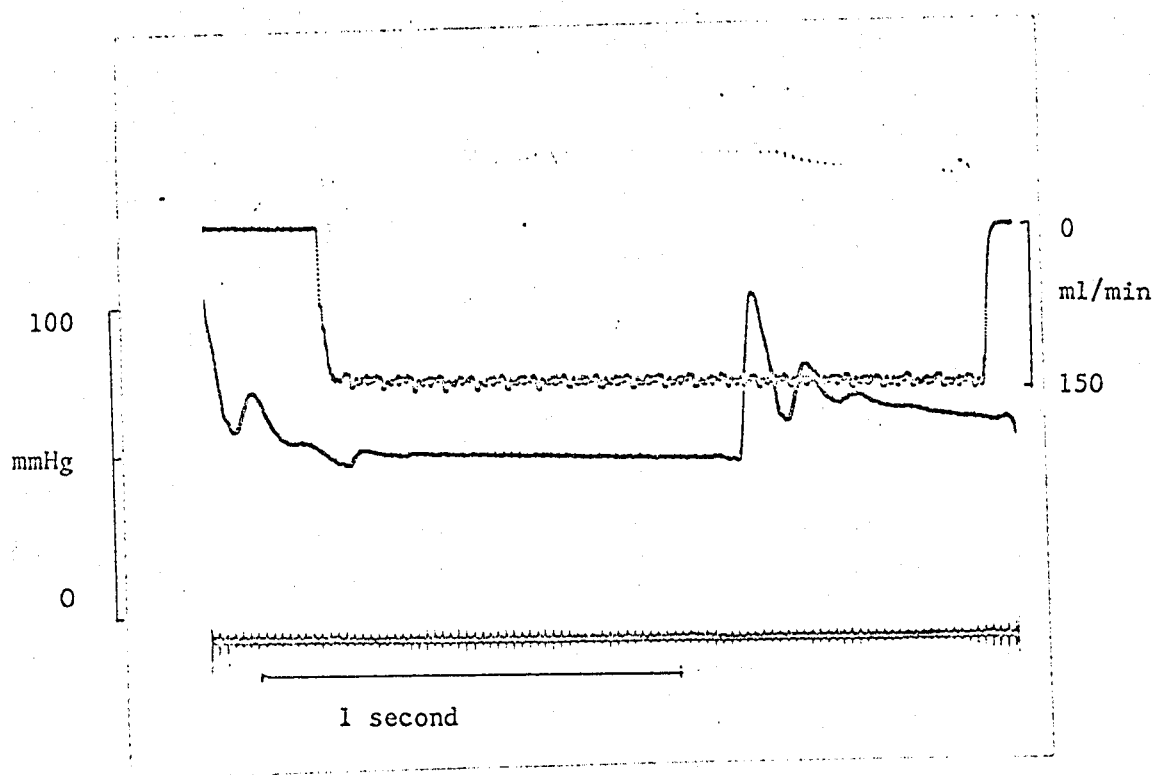
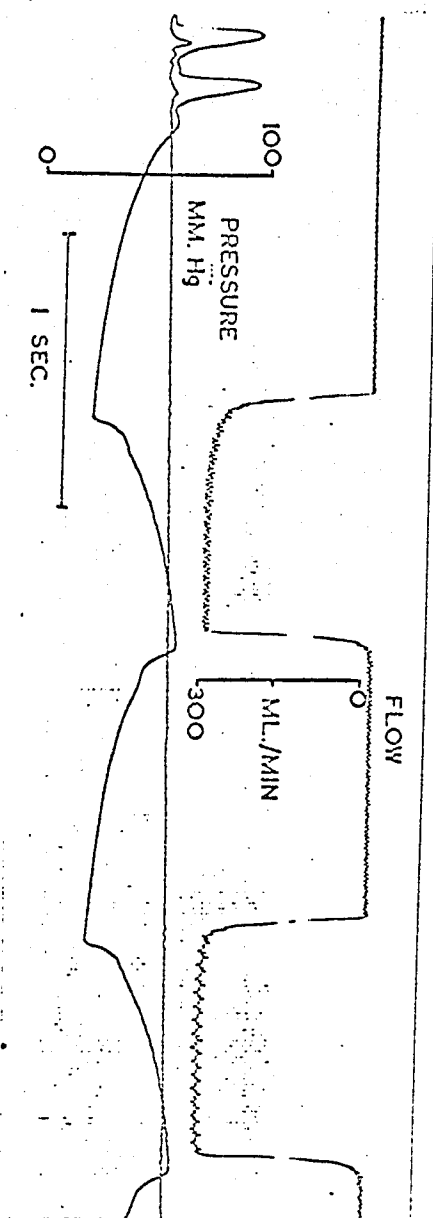


FIGURE 50: Prolonged steady state response to a square wave infusion

FIGURE 51: Pressure responses to 2 consecutive square wave infusions



The general conclusion was reached that vagus nerve stimulation, or any other of the factors previously mentioned, did not have an immediate effect on the systemic arterial circulation. It may well be that these effects do occur, but they are not immediate, so that the response to a square wave infusion can be measured, in this initial period, without their disturbing influence.

(vi) Linearity of the system:

Evidence for the linearity of pressure - flow relations across the systemic arterial circulation has already been considered in reference to Fig. 36 and 38 . Both the steady-state and transient state studies suggest that over a physiological range, these pressure-flow relations can reasonably be approximated by a linear function.

The treatment of the transient pressure response in Fig. 38 , in reference to eq. (22) suggests that pressure-volume relations in the system, are also linear too, over the range tested. This is supported by much of the work in the literature on excised vessels (see, for example, Fig. 3).

Further evidence concerning the linear relations of pressure, flow and volume, in the system, over a limited range, is furnished by the finding of an exponential pressure response to a step function. The original derivation by Frank of this response (equations (1) to (6)) was based on linear equations (equations (1) and (2)). Therefore, if a single exponential pressure response is generated to a

square wave infusion, it must mean that the system is behaving in a linear fashion over that range. As the transformation of this exponential pressure response yields a straight line on the phase plane plot, the straightness of the latter becomes an index of the linearity of the system. Any deviation from a straight line on the phase plane plot, does not necessarily mean that the system is non-linear. However, if it can be proved that the system is in a steady-state during the time of testing (for example, by superposition of 2 successive negative phase plane plots), then it is strongly suggestive that any non-linearity of the phase plane plot, is due to a non-linearity in the system.

In practice, the phase plane plots were used as an index that the two major conditions of (1) linearity, and (2) steady-state of the system, were fulfilled during the time of each square wave infusion. If a straight line was found on the phase plane plot, then both conditions were considered to be satisfied. If 2 successive negative phase plane plots could not be closely superimposed, then it was assumed that the system was not in a steady-state during the time of testing. If 2 such plots could be superimposed, but the plots were not linear (e.g.: in the cholesterol fed animals - see later), then it was assumed that there was a basic non-linearity in the system.

This section has considered some factors potentially capable of modifying the system response to a square wave infusion. The effects

* Positive phase plane plots refer to type 'a' curves : negative phase plane plots refer to type 'b' curves (see Fig.9).

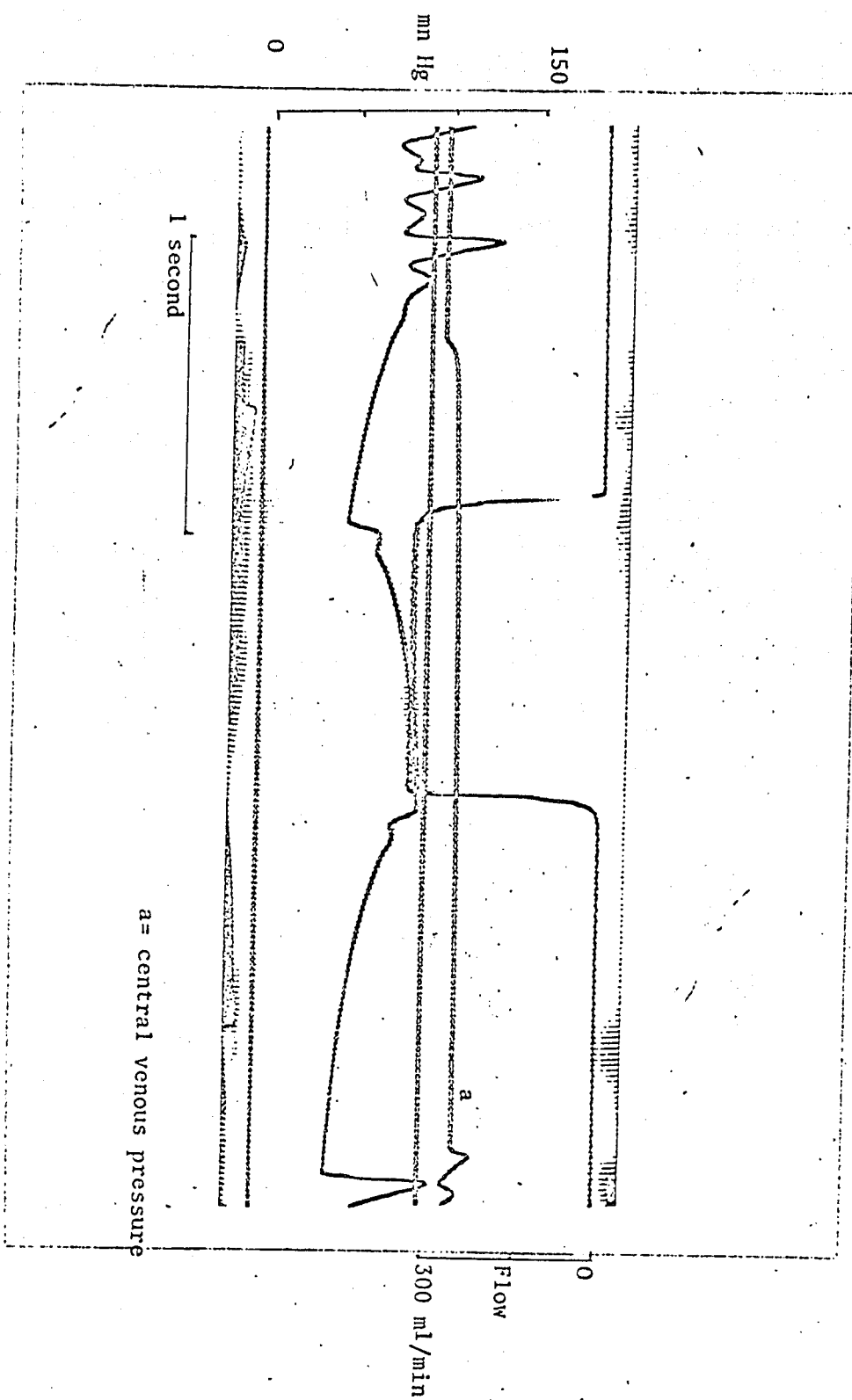
of pressure recording at various sites in the system, aortic valve malfunction, turbulence, and possible artefacts, have all been considered to be negligible or not present. The linearity of the phase plane plots have been suggested to be a good index for fulfillment of the two principal conditions of linearity and steady-state, required before application of the theoretical analysis as already discussed.

4. RESPONSE OF THE SYSTEMIC ARTERIAL CIRCULATION TO THE DEFINITIVE SQUARE WAVE INFUSION TECHNIQUE

The technique finally developed for the square wave infusion method was as follows. The infusion was given to the animal through the right carotid artery. The pressure response was measured from the right femoral artery. During the time of the infusion, the heart was arrested by vagus nerve stimulation, and the respiratory activity of the animal was also arrested. Because sudden respiratory arrest was sometimes followed by a brief period of blood pressure fluctuation (see Fig.49), periodically throughout each experiment, a trial of respiratory arrest alone was performed and the blood pressure response monitored. If a period of fluctuation in the latter was noted, the giving of the square wave infusion was delayed to beyond this unsteady phase.

The pressure response of the systemic arterial circulation to a square wave infusion under these controlled circumstances is shown in Fig. 52 . There is a period of initial oscillation lasting approximately 100 msecs. which is probably associated with inertial effects (see later). The transient pressure response then settles down into a smooth exponential curve with a time constant that is normally in the range of 500 msecs. If the square wave infusion is continued for a sufficiently long time, then this exponential curve finally reaches its asymptote, or steady-state pressure response. On terminating the

FIGURE 52: Typical pressure response of the system to a square wave infusion



square wave infusion, a similar, but inverted, sequence of events takes place.

Analysis of such a pressure response on an oscilloscope phase plane plot is shown in Fig.44 . Familiarity with this transformation is best gained by considering this figure in company with those of Fig.8 and 9 . The flow rate of the infusion was obtained from the primary recording (as in Fig.52) by measurement of the deviation of the linear velocity transducer recording (top line) from the zero line. The time constant of the system was measured from the oscilloscope phase plane plot by the tangent of the acute angle which the plot makes with the ordinate (i.e.: $P/dP/dt$). The slope resistance of the system was calculated as shown in Fig.44 , where ΔP_{ss} is the difference between the two steady-state pressures. In this instance, which is typical of many, steady-state pressures were not quite reached, and extrapolation of the linear plot to the abscissa where $dP/dt = 0$, was required.

The angle which the straight line plot makes with the ordinate is a function of the time constant of the system. It can be seen in Fig.53 that the two plots are not parallel with each other, meaning that the upgoing curve has a different (smaller) time constant than the downgoing curve. As the time constant is the product of the resistance and the compliance of the system, it could be changed by alterations in either, or both, of these parameters.

This is not a time dependent phenomenon, as the effect occurs whichever upgoing or downgoing curve is monitored first, and it also occurs when two infusions are given in rapid succession. Fig.53 also demonstrates that the systemic circulation is in a steady-state during this time, because careful examination of the phase plane plot reveals that two downgoing curves are superimposed on top of each other. When 2 successive downgoing pressure curves are given, as in Fig.54, it can be seen that they have a very similar slope. All this suggests that the system is undergoing a hysteresis phenomenon. This idea is well supported by work in the literature on excised vessels (see, for example, Fig.4 . BERGEL 1961, REMINGTON, 1967). In these studies, as in Fig.4 , compliance values are greater during deflation of the vessel than they are during inflation. This is the most likely explanation of the greater time constants obtained from the downgoing (deflationary) pressure curves. A good example of this presumed hysteresis effect is shown in Fig. 55 . In calculation of the results, after taking proper precautions that the system was in a steady-state during the time of testing, any difference in the slopes of the positive and negative phase plane plots was assumed to be due entirely to hysteresis in the compliance element. This lead to the calculation of separate compliance values for the upgoing (C_u) and downgoing (C_D) pressure responses.

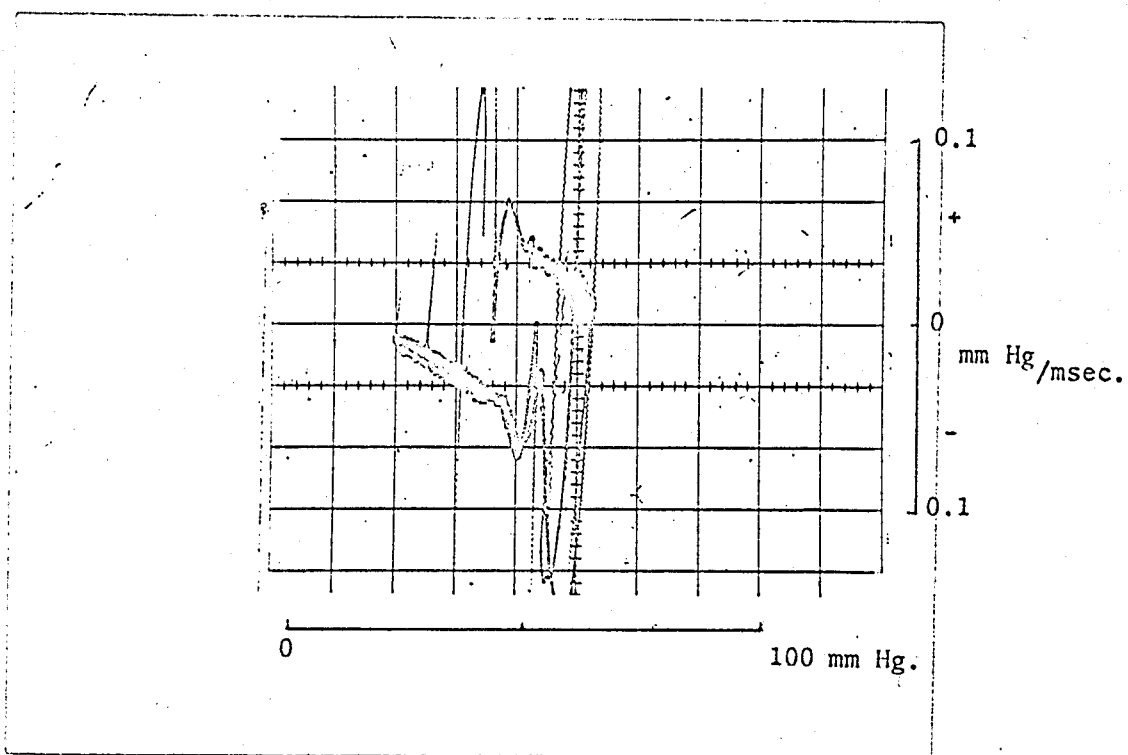


FIGURE 53: Oscilloscope phase plane plot

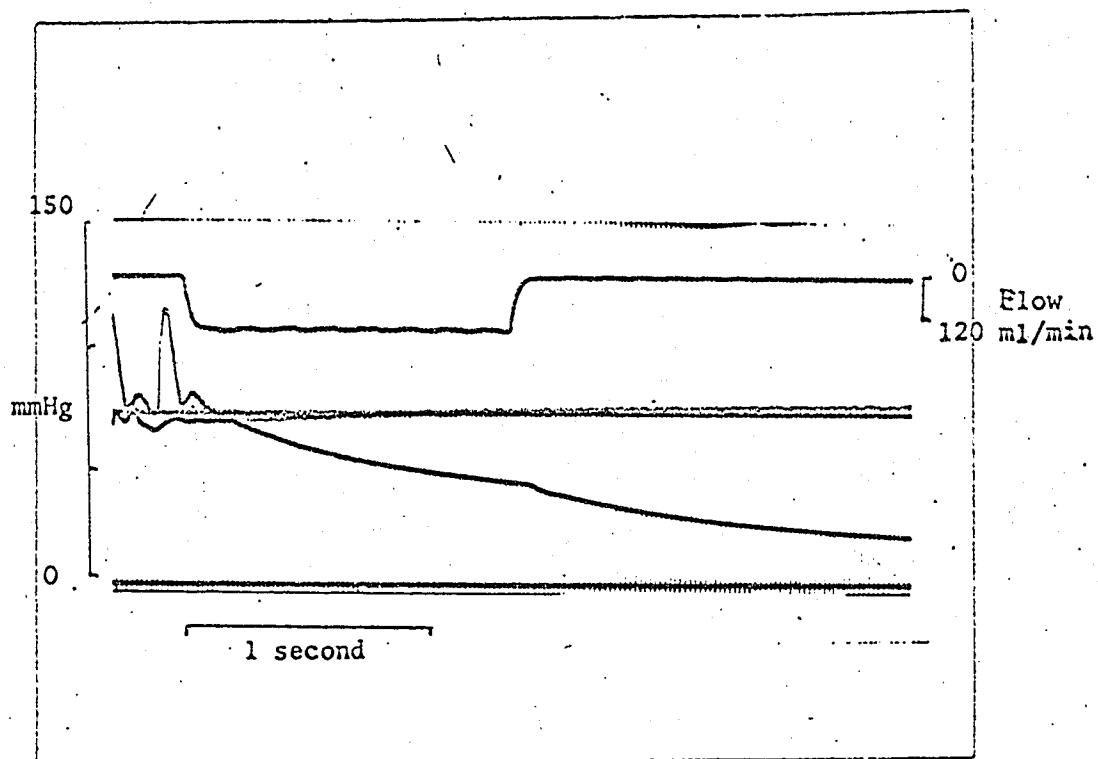


FIGURE 54: Pressure response to a square wave infusion of low flow rate

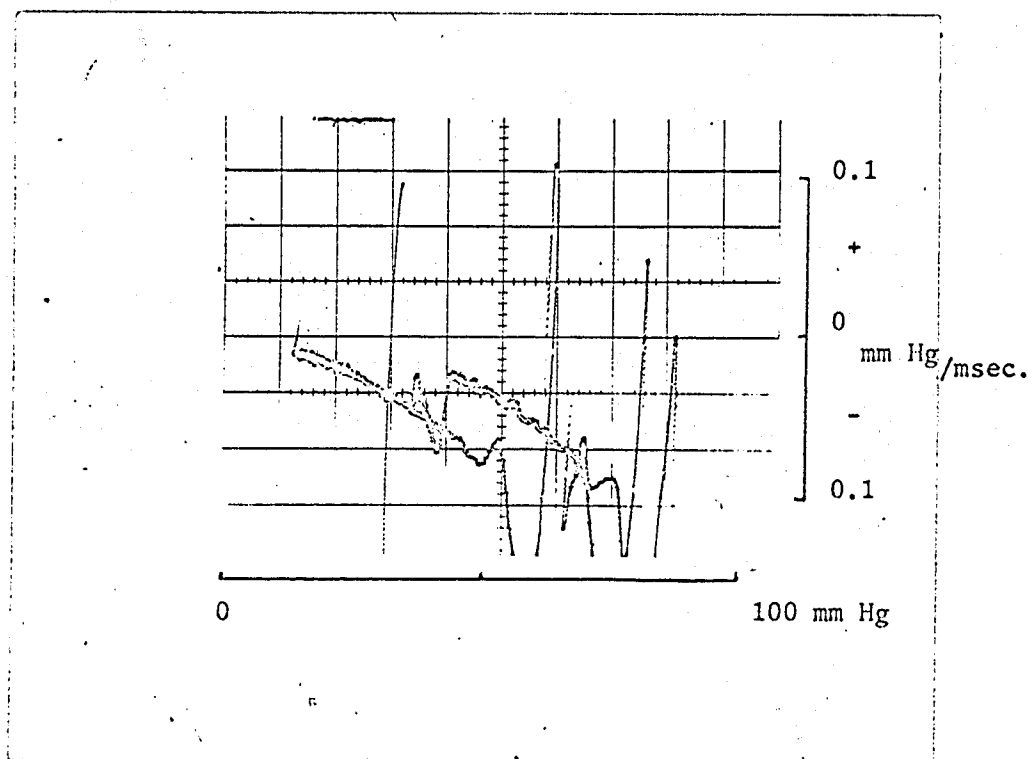


FIGURE 54a: Phase plane plot of the pressure response to a low infusion rate.

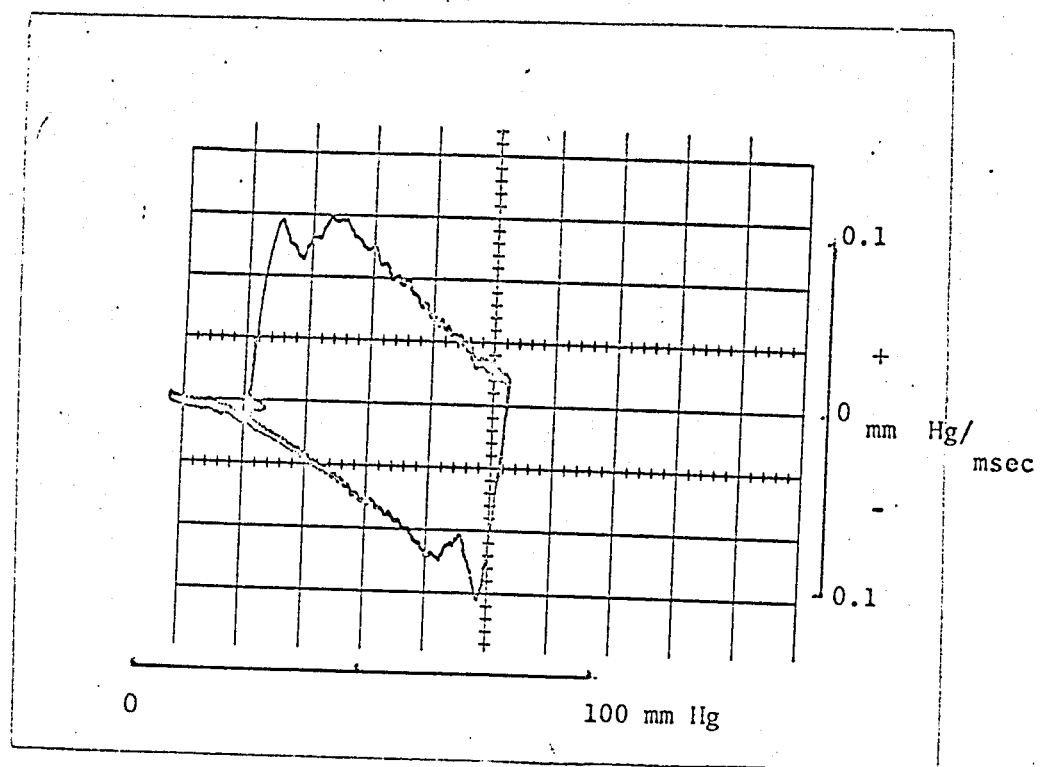


FIGURE 55 : Oscilloscope phase plane plot

TABLE 9

Sequence of values obtained from a single normal rabbit

Wt.	$\bar{P}$ mm Hg	H. Rate p.min.	$\bar{P}_D$	$\bar{P}_U$	R_S	p^+	C_D	C_U	
7.8 lbs.	105	280	1400	-	-	-	-	-	
	105	270	1320	-	-	-	-	-	
	102	270	1260	-	-	-	-	-	
	83	280	812	384	.15	28	.09	.042	
	86	270	758	334	.14	34	.09	.040	
	80	270	633	452	.14	35	.075	.054	
	77	270	640	516	.17	28	.062	.050	
	70	270	640	576	.17	28	.062	.050	
	27	270	-	314	.12	18	-	.043	20 ml haemorrhage
	70	255	614	-	.14	31	.073	-	20 ml returned
	63	270	527	478	.15	30	.058	.053	
	23	240	504	364	.11	18	.076	.055	20 ml haemorrhage
	59	240	573	534	.15	29	.057	.06	20 ml returned

 $\bar{P}$ = mean arterial pressure. Other symbols as before.

TABLE 10

Calculation of mean parameter values from a series of normal animals

wt. lbs.	τ_D msecs	S.D.	P.R.U. min. R_S	S.D.	P^+ mm Hg	S.D.	C_D ml/ mmHg	S.D.	C_y ml/ mmHg	S.D.
7.71	614	± 180	.15	$\pm .01$	23	± 3	.058	$\pm .004$	.034	$\pm .002$
7.5	729	$\pm$	.16	$\pm .02$	23	± 7	.050	$\pm .002$	.037	$\pm .006$
7.7	802	± 330	.14	$\pm .02$	27	± 5	.071	$\pm .012$	.045	$\pm .006$
5.5	659	± 116	.22	$\pm .01$	26	± 3	.046	$\pm .011$	.027	$\pm .003$
6.0	614	± 95	.29	$\pm .06$	19	± 4	.036	$\pm .006$		
6.4	795	± 150	.22	$\pm .01$	15	± 2	.052	$\pm .004$	.026	
5.9	639	± 148	.17	$\pm .01$	27	± 2	.049	$\pm .004$	.037	$\pm .003$
6.7	744	± 93	.22	$\pm .02$	25	± 3	.054	$\pm .005$	.026	$\pm .001$
7.5	780	± 187	.17	$\pm .01$	28	± 6	.006	$\pm .017$	.048	$\pm .01$
7.5	890	± 175	.21	$\pm .035$	18	± 4	.065	$\pm .015$	.041	
5.9	922	± 106	.22	$\pm .024$	24	± 6	.070	$\pm .012$	.043	$\pm .007$
5.2	1010	± 272	.26	$\pm .046$	23	± 4	.053	$\pm .006$	.052	$\pm .008$
5.0	937	± 88	.41	$\pm .04$	24	± 5	.036	$\pm .001$	.022	$\pm .001$
6.2	453	± 43	.17	$\pm .02$	19	± 2	.042	$\pm .004$	.039	$\pm .002$
6.3	518	± 75	.16	$\pm .02$	19	± 3	.053	$\pm .004$		
6.8	780	± 93	.21	$\pm .05$	23	± 4	.064	$\pm .008$		

Table 10 shows the mean values for a variety of parameters obtained from 16 normal animals. The mean value for the whole group for slope resistance was 0.21 mm Hg/ml.p.min. The mean value for the 'critical closing pressure' was 23 mm Hg. The mean value for the time constant of a pressure curve during deflation (τ_D) was 743 msec. The mean value for compliance of the system measured during deflation (C_D) was 0.054 ml/mm Hg. $\pm$.0028: when measured during inflation (C_U), the mean value was 0.037 ml/mm Hg. $\pm$.0026. This was a significant difference between C_D and C_U ($t = 4.5$, for 27 degrees of freedom, $p < .001$).

Table 9 show typical values obtained during a single experiment.

It is difficult to assess definitively the accuracy of the values obtained, because this depends largely on the accuracy of any extrapolations made to the phase plane plot. In most cases, this was not a problem and the values obtained for the time constant and ΔP_{SS} were accurate to two significant figures. It follows as a consequence of this, that values for resistance, compliance, and 'critical closing pressure' were also accurate to this level. In instances where the phase plane plots were curvilinear, as in the rabbits fed cholesterol, accuracy was slightly less than this.

Fig.56 shows the results of a phase plane plot of the response to a square wave infusion while the heart was still beating at a rate of 180/min. (vagal stimulation caused brady cardia, rather than arrest,

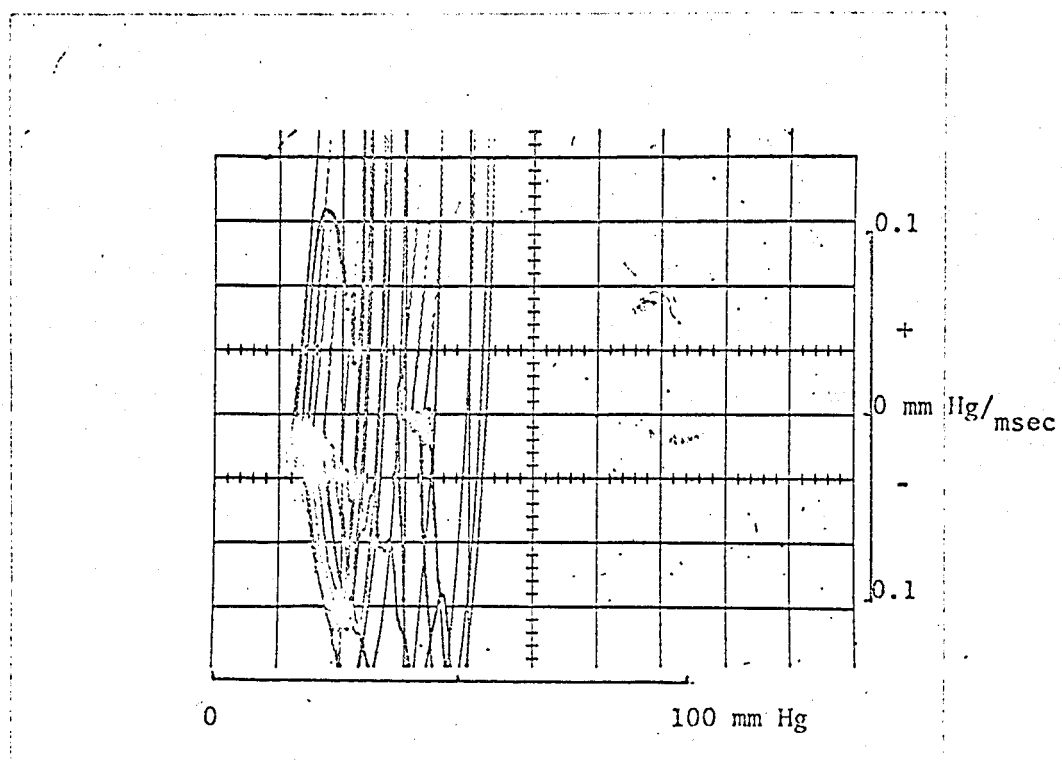


FIGURE 56: Oscilloscope phase plane plot of the response to an infusion, given while the heart continued to beat normally.

in this instance). No calculations were made from this plot, but it is presented here to indicate the possibilities that may occur for giving the square wave infusion to animals with much lower heart rates than the rabbit (see 'Discussion').

(a) Consideration of the inertial factor:

The experiments of PETERSON (1952, 1954) showed that when a square wave was imposed on the systemic arterial circulation, there was an initial pressure peak (see Fig.6) which he called an 'acceleration transient'. The initial oscillation on the transient pressure response to a square wave infusion in these experiments, suggests that it is of the same nature.

The square wave infusion apparatus has a constant build-up time of approximately 30 msec. Therefore, with progressively increasing flow rates, the blood in the systemic circulation is subject to progressively increasing accelerations. The top half of Fig.57 shows the pressure response when the system is subject to 102ml/sec./sec. acceleration. The bottom half of the same figure shows the response when it is subject to 139ml/sec./sec. acceleration. It can be seen that the height of the initial oscillation over the presumed backward extrapolation of the smooth curve that follows it, is greater when the acceleration is greater. Furthermore, the time taken to reach the peak of the pressure oscillation is equal to the build-up time of the square wave infusion i.e.: the period when acceleration is

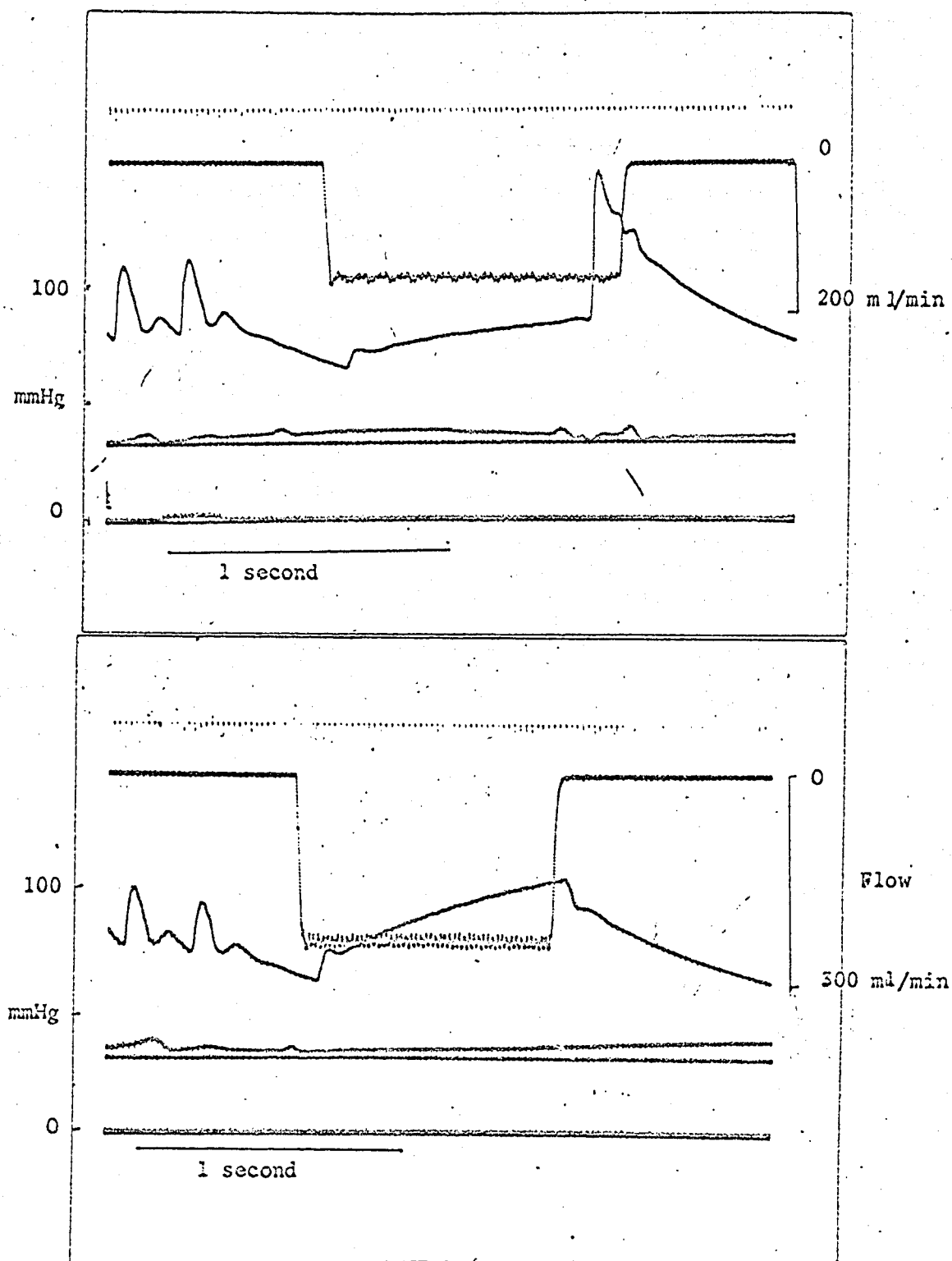


FIGURE S7: The pressure responses to two different infusion rates

occurring. The time lag between the beginning of the square wave infusion and the beginning of the pressure response is due to the transmission time of the pressure wave down to the right femoral artery.

Fig.58 shows a plot of the height of the initial pressure oscillation against infusion rate (which is a direct function of the acceleration of the blood). The smooth exponential curve which follows the initial oscillation is extrapolated backwards, and the maximum height of the initial oscillation measured above this. It can be seen that the plot taken from a sequence of upgoing (inflationary) pressure curves, and the plot of a sequence of downgoing (deflationary) pressure curves, are approximately linear. All recordings are taken from the same rabbit. The linear plots obtained are highly suggestive that the initial oscillation is the result of an inertial effect. The height of the oscillation on the deflationary plot is less than that of the inflationary plot, and this may reflect the hysteresis effect of the vessel wall (see discussion).

An approximate calculation of the magnitude of this inertial component can be made in the following manner. Acceleration of the blood is not constant during the 30 msec. build-up time. Therefore, the pressure generated due to the inertial component is not constant also. The total pressure developed during any build-up time (dt) is $\int \Delta P dt$, where ΔP is the extra pressure developed due to the inertial component at any moment. This value is given approximately by

FIGURE 58: Plot of the height of the initial pressure oscillation, against infusion rate.

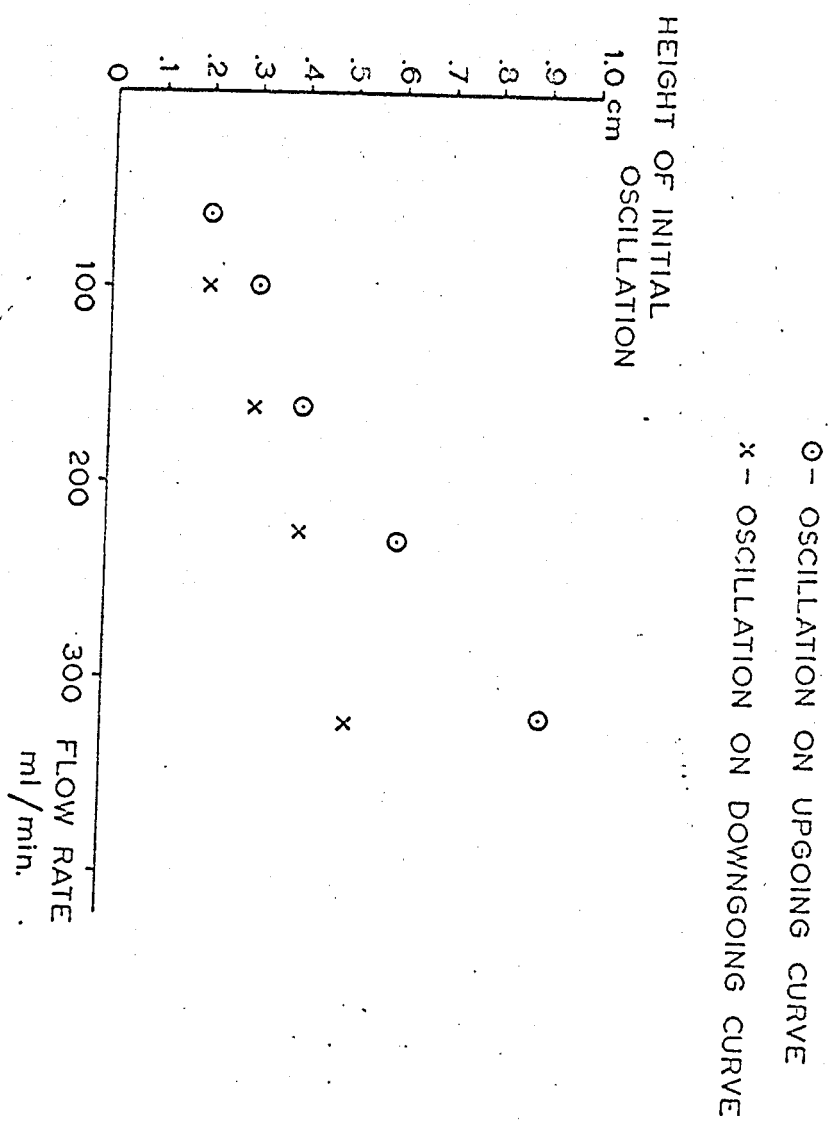


TABLE 11

Inertance Calculations

Wt. lbs	P _{MAX} mm Hg.	F <u>ml.p.min.</u> 30 msecs.	L gm.cm. ⁻⁴
6.2	1.3	62	25.3
	4.0	97	49.8
	5.3	161	39.8
	8.0	224	43.2
	11.9	320	45.0
6.1	1.6	82	23.6
	2.9	159	22.0
	4.0	218	22.2
	4.0	317	15.3
6.7	4.0	153	31.6
	5.3	218	29.4
	8.0	326	29.7
5.1	3.6	195	22.3
	4.8	278	20.9
	3.6	213	20.4
5.8	6.9	280	29.8

P_{MAX} = maximum pressure increment of initial
oscillation over backward extrapolation
of exponential curve.

Mean value for L = 29.4 gm.cm.⁻⁴

$$L = \frac{P_{MAX}}{F} \times \frac{.5 \times 1330 \times 60}{33} \text{ gm.cm.}^{-4}$$

multiplying half the maximum extra pressure developed ($\Delta P_{MAX} \times 1/2$) by dt. The average acceleration of the blood during a build-up time of 30 msec. (dF/dt_{AV}) is calculated. The time that this is operative is also dt. Therefore, the inertance (L) of the systemic arterial circulation then becomes:

$$L = \frac{\Delta P_{MAX} \times 1/2}{dF/dt_{AV}}$$

Where P_{MAX} is expressed in mm Hg., and dF/dt in ml/min/sec, the conversion factor to give a value for L in gm. cm.⁻⁴ becomes 7.98×10^4 . A series of values calculated for L are shown in Table 11. The mean value for the whole group was 29.4 gm. cm.⁻⁴. In terms of vessel dimensions, inertance is expressed in the following way

$$L = \frac{\rho x}{\pi r^2}$$

ρ = density of blood (1.055)
 x = effective length of mass accelerated

If the mass of blood to be accelerated is considered to be that contained in the whole length of aorta (which is assessed as a cylinder 23 cms. long with a radius of 0.2 cms.) then inertance, from the above expression, is calculated to be 194 gm. cm.⁻⁴. Thus it can be seen that the effective mass accelerated is considerably less than this (i.e.: 29.4 to 194 gm. cm.⁻⁴).

(b) Correlation with the Fick method for measuring cardiac output.

From the phase plane plot of each square wave infusion, it was possible to calculate the slope resistance (R_s) and the critical

closing pressure (P^+), as previously discussed. If the mean arterial blood pressure (which was taken as the diastolic pressure plus one third of the pulse pressure) is also measured, immediately prior to giving the square wave infusion, then the cardiac output (F) of the animal at that time can be calculated according to the following equation:

$$F = \frac{(\bar{P} - P^+)}{R_s} \quad \text{Where } \bar{P} = \text{mean arterial blood pressure.}$$

Cardiac outputs of the animals were also measured by the Fick method, immediately before the relevant square wave infusion, as discussed in the 'Methods' section.

The results of plotting 21 determinations of cardiac output in 15 different animals by both methods against each other, are shown in Fig.59 . Calculation of the correlation coefficient between the two yields a value of $r = + 0.80$, where $N = 21$. The standard error of estimate of Y on X (Fick method) is 35.7. Changes in cardiac output in any one animal showed good correspondence between the magnitude of the changes as measured by either method.

(c) Correlation with compliance values measured by other methods:

As described in the 'Methods' section, compliance values were obtained on as long a length as possible of the excised aorta, by performing pressure-volume studies such as that shown in Fig.60 . The apparatus used is shown in Fig.29 . The average length of the

FIGURE 59: Plot of cardiac output measured by the Fick method, against that calculated from the response to a square wave infusion.

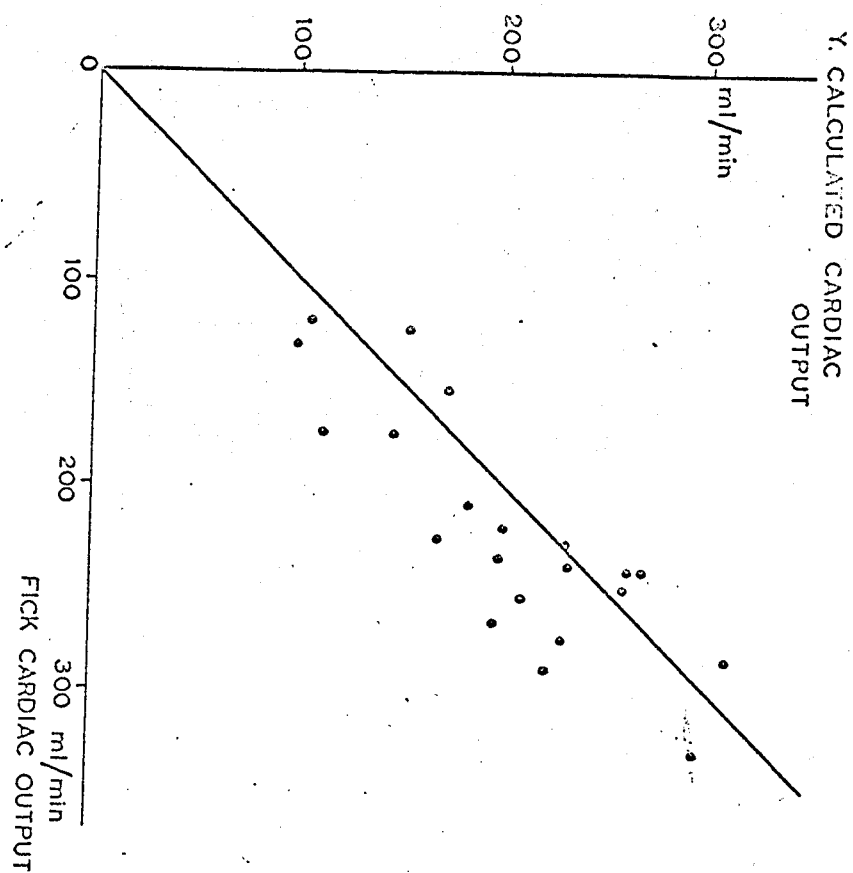


FIGURE 60

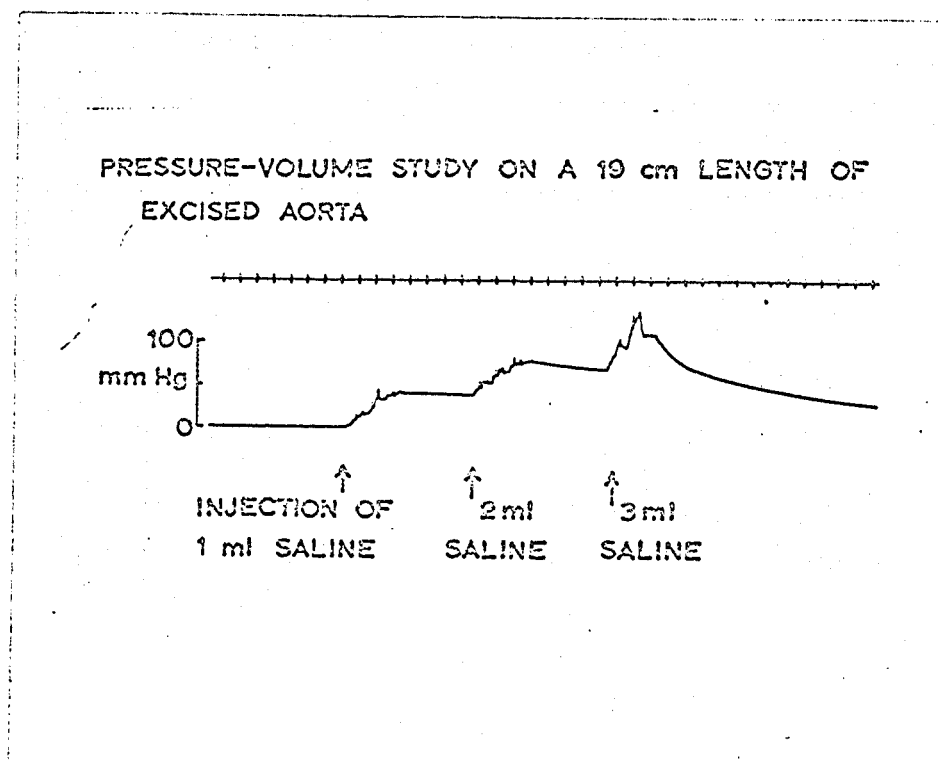


TABLE 12

Compliance values of the excised aorta

Wt. lbs	Length of aorta tested cm.	C _y ml/mm Hg.	Range
6	19.0	.039	.035 - .043
5	19.0	.030	.025 - .038
6	19.0	.046	.035 - .054
5	18.5	.045	—
6	19.5	.044	.034 - .052
5	19.0	.032	.030 - .035
5	20.0	.031	.029 - .034
5	18.5	.026	—
5	20.0	.028	—
5	19.0	.038	.037 - .040
5	13.0	.028	.024 - .030

(1) Mean compliance value of group = $.035 \pm .0022$ (2) Mean compliance, from Table 10 'in vivo'
= $.037 \pm .0026$

Statistical inference between (1) and (2)

$$t = 0.44 \quad p = 0.6 - 0.7 \quad H_0$$

aorta from the aortic valve to iliac bifurcation was 23 cms. Generally the excised specimens (held at their 'in situ' length) were a little shorter than this, as shown in Table 12 . It was not always entirely possible to make leak-free specimens of this length, but it was generally possible to obtain results such as that shown in Fig. 60 , where breakdown occurred at a pressure of approximately 100 mm Hg. Under these circumstances, it was only possible to make an adequate assessment of aortic compliance during inflation of the specimen. Values obtained in 11 animals are shown in Table 12 . . The mean value of the group was 0.035 ml/mm Hg. The mean compliance value during inflation of the vessel found in 13 live normal rabbits by the square wave infusion method was 0.037 ml/mm Hg. At 't' test performed on these 2 groups, with 22 degrees of freedom, yielded a value $t = 0.44$, which gives a statistical probability of 0.7 to 0.6 that the 2 groups belong to the same population. Therefore, there is good correspondence between compliance values obtained by the square wave infusion method and those obtained by an alternate method.

The mean pulse wave velocity of normal animals was 5.3 metres/second. Using the Bramwell-Hill formula, a value can be calculated for C_{inc} in the following manner:

$$5.3 = 0.9 \times 0.357 \left(\frac{1}{C_{inc}} \right)^{1/2}$$

Note: The formula is modified by the factor 0.9, which accounts for the viscous effect (see 'Introduction' and BERGEL 1961).

Solving for C_{inc} gives a value of 0.0037 ml/mm Hg/V, where V equals the volume of the aorta at which the pulse wave velocity was measured. This corresponded to a pressure of 80 mm Hg. Approximate aortic dimensions at post-mortem are 23 cms. length and 0.2 cms. radius. This gives a cylinder of equivalent volume of 2.89 ml. The normal mean compliance value during inflation is 0.037 ml/mm Hg. Therefore, the total volume of the aorta when distended to a pressure of 80 mm Hg would be approximately $2.89 + 2.96 = 5.85$ ml.

Now C_{inc} is related to compliance (C) in the following fashion:

$$\begin{aligned} C &= C_{inc} \times V \\ &= .0037 \times 5.85 \\ &= .022 \text{ ml/mm Hg.} \end{aligned}$$

Thus compliance values calculated in this manner from pulse wave velocity measurements are considerably smaller than those measured by the square wave infusion method.

It is also possible to calculate a value for compliance of the system from knowledge of the dimensions of the vessel, and its incremental modulus (E_{inc}).

$$\text{Thus: } \frac{\frac{d(P.r)}{a}}{\frac{2\pi dr}{2\pi r}} = E_{inc} = \frac{d(P.r)}{a} \times \frac{2\pi r}{2\pi dr}$$

Where r = radius of vessel
 a = wall thickness
 P = transmural pressure

dr , dP , are small increments in r and P respectively.

Solving for dP:

$$dP \approx \left(\frac{E_{inca}}{r^2} \right) \cdot dr$$

(ad P.dr is negligible against r. dP).

Now:

$$dV = 2 \pi r l \cdot dr$$

Hence compliance (dV/dP) is:

$$\frac{dV}{dP} = \frac{2 \pi r^3 l}{E_{inca}}$$

The incremental modulus of a length of thoracic aorta wall was measured by holding the specimen at its 'in situ' length (usually about 10 cms.). Longitudinal increments were caused by addition of weights to a long lever which was attached to the other end to the vessel. Typical values for E_{inc} were 2.6 dynes/cm. $\times 10^6$ and for wall thickness 0.058 cms. (derived from the density of the specimen). It has been seen previously that the volume of the aorta at 100 mm Hg pressure is approximately 6 ml. Substitution of these values in the above formula yields a value for C of 0.021 ml/mm Hg.

Again it can be seen that this value is much smaller than those measured by the square wave infusion method. However, this calculation and the one based on pulse wave velocity values before it, can really only be expected to give an order of magnitude for the compliance value. This is due to the difficulties in properly assessing the initial volume, V, (which may be somewhat greater than that of the aorta alone), and the incremental modulus.

The question of a hysteresis phenomenon occurring in the vascular bed has already been discussed. It was found throughout the investigation, that compliance values varied during the course of a single experiment. In some animals, the range of variation in the values measured from the downgoing pressure curve was as high as 0.09 to 0.05 ml/mm Hg. This is a significant difference, outside the limits of experimental error. It is suggestive that smooth muscle contraction is having an influence on the elasticity of the vascular wall. A moderate inverse correlation of $r = -0.57$ was found between the change in slope resistance and the change in compliance value: 't' value for this group was 3.44 which gives a value at $p < .01$.

(d) Observations on the 'critical closing pressure' of the system:

All varieties of techniques used in this investigation have shown that a 'critical closing pressure' exists across the systemic arterial circulation. At zero flow rate, there is a mean positive pressure axis intercept of 23 mm Hg $\pm$ 3.7. The lowest and highest values recorded in this investigation were 9 and 52 mm Hg, respectively. If the flow rate is kept at zero for more than 2 - 3 seconds, the steady-state pressure ('critical closing pressure') gradually begins to fall, presumably from the effects of hypoxia, as can be seen in Fig. 61 .

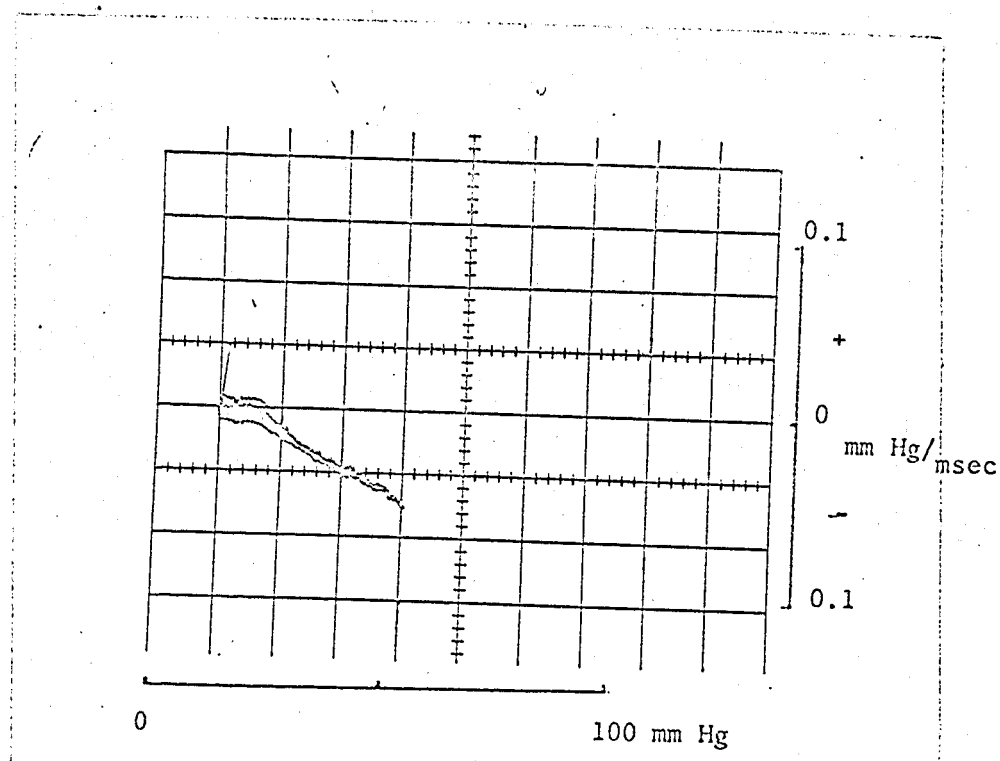


FIGURE 61: Oscilloscope phase plane plot showing a gradual fall in critical closing pressure.

TABLE 13

Correlations between R_s and 'critical closing pressure'

N	$\bar{R}_s$	$\bar{P}^+$	Range of P^+	' r_a '	P (r_a)	' r_b '
9	.14	27	28 - 18	+.63	>.05	+.75
7	.16	23	34 - 12	+.82	<.05	+.75
8	.14	16	24 - 9	+.86	<.05	+.85
5	.11	18	21 - 13	+.88	<.05	+.75
5	.21	18	22 - 14	+.84	>.05	..08
4	.22	26	30 - 21	+.08	>.05	
4	.29	19	24 + 17	+.62	>.05	
4	.17	32	34 - 26	-.84	>.05	

' r_a ' = correlation coefficient between R_s and P^+ to which' r_b ' = correlation coefficient between R_s and $\bar{P}$ $\bar{P}$ = mean arterial pressure immediately prior to infusion

N = number of determinations

The importance of this 'critical closing pressure' in the determination of the true resistance of the system has already been discussed in reference to 'chord' and 'slope' resistances and Fig. 2 . The chord resistance is approximately twice the magnitude of the slope resistance and can give ambiguous information concerning the state of the vascular bed. Table 13 shows a series of correlation coefficients between the slope resistance of an animal and its 'critical closing pressure'. Further evidence that changes in 'critical closing pressure' of the animal are associated with changes in its resistance are seen in reference to the phase plane plot of Fig.62 . Here a change in chord resistance occurred during a square wave infusion and was associated with a fall in 'critical closing pressure'. It is not possible to say whether there was a decrease in slope resistance, at this time. Table 13 shows the correlation coefficients of slope resistance, and mean arterial blood pressure, immediately prior to giving each square wave infusion.

(e) Hydraulic, electrical, and mathematical models of the systemic arterial circulation:

Foregoing sections have considered correlation of the various property values (resistance and compliance) obtained by the square wave infusion technique with those obtained by standard methods. This section will consider correlation of the behaviour of the systemic arterial circulation with various physical systems. In other

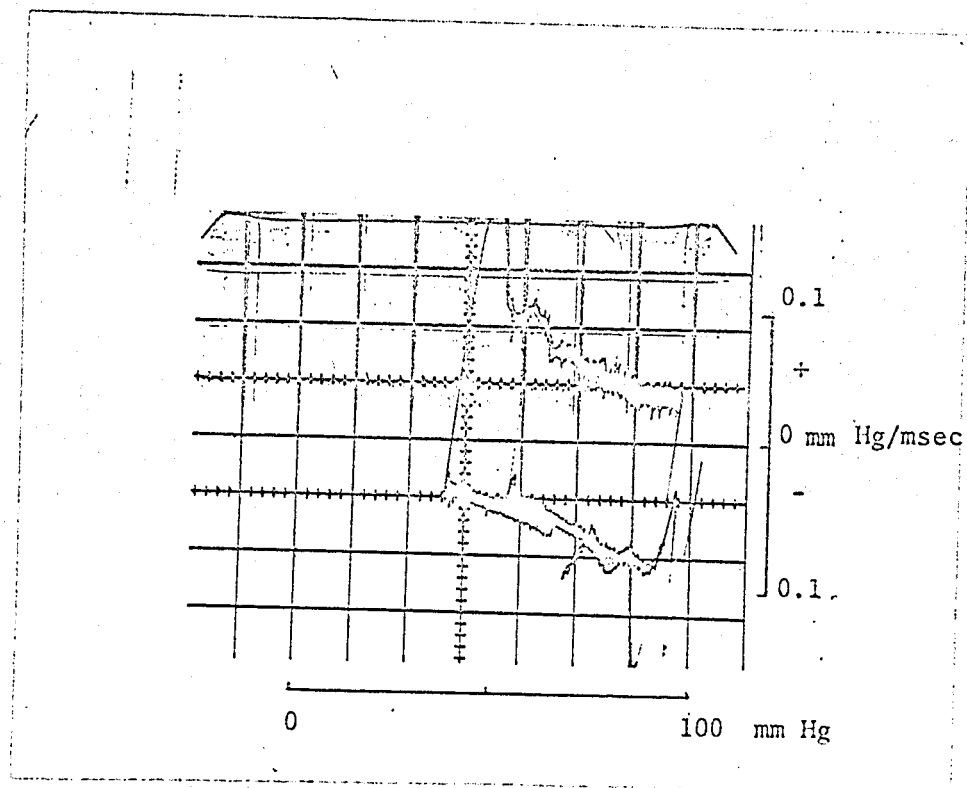


FIGURE 62: Oscilloscope phase plane plot showing a change in chord resistance during an infusion.

words, simple models will be built to match the behaviour of the systemic arterial circulation.

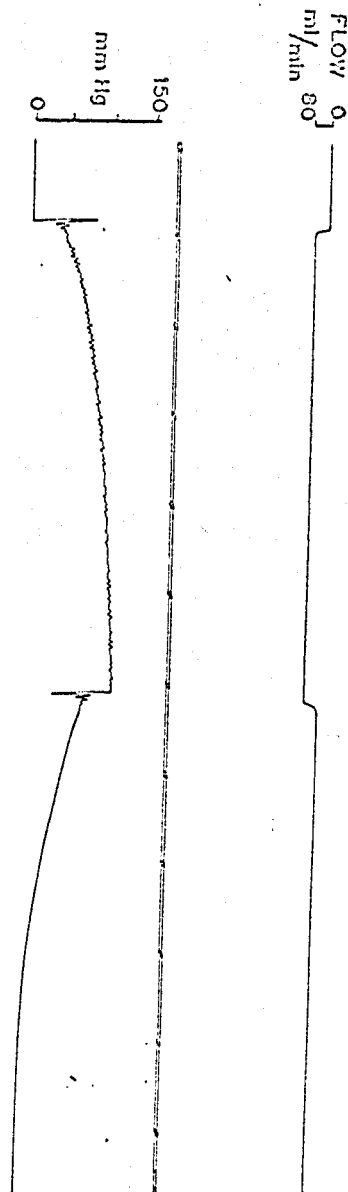
The original working hypothesis of this thesis was that the systemic arterial circulation behaved primarily as a linear first order system. This cannot be strictly true, because of the initial oscillation which occurs in the response to a step function. This suggests that the system is behaving as a higher order system. In order to clarify this point further, hydraulic and electrical models were made of the system.

The hydraulic model used is best followed in reference to Fig.29 . The peripheral resistance of the animal was represented by a 2.5 cm. length of 22 G needle. The compliance of the animal was considered to be represented by virtually the whole length of the excised thoracic and abdominal aorta (aortic arch to iliac bifurcation). They were connected together as shown in Fig.29 . This then represented a simple hydraulic model of the systemic arterial circulation.

The response of such a model to a square wave infusion of saline is shown in Fig.63 . It can be seen that the general character of the response is very similar to that obtained in the living animal. The initial oscillation lasts for the 30 msec. or so during which the saline solution is being accelerated. It then settles down to a smooth exponential response. The time constant of the curve shown in Fig. 63 was 2,200 msec. The slope resistance presented to outflow from the aorta was 1.12 mm Hg/ml.p.min. This

FIGURE 63

RESULT OF MODEL STUDY OF SYSTEMIC ARTERIAL CIRCULATION

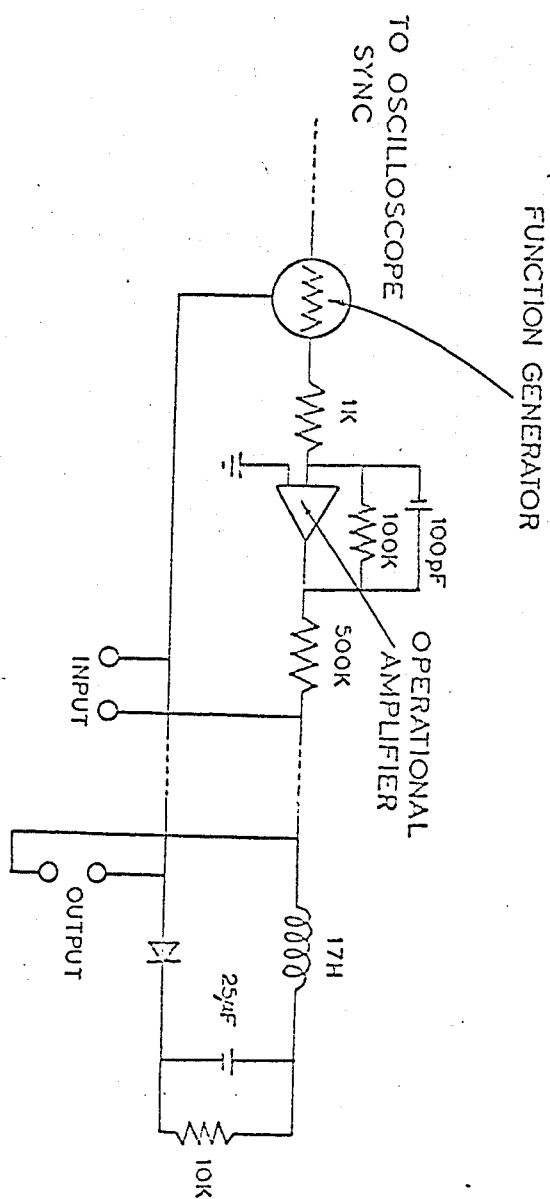


is higher than the resistance normally presented by the rabbit and accounts for the long time constant of the model. From these figures, a value of 0.033 ml/mm Hg. was calculated for the compliance of the aortic specimen. If the initial oscillation is assumed to be entirely due to inertial forces, then the value for inertance of the model is calculated to be 756 gm. cm.⁻⁴. It was not possible to maintain entirely leak-proof specimens of sufficient length to repeat this study adequately. The downgoing curve, after cessation of the square wave infusion, was of a similar nature, although it was not possible to examine it quantitatively for any hysteresis effect, because a slight leak developed. This study was very valuable, however, in helping to crystallise ideas concerning a definitive model of the systemic arterial circulation.

The above study, and the response of the living animal to a square wave function, suggested that an electrical analogue model of the systemic arterial circulation should be composed of the components shown to the right of Fig.64 (see system labelled 'output'). It can be seen that when this system is subjected to a similar type of input (shown on the top tracing of Fig.65) as that given to the animal, the response (shown on the bottom tracing of Fig.65) is of the same character.

The input to the animal was not a perfect square wave infusion, but had a build-up time of approximately 30 msec. This type of function was generated electrically by 'clipping' pure

FIGURE 64: Electrical circuitry 1) to simulate the exact form of the square wave infusion
2) to provide a model of the systemic arterial circulation *



* seen to the right of
the "output" terminals

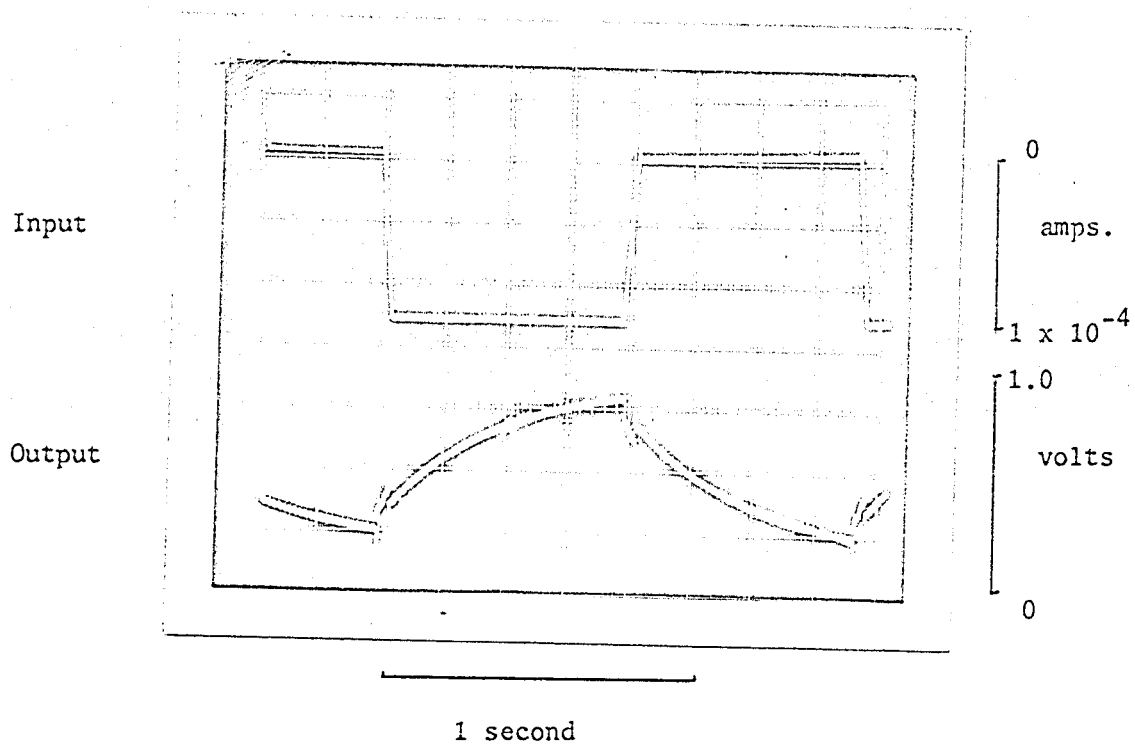


FIGURE 65: Input and output response of the electrical model of the systemic arterial circulation shown in the previous figure.

triangular waves with . operational ampli (D-12, Data Device Corporation, Hicksv , N.Y.). The circuit used is shown in Fig.64 . By this means, a 'square' wave pulse with a build-up time of 30 msec. could be given to the electrical analogue model.

Component values were matched to those of the living animal in the following manner:

Let 1 volt be equivalent to 100 mm Hg. Hence, the current (I) through the circuit at a steady state pressure of 100 mm Hg is:

$$I = \frac{1}{10 \times 10^3} = 1 \times 10^{-4} \text{ amps.}$$

Let 1×10^{-4} amps. be equivalent to a flow of 300 ml/min. in the living animal. Therefore, (1) an electrical resistance of 10K becomes equivalent to a resistance of $\frac{100}{300}$, or 0.33 PRU.min in the

living animal.

The time constant of the circuit (τ)

$$= R.C.$$

$$= 1 \times 10^4 \times 25 \times 10^{-6}$$

$$= .0042 \text{ minutes}$$

As the resistance is 0.33 PRU.min, the compliance (C) becomes:

$$C = \frac{.0042}{0.33}$$

$$= 0.013 \text{ ml/mm Hg.}$$

Therefore (2), an electrical capacitance of $25 \mu F$ becomes equivalent to a compliance of 0.013 ml/mm Hg. in the living animal.

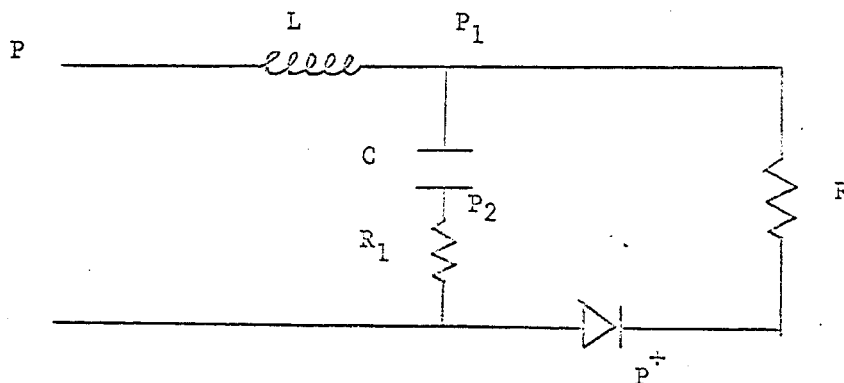
Let the extra height of the initial oscillation associated with inertial effect be 5 mm Hg. This then becomes equivalent to 0.05 volts. The average rate of change of volume flow is 300 ml/min in 30 msecs, or 33×10^{-4} amps/sec.

$$\text{Then, as: } L = \frac{\Delta P}{dI/dt} = \frac{5 \times 10^{-2}}{33 \times 10^{-4}} = 165 \text{ Henries}$$

This value then has the equivalence of $\frac{5 \times 1330}{\frac{300}{60} \times 33}$, or 40.3 gm. cm.⁻⁴.

The calculated inductance value is higher than the value actually used in the circuit. This probably occurs because the maximum rate of change during the 'build-up' time for the actual square wave infusion is greater than the average value used here.

This model does not take account of (1) the hysteresis effect, and (2) the 'critical closing pressure'. The former can be accounted for by placing a resistor in series with the 25 μ F capacitance (R_1). The critical closing pressure phenomenon can be accounted for by placing a diode on the negative side of the circuit (P^+). Thus:



Classification of analogous systems is usually made in terms of their mathematical description. The behaviour of the above model is as follows:

$$(1) P = DF.L + P_1 \quad \text{Where } D = \text{the differential operator, } d/dt.$$

Consider P_1 :

$$(2) P_1 = \frac{1}{D} f_c \cdot \frac{1}{C} + f_c \cdot R_1$$

On differentiation

$$(3) DP_1 = f_c \cdot \frac{1}{C} + D \cdot f_c \cdot R_1$$

$$\text{Now: } f_c = P_2 \cdot \frac{1}{R_1} : \text{ or } Df_c \cdot R_1 = DP_2$$

Therefore, from (3)

$$f_c = C \cdot DP_1 - DP_2$$

$$(4) F = f_c + f_R \\ = C \cdot DP_1 - DP_2 + (P_1 - P^*) \frac{1}{R}$$

Substituting (1) in (4)

$$F = C \cdot DP - CL D^2 F - DP_2 + P \frac{1}{R} - \frac{L}{R} DF - \frac{P^*}{R}$$

Rearranging:

$$(5) CLD^2F + \frac{L}{R} DF + F = C \cdot DP - DP_2 + (P - P^*) \frac{1}{R}$$

Equation (5) is a non-homogenous linear second order equation in terms of F . A number of solutions for F in terms of P , P_1 , and P_2 are possible. The highest order of any of these is a third order one,

in terms of P_1 and P_2 (from double differentiation of eq. (4)). The system is classified, accordingly, as a third order system.

It can be seen, that when the first and second derivatives of F are zero (i.e.: when flow through the system becomes constant), and the contribution of DP_2 (which is minor) ignored, then eq. (5) reduces to that of eq. (18) and the system behaves as a first order system. Therefore, this system behaves very like a first order one, in the absence of acceleration.

This model does not describe a perfect analogy with the controlled system in the systemic arterial circulation, for it considers the vascular bed only as a 'lumped' system. In the real system, spatial coordinates are also important and this leads to the development of a system of partial differential equations. However, the lumped system shown above, is a useful approximation, particularly when pulsatile flow is not considered.

5. THE EFFECTS OF VARIOUS STRESSES ON THE CARDIOVASCULAR SYSTEM.

Previous sections have dealt with the development and assessment of this method of analysing the systemic arterial circulation. This section will consider changes in property values induced by common stresses on the system, as measured by the same method. All pressure responses discussed below are to square wave infusions of identical rate (for each set of experiments). The time marker shown on the tracings is at a one second interval.

(a) The effects of high and low CO₂ concentrations on the systemic arterial circulation:

Fig.66 refers to an experiment in which a rabbit was ventilated with a mixture of 10% CO₂ and 90% O₂ for three minutes. Analysis of the phase plane plot shows that this caused a considerable increase of the slope resistance of the animal (from .22 to > .30 mm Hg/ml.p.min.). The plot also shows that this was associated with an increased 'critical closing pressure', from 24 to 40 mm Hg. As a result of the increase in slope resistance, the time constant of the downgoing pressure curve increased from 580 msec. to 1250 msec. The extra oscillation at the beginning of the lower pressure tracing is almost certainly due to an unsolicited heart beat. This makes exact calculation of the slope resistance not possible as the total input into the system is not known. However, if the stroke

FIGURE 66

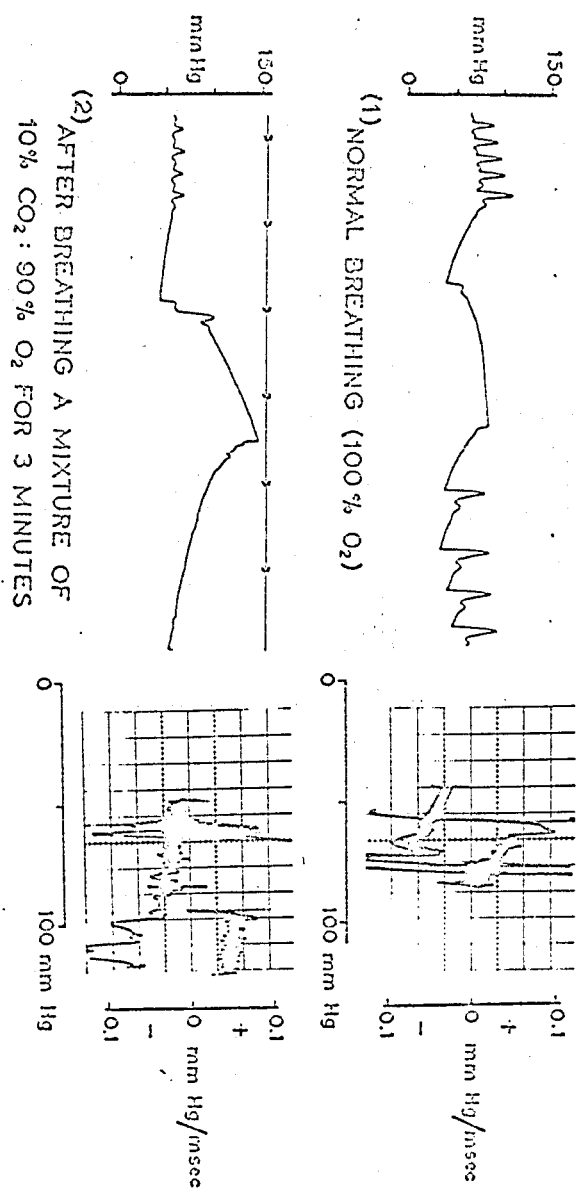
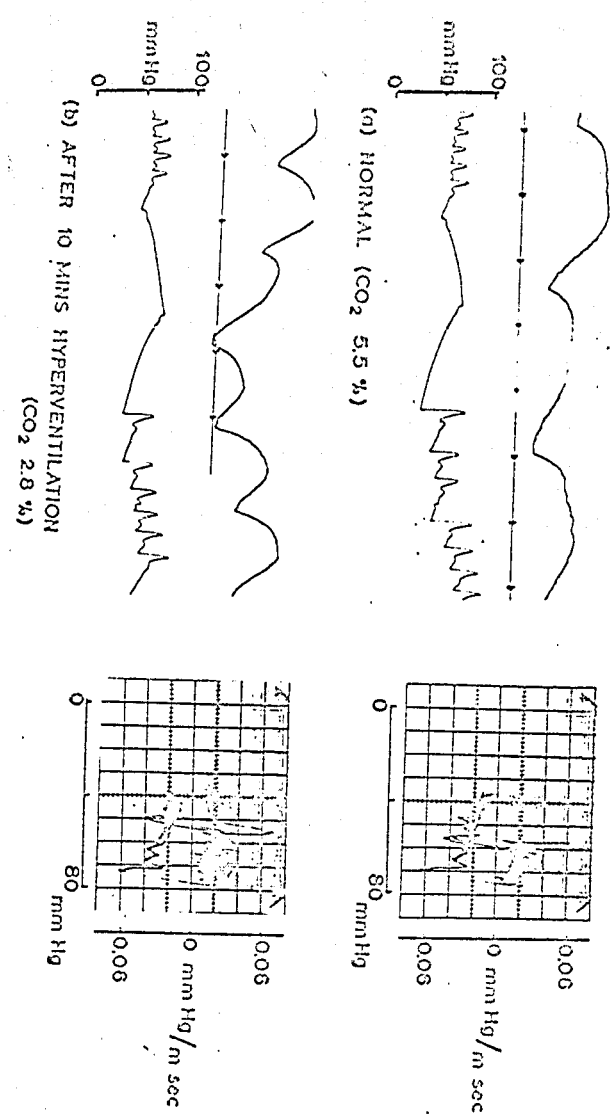
THE EFFECTS OF BREATHING A MIXTURE OF HIGH CO_2 CONCENTRATION

FIGURE 67

THE EFFECTS OF HYPERVENTILATION



volume is estimated to be 1.5 ml., the slope resistance still undergoes an increase to 0.30 units. Of interest is the fact that the second oscillation at the beginning of the lower tracing is much higher than the first (which is due to the square wave infusion). This indicates that the rate of cardiac acceleration is greater than the square wave infusion acceleration.

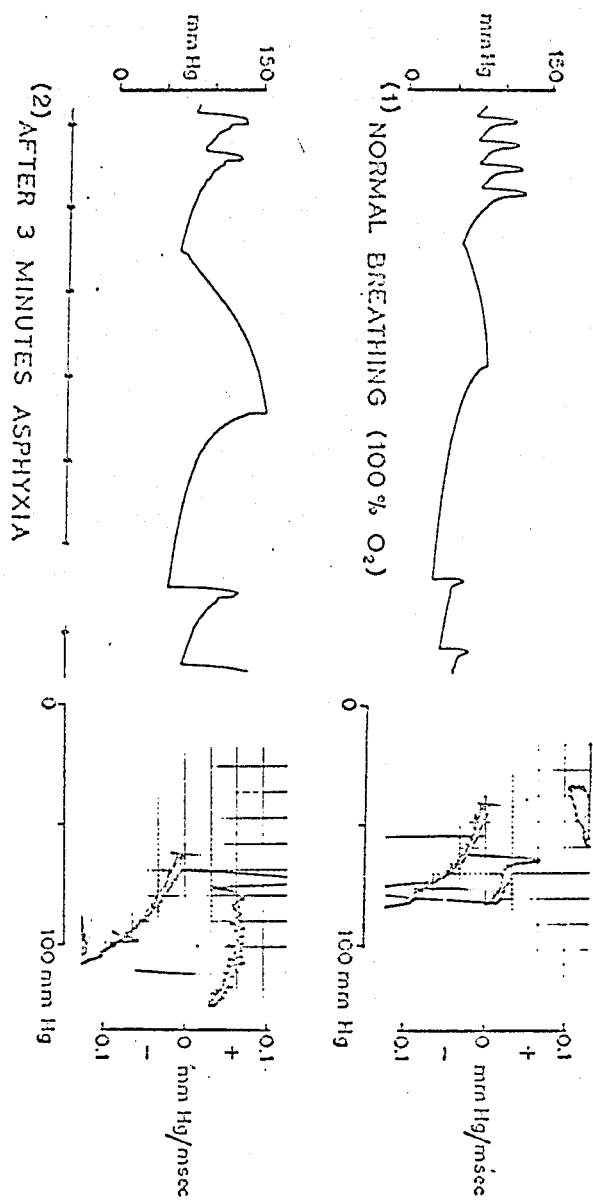
A low CO₂ concentration in the expired air was induced by hyperventilation at a rate of 40 - 50 breaths/min. for a period of 10 minutes, or so. The CO₂ content of the expired air was measured with a LBI. Bechman Medical Gas Analyser. In the experiment shown in Fig.67, this caused a fall in expired air CO₂ concentration from 5.5% to 2.8%. However, as can be seen from analysis of the phase plane plot, this had very little effect on the slope resistance, or 'critical closing pressure' of the animal. This experiment was repeated in three different rabbits with the same result.

(b) The effects of asphyxia on the systemic arterial circulation:

Fig.68 shows the effect of three minutes asphyxia. This was caused by clamping the inflow to the tracheal cannula. In the lower group of pictures, the animal is not in a constant state during the time of the square wave infusion. This is shown by the marked deviation from linearity of the positive phase plane plot. Now withstanding this, however, it can be seen that there is a marked increase

FIGURE 68

THE EFFECT OF ASPHYXIA



in slope resistance and some increase of the 'critical closing pressure' (from 39 to 52 mm Hg.). There is little change in systemic blood pressure under these circumstances, which suggests that the cardiac output is decreased.

(c) The effects of haemorrhage on the systemic arterial circulation:

Rabbits were subjected to sudden arterial haemorrhage by withdrawal of 15 to 20 ml of blood into a glass syringe attached to the infusion line in the right carotid artery. This volume was removed, over a period of 10 to 15 seconds, after 5 - 8 ml blood had already been removed to prime the square wave infusion apparatus.

A typical result is shown in Fig.69 . It can be seen that 30 seconds after removal of 20 ml of blood, there is a fall in critical closing pressure from 30 to 18 mm Hg. This is accompanied by a decrease in slope resistance from 0.15 to 0.11 mm Hg/ml.p.min. Upon returning the 20 ml of blood, these parameters return to their previous values (i.e.: 29 mm Hg and 0.15 mm Hg/ml.p.min.). Calculation of the chord resistance changes in this case yields a quite different pattern. Upon loss of the 20 ml of blood, chord resistance is calculated to increase from 0.29 to 0.51 mm Hg/ml.p.min. On returning the blood, this value falls to 0.30 mm Hg/ml.p.min. again. With such a significant 'critical closing pressure', this chord resistance pattern is readily understood by reference to

FIGURE 69

THE EFFECT OF SUDDEN HAEMORRHAGE

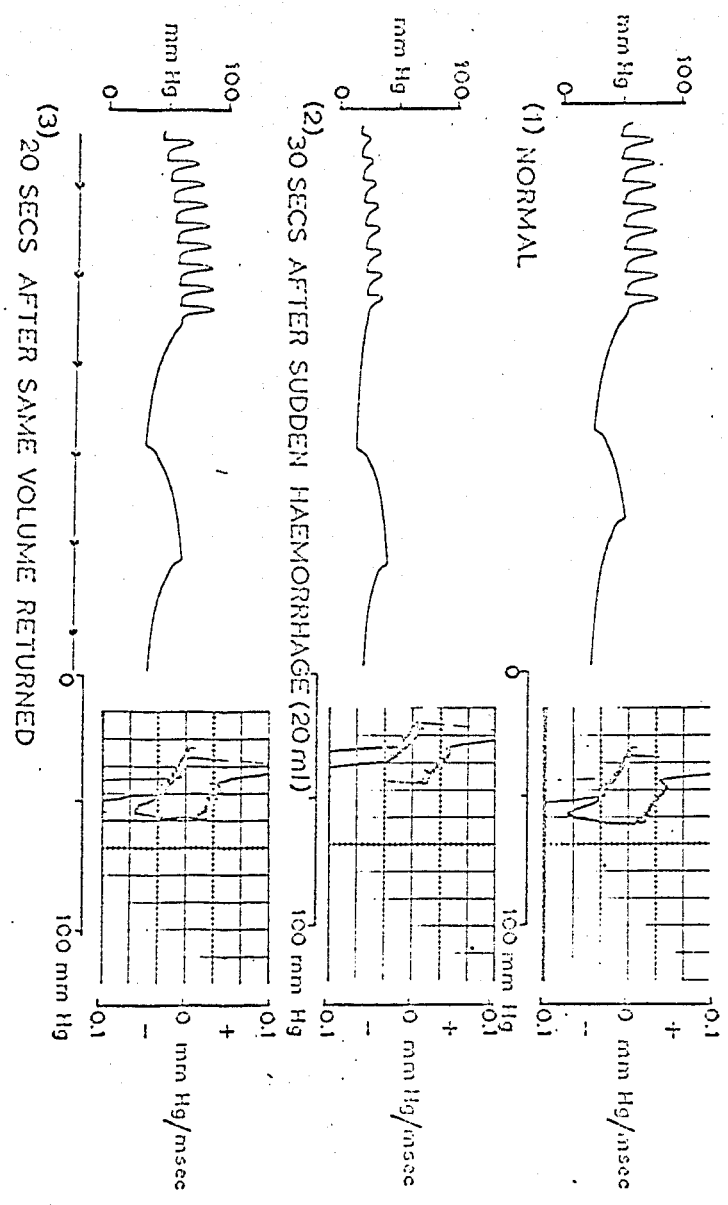


TABLE 14

The immediate effects of sudden heamorrhage

nt.	P	R _s	R _c	C _D	P*	
6.8	87	.22	.31	.047	26	10 ml. HAEM.*
	65	.19	.29	.060	22	
7.5	69	.16	.32	.070	34	25 ml. HAEM.
	59	.19	.34	.046	26	
7.2	86	.22	.37	.052	35	15 ml. HAEM. 15 ml. RETURNED
	54	.22	.48	.048	29	
	84	.24	.40	.054	34	
7.4	43	.10	.17	.060	18	21 ml. HAEM. 21 ml. RETURNED
	26	.08	.16	.060	13	
	43	.13	.23	.051	19	
7.6	50	.16	.28	.075	21	20 ml. HAEM. 20 ml. RETURNED
	22	.12	.20	.054	9	
	39	.13	.21	.092	15	
7.8	70	.17	.28	.062	28	20 ml. HAEM. 20 ml. RETURNED
	27	.12	.36		18	
	70	.14	.25	.073	31	
	63	.15	.29	.058	30	20 ml. HAEM. 20 ml. RETURNED
	23	.11	.51	.076	18	
	59	.15	.30	.057	29	
7.5	59	.18	.32	.048	26	20 ml. HAEM.
	25	.12	.23		12	
	28	.15	.32		15	
	52	.18	.33	.046	24	20 ml. RETURNED
	63	.16	.29	.051	23	
7.1	57	.15	.27	.057	25	10 ml. HAEM. 10 ml. RETURNED
	27	.14	.47		19	
	51	.16	.33	.063	26	

P = mean arterial pressure mm Hg

P* = critical closing pressure mm Hg

R_s = slope resistance mm Hg/ml.p.min.R_c = chord resistance mm Hg/ml.p.min.C_D = compliance calculated from down going pressure curve

nt = weight of animal in lbs.

* Precedes measurements of R_s, C_c, C_d and P* by 2-3 minutes in all cases

Fig. 2 . This is a further example of the ambiguities in interpretation of haemodynamic data that measurement of chord resistance (which is the common practice, particularly in regard to calculation of 'Total peripheral resistance') can cause.

This type of experiment was performed on 9 rabbits. The results from eight of them are shown in Table 14 . It can be seen that in only one case was sudden haemorrhage followed by an increase in slope resistance. It was followed by an increase in chord resistance in five cases. There was also an increase in chord resistance, without corresponding increase in slope resistance, in the experiment not shown (for reason of space) in Table 14. The linear correlation coefficient between R_s and R_c is calculated to be $r = + 0.55$ ($t = 3.6$, $p < .01$ that H_0 correct). The same coefficient between ΔR_s and ΔR_c is calculated to be $r = - 0.15$ ($p > .5$ that H_0 correct). These results show that there is no simple linear correlation between R_s and R_c .

Blood was normally returned to the animals within a period of three minutes, because of the marked hypotensive response which the manoeuvre often caused. However, in one experiment, in which the animal was bled 20 ml, blood was not returned for a period of eight minutes. After the initial drop in slope resistance and critical closing pressure, these values began to rise again towards their pre-haemorrhage level. This suggests that the early drop in slope resistance and critical closing pressure is only the first phase of the

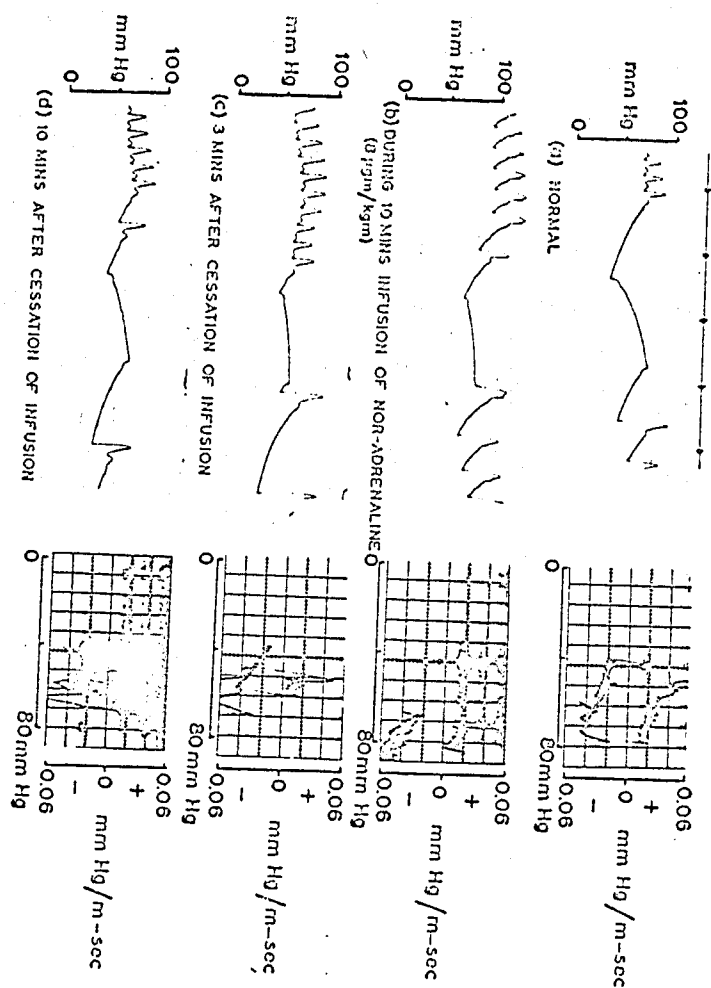
response of the animal to haemorrhage.

(d) The effects of nor-adrenalin infusion on the systemic arterial circulation:

Fig. 70 shows the effects of a ten minute infusion of nor-adrenaline, in a dose of 8 $\mu\text{gm/Kgm}$, into the femoral vein of a rabbit. The most marked effect was an increase of the critical closing pressure from 29 to 51 mm Hg. This was associated with a significant increase in mean blood pressure of the animal from 71 to 102 mm Hg. Three minutes after stopping the infusion, this critical closing pressure returned to normal. During the nor-adrenalin infusion, slope resistance decreased from 0.25 to 0.15 mm Hg/ml.p.min. Three minutes after stopping the infusion of the drug, slope resistance was still low at 0.16 mm Hg/ml.p.min. As 'critical closing pressure' of the vascular bed had now fallen to normal levels, the net effect was to decrease the chord resistance level to below normal. This effect could act as a mechanism for development of the well-known phenomenon of post nor-adrenalin infusion hypotension (see, for example, MAZURKIEWICZ 1967). Ten minutes after stopping the infusion, all parameters returned to normal. This same general pattern was repeated on giving a second infusion to the same rabbit. These results are summarised in the table below.

FIGURE 70

THE EFFECTS OF NOR-ADRENALINE INFUSION



R_s	R_C	p^+	
.25	.39	29	
.15	.39	51	During N-A infusion
.16	.29	27	3 mins. after N-A infusion
.22	.37	32	10 mins. after N-A infusion

An attempt was made to repeat this experiment on two other rabbits, but a sufficiently long heart stoppage could not be obtained, presumably because of the nor-adrenalin effects on cardiac irritability.

(e) The effects on property values in the systemic arterial circulation, of long term cholesterol feeding.

Twenty-four, 6 week old, 2 lb., male rabbits, were divided equally amongst a control group, and a group that was fed 3% cholesterol. The cholesterol (NBC Corp., Cleveland, Ohio) was thoroughly mixed with the rabbit chow (Purina, Montreal). It was not found necessary to dissolve the cholesterol in ether. Experiments were performed on both these groups after a period of feeding of $5\frac{1}{2}$ to 7 months. Control and cholesterol fed rabbits were alternated as the experimental animal during this time. Cholesterol fed animals were even more fickle to anaesthesia than their normal brethren, and it was only possible to obtain results from 7 of them.

A typical phase plane plot of an animal fed 3% cholesterol for a period of 6 months is shown in Fig. 71 . Comparison with that from a normal animal (Fig.72) shows that there is a marked deviation from linearity on the negative phase plane plot. This occurred in 5 out of the 7 cholesterol fed animals. As steady-state pressure-flow plots in these animals were linear, the assumption was made that the deviations from linearity in these phase plane plots were a function of the compliance element in the vascular bed. A tangent to the curve at any particular pressure level would give the time constant of the system at that point, and from this the compliance value could be calculated in the usual way. Using this method, it was found that in a pressure range from 20 to 80 mm Hg. there was a significant increase in the compliance value (during vessel deflation) in the cholesterol fed animals. Results are shown in Table 15 . This also shows that there was a significant increase in compliance value during inflation of the vessel over a pressure range of 60 to 100 mm Hg. Two static compliance studies were performed on 50% segments of the aortic length, over a pressure range of 0 to 100 mm Hg. These specimens had a slow leak, but were suggestive of an increased compliance value in the excised specimen. A paper by NICHOL (1955) gave good corroborative evidence for these findings in the excised thoracic aortas of cholesterol fed rabbits, over a range of 0 to 70 mm Hg.

There was no significant difference in the measured pulse wave velocity of these two groups. There was a significant difference of

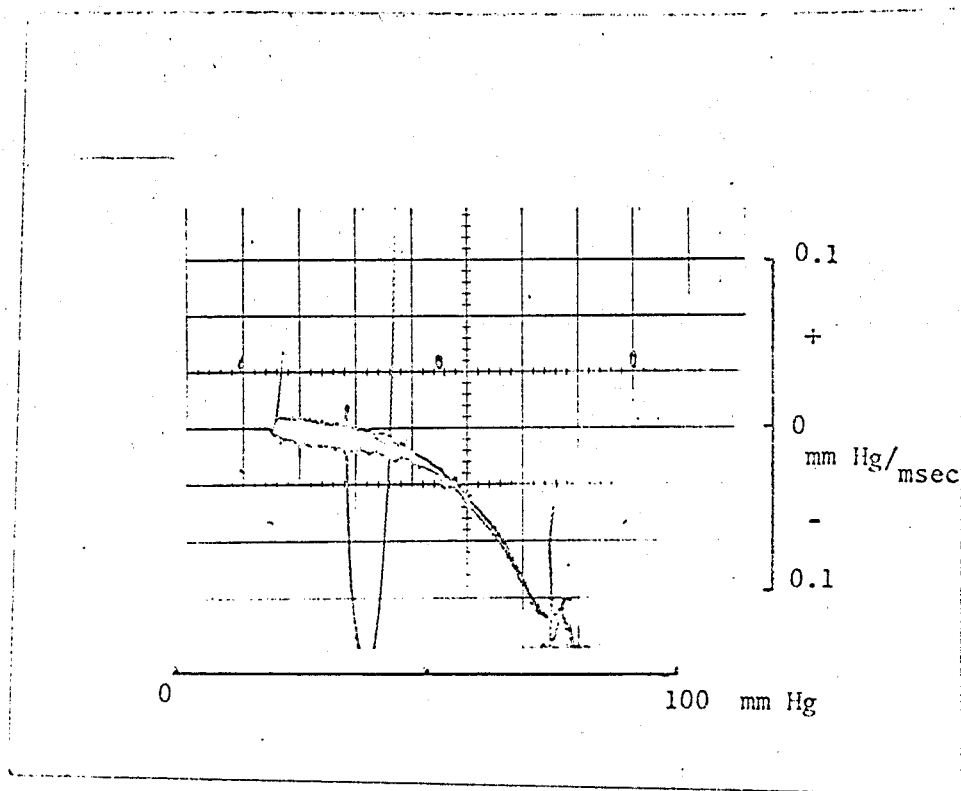


FIGURE 71: Oscilloscope phase plane plot from a cholesterol-fed animal.

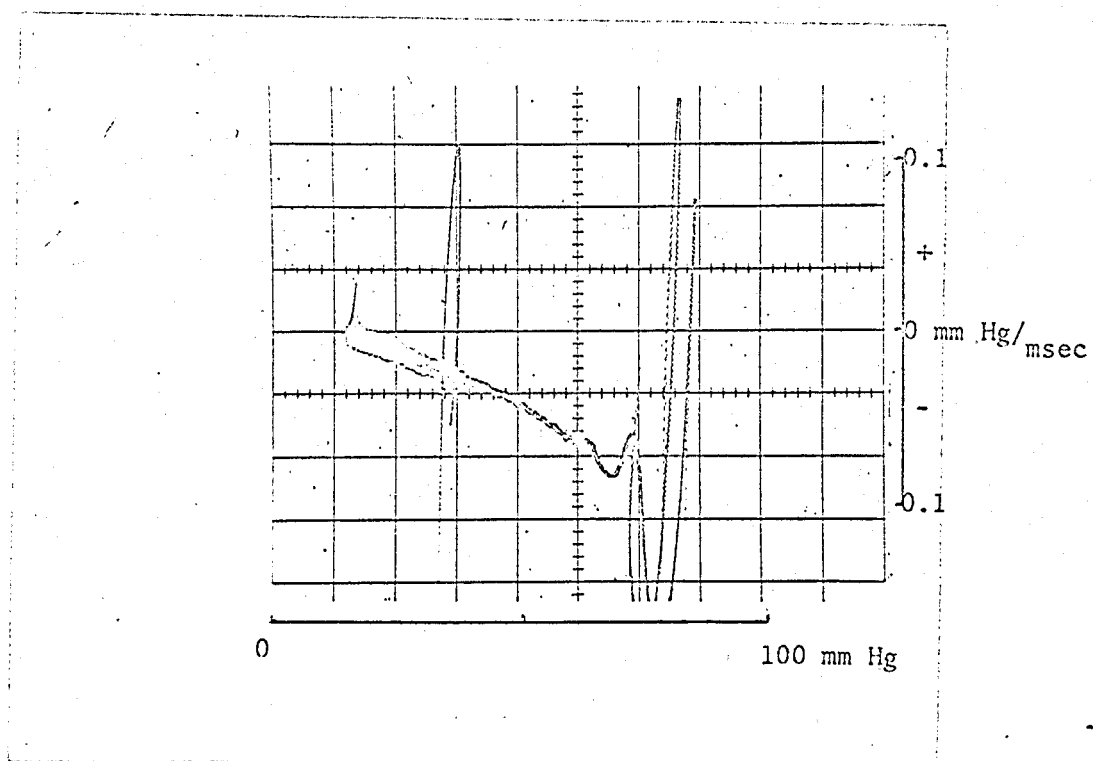


FIGURE 72: Oscilloscope phase plane plot from a normal animal.

TABLE 15

Comparison of control and cholesterol fed animals.

Wt.	R _s	C _D	C _U	Serum Cholesterol mgms %	Pulse Wave Velocity Metres/sec
7.1	.15	.058	.034	120	5.2
7.5	.16	.050	.037	126	5.2
7.75	.14	.071	.045	59	5.2
6.4	.22	.052	.026	41	5.0
6.8	.22	.054	.026	37	-
7.5	.17	.066	.047	26	4.8
7.5	.21	.065	.045	36	6.4

$$\bar{C}_U = .037 \pm .003$$

$$\bar{C}_D = .059 \pm .003$$

$$\bar{R}_s = .18 \pm .01$$

Control Animals (A)

Wt.	R _s	C _D	C _U	Serum Cholesterol mgms %	Pulse Wave Velocity Metres/sec
7.45	.11	.088	.062	595	5.1
7.6	.14	.071	.051	318	6.2
7.2	.21	.077	.065	750	6.4
7.6	.14	.078	.095	611	5.3
7.4	.09	.073	.071	566	5.3
7.1	.14	.096	-	735	5.3
7.6	.12	.054	.095	680	5.2

$$\bar{C}_U = .073 \pm .007$$

$$\bar{C}_D = .076 \pm .005$$

$$\bar{R}_s = .14 \pm .01$$

Cholesterol Fed Animals (B)

Statistical Inference Between (A) and (B)

$$\bar{C}_U : r = 4.4 \quad p < .01$$

$$\bar{C}_D : r = 2.84 \quad p > .01 < .02$$

$$\bar{R}_s : r = 2.35 \quad p < .05 > .02$$



FIGURE 13: Control (left), and cholesterol-fed rabbit aorta.



-FIGURE 74: Photomicrograph of aorta from a cholesterol-fed rabbit, showing destruction of the elastic lamina.

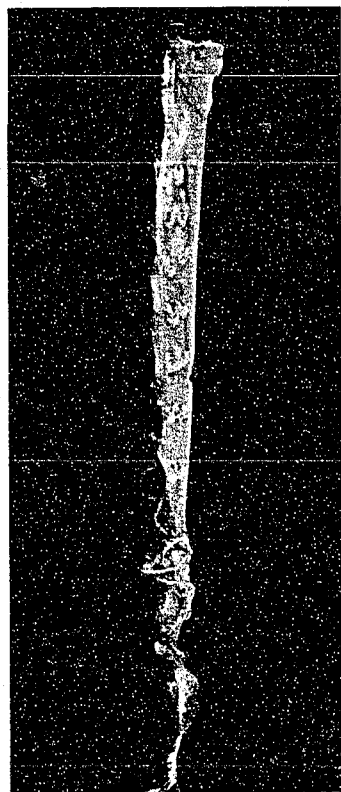


FIGURE 75: Incidental finding, in a cholesterol-fed rabbit, showing remarkable localisation of the atheromatous process to the points of intercostal branching.

the serum cholesterol in the two groups. The mean value for the control group was 63 mgms %: for the cholesterol fed group it was 607 mgms %. Fig.73 shows the macroscopic difference in appearance of the intima in the two groups. All cholesterol fed rabbits showed the same gross thickening of the intima as that to the right of Fig. 73 . Microscopic examination, Fig.74 , shows the destruction of the elastic lamina of the aorta, which probably accounts for the increased compliance values found. Fig.75 is shown, because of the regular pattern of distribution of cholesterol deposits about the branching points of the intercostal vessels. This incidental finding is recorded here because it is suggestive that local haemodynamic conditions can be important in the genesis of this disease.

DISCUSSION

This approach to analysis of the circulatory system has, to the writers knowledge, only been used once before. In the study of PETERSON (1954), a number of rapid square wave infusions were given in between the normal heart beats of a dog (see Fig. 6). Pressure was monitored in the region of the ascending aorta by a catheter introduced through the femoral artery. Although some calculations were performed concerning the height of the 'acceleration transient' (see later), the infusions given were generally not of long enough duration to perform the type of analysis undertaken in this study. Cumulative infusions of saline were given and velocity of blood flow was measured by high speed photography.

Apart from Peterson's study, there has been little attempt to study the circulation in terms of a transient analysis, as shown here. In 1960, McDonald wrote in his monograph, in reference to Peterson's experiments, that "the technique of using an artificial injection of known parameters is clearly an important advance, but difficulties in interpreting Peterson's results emphasize the difficulties inherent in the analysis of transients". This investigation, unwittingly at first, has been an attempt to enlarge and develop further these ideas.

The mechanical system finally developed to give and monitor the square wave infusion of blood worked well. It used a different principle than that of Peterson. One advantage of the present

technique is that the animals own blood was used as the infusion medium in alternate withdrawal-infusion cycles. In Peterson's experiments, cumulative infusions of saline were given which might lead to undesirable viscosity and blood volume effects. Furthermore, monitoring of infusion rates by a linear velocity transducer is probably more convenient than the photographic method which Peterson used.

One source of set-backs in this investigation was that rabbit was chosen as the experimental animal. It was frequently difficult to keep them in good condition for the 2 to 3 hours or so of the experiment. This accounts for the generally low blood pressures throughout the study. In any future experiments, small dogs would probably be more suitable because of their better tolerance to anaesthesia, and the fact that vagus nerve stimulation can produce a reasonably long period of cardiac arrest (EADIE and McCRAE 1934). The cat also may be a very suitable animal, provided a longer period of cardiac arrest can be obtained.

A major development in this technique has been the attempt to isolate the system from disturbing influences during the time of testing. Stimulation of the right vagus nerve proved to be a satisfactory method for nullifying the effects of the heart beat on the system. Originally, it was felt to be desirable to avoid this, in view of the fact that stimulation might have an effect on the vascular bed, as other parasympathetic nerves (chorda tympani, lingual nerve, pelvic

visceral nerves) are well known to contain vasodilator fibres (LOVATT EVANS 1956). However, good evidence is provided by the double infusion pulse of Fig. 51 and other functions already discussed, that the system is in a steady-state during the time of testing. Provided that the central end of the nerve is transected (and provided the sympathetic chain not included) vagal stimulation is a suitable method for causing transient cardiac arrest.

Effects associated with the respiratory activity of the animal proved to have the most potent disturbing influence on the system. It is well known that on increasing intra-thoracic pressure, by means of a Valsalva manoeuvre, there is an immediate rise in blood pressure (SHARPEY-SCHAFER 1965) which is approximately proportional to the rise in intra-thoracic pressure. Similar effects were noted with positive pressure ventilation in these animals. As this effect occurs immediately (Fig. 46), a mechanical cause is most likely. With an increased intra-thoracic pressure, there is a decreased effective compliance of the vessels. This results in a greater proportion of the total flow into the system occurring in an axial direction. This then has the effect of raising arterial blood pressure. Further evidence that this is due to a mechanical effect comes from the fact that it is abolished on opening the thorax widely.

This effect was circumvented in the present technique by stopping ventilation for a period of 2 to 3 seconds to allow the infusion to be given, whilst the rabbit was kept under neuro-muscular blockade. As

stopping the positive pressure ventilation brought its own problems, in any future investigation, the technique of choice would probably be to open the thorax widely at the sides (rather than through the sternum) with self-retaining retractors. There would then be no need to stop ventilation and the giving of neuro-muscular drugs could be avoided. Opening of the abdominal cavity to equalise pressures there, would probably not be necessary unless violent respiratory movements were being made.

Giving the rabbit positive-pressure ventilation in a closed thorax had a variable hypotensive effect. The presumed mechanism of this is that venous return is reduced to the right side of the heart by the increased intra-thoracic pressure. This results in a diminished inflow into the left side of the heart and ultimately in a reduced stroke volume — hence hypotension. On stopping the ventilation, as in Fig. 48, there is a fluctuant rise in blood pressure before it finally settles out at its normal level. This corresponds to the 'overshoot' of blood pressure seen on releasing a Valsalva manoeuvre (SHARPEY-SCHAFER 1965). The latter has been explained as being due to both increases in stroke volume and vasoconstriction (SHARPEY-SCHAFER 1955). It can clearly be seen in Fig. 48 that the initial overshoot of blood pressure on stopping positive pressure ventilation is terminated by a fall in slope resistance. This most probably results from a baroreceptor reflex. Fig. 49 also shows, on stopping ventilation, the presence of the so-called Traube waves, which are said to be due to oscillations of

the vasomotor centre at the rhythm of the respiratory centre (see DORNHURST et al 1952). However, coincident changes in stroke volume were not monitored in the above paper, and there was no evidence in this investigation to suggest a background of undulating vasomotor activity at such a frequency.

Other disturbing influences on the system (such as the 'myogenic reflex' of Bayliss, see FOLKOW 1952) did not manifest themselves within the immediate period of testing. This was assessed by the relationship of two successive negative phase plane plots. If these were superimposed one on top of the other (as in Fig. 44), then was good evidence that the system was in a steady-state. Provided care was taken to avoid the respiratory complications discussed, this was usually the case.

Thus, after a period of development, it was found that there were no insurmountable barriers to application of the standard engineering technique of transient analysis to the rabbit systemic arterial circulation. The largest problems were (1) to design equipment capable of giving a repeated square wave infusion of blood and (2) to isolate the system under test from disturbing influences which, it turned out, were those principally linked to respiratory activity. As the total operation took approximately two seconds (and could be designed to take less, depending on the timing and rate of the square wave infusion), time dependence was a relatively unimportant factor.

The greatest defect in the technique lay in analysis of the phase plane plots. The latter proved to be a very valuable way of

transforming the primary pressure response, but the extrapolations of these plots often required were sometimes difficult to define. This problem could be eliminated by use of a magnetic tape recorder and an analogue-to-digital computer. Best fit programs could be designed and an entirely objective assessment made of the pressure response. It would be a simple matter of further programming to provide direct read-outs for all the parameters, including cardiac output, calculable from this response. In this manner, maximum accuracy could be achieved with minimum effort.

Application of the general technique has attempted to answer some of the questions raised by the literature review on page .

(a) Resistance:

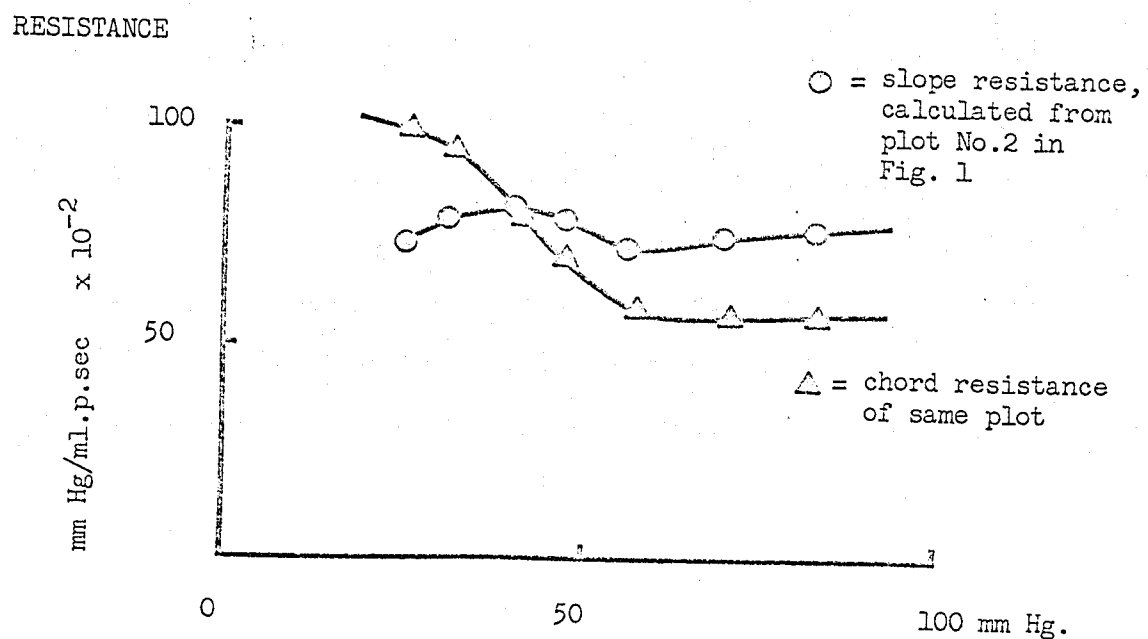
Both the steady and transient state studies have shown that pressure-flow relationships across the whole systemic arterial circulation are more or less linear under pressures of 100 mm Hg. Although there have been surprisingly few attempts to investigate this relationship directly, the results of the many studies on pulsatile blood flow, based on Womersley's essentially linear equations (e.g.: (15)), have shown this to be a reasonable approximation (see, for example, the study of DICK et 1968). Whilst much emphasis is often placed on the non-linearities between pressure and flow (see, for example, PETERSON 1960) that undoubtedly occur over a wide range of

pressures, within smaller, yet still useful limits, a linearity postulate remains reasonably valid.

This investigation has supplied abundant evidence that a 'critical closing pressure' of significant magnitude occurs across the whole systemic arterial circulation. This modifies the effective pressure gradient across the system, as PERMUTT and RILEY (1963) have shown, and requires the introduction of terms such as chord resistance and slope resistance to avoid ambiguities in interpretation and communication. The reader is referred back to Fig. 2 which demonstrates the difficulties that may arise in interpretation of chord resistance values. Slope resistance values, as this investigation has shown, can be of the order of half the chord resistance values. Moreover, and most importantly, they can vary in opposite directions to one another. Most haemodynamic studies are interpreted in terms of chord resistance. Total peripheral resistance is virtually always expressed as a chord resistance. However, this investigation has shown that these values can be totally misleading as an index of the vascular tone of the small vessels.

Physiologists earlier in this century expressed total peripheral resistance in terms of a kind of slope resistance, in which the critical closing pressure was considered to have a fixed value of 20 mm Hg. (BAZETT et al 1935, BROEMSER and RANKE 1930). This practice however, lapsed into disuse before the last war. The tendency at present, even when the critical closing pressure is known, is to ignore

it and calculate chord resistances. An example of this is shown in Fig. 1 where a plot of chord resistance vs. pressure has been made, (NICHOL and BURTON 1951). This is very misleading. If the primary pressure flow data are replotted in terms of slope resistance, the following graph is obtained.



This gives a truer interpretation of the situation in terms of the vessel tone, which it can be seen, has changed relatively little. It has been difficult to express pressure-flow relations across the whole arterial circulation in terms of slope resistance because of inadequate knowledge of the critical closing pressures. It is one of the advantages of the technique described in this investigation, that it provides a rapid, simple method for assessment of slope resistance across

the whole arterial circulation.

The study of the effects of nor-adrenalin infusion in Fig. 70 , has shown a situation in which a rise in critical closing pressure (CCP) has been associated with a fall in slope resistance. This suggests that the vessels primarily responsible for the slope resistance (presumably, the arterioles) are not, at least in this case, responsible for the critical closing pressure phenomenon. If that were the case, one would expect a close positive correlation between slope resistance and CCP. Table 13 shows that while this commonly does occur, it is not always so. In the paper of NICHOL, BURTON et al 1951, they show that there is little change in CCP until the reduction in flow across the rabbit ear is greater than 70% of its value at maximum vasodilation. There is then a rapid increase of CCP with further reductions in flow (caused by a variety of vasoconstrictive agents). This evidence suggests that the vessels responsible for CCP are different from those determining slope resistance, as the author's of the paper initially point out. However, they then proceed to transform the data and find a highly positive linear correlation coefficient between CCP and the logarithm of the reciprocal of the percentage reduction in flow. The conclusion is then drawn that the vessels determining CCP and vascular resistance are mostly the same. It can be argued, however, that the data prior to this transformation provided a more accurate reflection of the situation, and did not entirely support the author's later conclusion. In a further

paper from the same laboratory, GIRLING (1952), showed that increasing frequencies of electrical stimulation to the sympathetic supply of the rabbit ear, caused an increasing CCP until a critical frequency of 30 cps. was reached. At frequencies greater than this, CCP abruptly returned to its no-stimulation level (presumably from refractoriness), but, interestingly, slope resistance continued to increase until higher frequency levels of stimulation were reached.

The simplest explanation of all these results is to assume that the vessels responsible for vascular tone are not necessarily the same as the ones responsible for the phenomenon of CCP. This is the conclusion, in essence, reached by FOLKOW and LOFVING (1957), who suggest that the activities of the pre-capillary sphincters are primarily responsible for CCP. The muscular, thick-walled arterials, which BURTON (1951) admits may have difficulty in complete closing for reasons of bulk alone, are then presumably responsible for the slope resistance of the animal.

Recognition that the functions of slope resistance and CCP may reside in different types of vessels is not entirely an academic matter. It may have some bearing on the different effects of adrenalin and nor-adrenalin on the circulation. Fig. 70 suggests that nor-adrenalin infusion has had a dilator action on the muscular arterioles, (which principally control the slope resistance) yet a constrictive effect on the vessels which control CCP. These latter vessels may indeed be the precapillary sphincters, which have been observed

microscopically to undergo complete closure in an all-or-nothing fashion (CHAMBERS and ZWEIFACH 1944). The activity of these sphincters are, in part, mediated by nervous action as NICOLL and WEBB (1955) found in direct microscopical studies on the bats' wing. Under these circumstances, the effect of catecholamines on the vascular bed could be the net result of both nervous and direct smooth muscle action. It could be postulated, for example, that all three primary substances (nor-adrenalin, adrenalin and isoprenaline) have a direct dilator action on the smooth muscle of the arteriolar wall, but that nor-adrenalin has a more pronounced effect in stimulating the nervous activity of the network controlling the pre-capillary sphincters. The net effect of the nor-adrenaline would then be to cause an increase in chord resistance. It is of interest to note that NICOLL and WEBB (1950), in testing the direct effects of nor-adrenalin and adrenalin on the bat wing, found that both these substances caused an increase in the frequency and strength of contraction of the pre-capillary sphincters. They were not able to estimate, however, which was the more potent of the two. They also found that breathing a mixture of 90% oxygen and 10% carbon dioxide caused a similar increase in activity of the sphincters. In this context, note the increased CCP of Fig. 66.

This scheme, is of course, quite conjectural, but evidence could be provided for it, if it was found experimentally that all three primary catecholamines caused a decrease in slope resistance, yet nor-adrenalin caused a much greater increase in CCP (as suggested by Fig. 70).

The nervous network which controls CCP, is presumed to be more sensitive to stimulation by nor-adrenalin than by adrenalin. This is somewhat supported by the experimental results which show that normal doses of adrenalin have a vaso-dilator effect, but that higher ones, particularly when given intra-arterially, have a vaso-constrictor effect (YUMANS et al 1955, BURN 1967).

Perhaps the single most important finding in this investigation has been the lack of correlation between slope and chord resistance. The experiments on the immediate effects of haemorrhage (see p.288). show a net dilation of the small vessels as a first response, which would not have been recognized by the conventional methods of calculation. A reassessment of the body response to haemorrhage and shock, considered in this light, could provide a more penetrating insight into these processes.

(b) Compliance

Lack of a good index of the elastic properties of blood vessels in the living animal has been a serious barrier to the development of physical theories for the circulation (MCDONALD 1960). The only methods commonly in use at present (measurement in excised tissues, or from pulse-wave velocity measurement in the living animal) are subject to difficulties in interpretation as previously discussed (p. 50). The square wave infusion technique developed

here presents a direct way of assessing compliance in the living animal.

Results of the phase-plane plots are suggestive that a hysteresis phenomenon is occurring. This fits well with the data obtained by BERGEL (1961), REMINGTON (1967) and others. According to Remington, this is not entirely a rate dependent phenomenon and therefore, is not strictly represented by a combination of capacitor and resistor in series as on p. 28Q. However, the latter is a useful approximation to the real situation. If the hysteresis effect is marked, then it will disturb the linearity of the whole system, but this did not appear to be the case in rabbits.

Results indicate that the compliance value in an individual animal can change significantly during the course of an experiment. While the investigation was not designed to assess this, it is suggestive that smooth muscle activity can affect the elastic properties of vessels, a long debated question (REMINGTON 1963). This finding would support the evidence of ALEXANDER (1954), COPE (1961) and WIGGERS and WEGRIA (1938).

The results of the long term cholesterol feeding experiments were similar to those found by NICHOL and BURTON (1955). The latter found, histologically (as in this study) destruction of the internal elastic lamina and a rise in the compliance value of the larger vessels in the lower pressure range. Cholesterol feeding is often thought to give rise to 'hardening of the arteries', but these

studies show that, in the rabbit at least, this is not the initial process. Hardening may occur later as the result of subsequent calcification.

Fig 75 shows an interesting finding. It has long been known by pathologists, from dissection of human cadavers, that atheromatous plaques tend to occur particularly about the branching points of the aorta (see MUIR, 1964). While rabbit and human atheromatous disease are not quite identical, Fig. 75, with its high and uniform localization of the disease process to the intercostal branching points, presents further evidence for this view point. It is highly suggestive that local haemodynamic factors are important in the genesis of this disease.

C. Inertance

There is virtually no attempt at quantitation of this property available in the literature. (FRANK 1905) was the first to point out its theoretical importance, but because of the unknown nature of its magnitude, the inertance factor was generally ignored in attempts to calculate stroke volume from the pulse pressure, an endeavour of considerable interest in the 1930's (e.g. WEZLER & BOGER). Peterson's studies (1954) were able to give a practical demonstration of the importance of this factor. In the present study, the height of the initial oscillation on the curve (equivalent to Peterson's acceleration transient) was directly

proportional to the speed of acceleration of the blood (see Fig. 58).

No measurements were made in this investigation of the pressure in the ascending aorta. For a correct measurement of the inertance presented by blood in the systemic circulation to the heart, this is necessary and one would expect the height of the initial oscillation to be much higher. The average figure presented, therefore, of 29.4 gm cm^{-4} for the inertance is too low. However, it does provide an approximate order of magnitude value useful for insertion in a simple model.

2. COMPOSITE PHYSICAL BEHAVIOUR OF THE SYSTEMIC ARTERIAL CIRCULATION

The 2nd half of the literature review was concerned with the composite physical behaviour of the systemic arterial circulation. In essence the goal here is to have such a complete understanding of the behaviour of the system that an analogue model can be built which will produce exactly the response of the living circulation. Beginning with the proposition of the classical 'Windkessel' theory by Otto Frank, in 1899, knowledge in this area has gradually evolved so that many experienced physiologists and engineers now believe that the circulatory system must be represented by a highly complex model. Typical of these are the electrical models developed by NODERGRAAF 1962, VAN TWEEL 1957, and WARNER 1959. These contain a large number of sections, basically arranged in a transmission line pattern as originally proposed by LANOES (1949). There is

good experimental evidence to support the transmission line hypothesis (REMINGTON, LAWTON, 1960) in that physical properties have been found to be distributed in the systemic circulation (BERGEL 1961). What place, then, has the rather simple model proposed on p. 280?

The answer lies in the rather restricted statement that the model on p. 280 adequately represents, in the rabbit, the response to a step or square wave function. There is good experimental evidence for this in the preceding pages. Calculations of cardiac output based on the above model give a correlation coefficient of 0.8 with those determined by the standard Fick method. The model is essentially that ultimately proposed by Frank with the addition of the resistance (R_1) to account for the hysteresis effect, and the Zenner diode with a breakdown voltage, whose importance has previously been discussed. As the imposed function is not periodic, the analytical problems related to wave reflection are avoided, and the model is accurate within the confines of its purpose. It is only when one is studying pulsatile blood flow (which admittedly, is the natural function) that a more complex model is required. The latter, however, by the very nature of their complexity, are difficult to build. There is no good experimental method for determining exactly how the physical properties of resistance, compliance and inertance should be distributed along the 'transmission line'. These complex models are built by empirical variation of the in-

dividual property values until the performance of the model as a whole matches that in the living animal. With increasing complexity there is an increasing number of 'correct' empirical models. They are generally built about the mathematical theory of pulsatile flow in an elastic tube (WOMERSLEY 1955). Whilst only accurate within restricted circumstances, the simple model proposed here allows the values of all of its individual components to be calculated. Using such a simple model, the effects of a variety of influences (e.g. drugs, the effects of breathing various gas mixtures, haemorrhage and shock) on total peripheral resistance and compliance, can be studied. The more complex models in current use are generally not so tractable.

The technique of imposing a square wave function on the circulation has not been widely used before. The preceding chapters have demonstrated some of its applications. In concluding this thesis, several further possibilities, as yet untested, suggest themselves.

It has already been demonstrated (see Fig. 32) that infusion of the blood into the circulation at a rate of 2 to 3 times that of the normal cardiac output will cause an isovolumic contraction of the left ventricle. Under these circumstances, measurement of the intra-ventricular pressure can lead to calculation of an index of contractility for the left side of the heart (SONNENBLICK 1966).

The high speed infusion could be timed to cover only one heart beat, so that pulmonary oedema would be avoided. This then raises the possibility for measurement of cardiac contractility, cardiac output, resistance, compliance, inertance and critical closing pressure within a period of a few seconds by giving 2 infusions, one of which is at a higher than normal rate to cause isovolumic contraction. Such a technique might be very useful in the elucidation of shock mechanisms, where it is important to differentiate between cardiogenic and peripheral elements.

Furthermore, if the accuracy of the phase plane extrapolations can be improved, it may be possible to breakdown the total peripheral resistance measurement (TPR) into several vascular segments. For example, following a TPR measurement the coeliac and mesenteric arteries might be clamped and a 'TPR' measurement repeated. The difference between the two would allow calculation of the contribution of the splanchnic bed to the total resistance. In this fashion, distribution of blood flow to the various vascular beds in a variety of circumstances, could be studied. Infusion at a high rate into the venous side of the systemic circulation with the heart temporarily arrested, in the presence of positive intrathoracic or intra pulmonary pressure (or blockage of the R atrium with an inflatable balloon) would probably allow some estimate of venous compliance to be made.

The only absolute requirement for analysing the circulatory response to a square wave infusion as outlined in this thesis, is that the circulation be in a steady state during the time of testing. Results have shown the rabbit systemic circulation to be adequately linear over the pressure range 30 - 100 mm Hg, except when diseased by the feeding of cholesterol. The following possibility exists, however, for the analysis of non-linear systems.

If pressure-flow relations are linear, but pressure-volume relations are not, then a non-linear phase plane plot will be obtained. However, at any one particular level of pressure (P_i), the compliance can be considered to have a particular value, C_i . This value can be obtained from the slope of the instantaneous plot of $P / \frac{dP}{dt}$ i.e. the slope of the tangent to the curve at the point where P equals (P_i). By taking a number of tangents to the phase plane plot, the non-linear pressure volume relationship can be evaluated.

If both pressure-volume and pressure-flow relationships are non-linear, as undoubtedly they are if a wide enough pressure range is considered, then it is difficult to establish them from a single square wave infusion. However, if 2 or 3 sequential infusions are given at different, but reproducible rates, then from the steady state pressures reached over the required range of flow rates, the non-linear pressure-flow relationship can be established.

Resistance at any one level of pressure (R_i) can then be determined from the tangent to the pressure-flow curve at that point. Using the R_i value so obtained, a value for compliance at that level of pressure (C_i) could be calculated from the tangent to the phase plane plot as previously described. In this somewhat laborious manner, almost certainly requiring a degree of a computerization, non-linear systems could be analysed by the square wave infusion technique.

The next step which this writer would like to take, would be the application of the technique to a more inherently stable animal than the rabbit, e.g. dog, or possibly, cat. The use of a magnetic tape recorder would allow analysis of the phase plane plots to be made in a wholly objective fashion. Ultimate application of this relatively simple but informative method to man will probably depend on finding a safe method of causing transient cardiac arrest. A pacemaker which provides paired electrical stimuli may well provide a solution.

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APPENDIX

Equations:

$$(1) \dots\dots\dots \frac{dQ}{dP} = C$$

$$(2) \dots\dots\dots \frac{dQ}{dt} = \frac{P}{R}$$

$$(3) \dots\dots\dots \frac{dP}{P} = \frac{-dt}{RC}$$

$$(4) \dots\dots\dots \log_e P + K = \frac{-t}{RC}$$

$$(5) \dots\dots\dots \log_e \frac{(P)}{P_0} = \frac{-t}{RC}$$

$$(6) \dots\dots\dots P = P_0 e^{-t/RC}$$

$$(7) \dots\dots\dots F = f_R + f_C$$

$$(8) \dots\dots\dots F = P \cdot \frac{1}{R} + C \cdot dP/dt$$

$$(9) \dots\dots\dots P \cdot \frac{1}{R} = -C \cdot dP/dt$$

$$(10) \dots\dots\dots \frac{dQ}{dt} = \frac{(P - P^+)}{R}$$

$$(11) \dots\dots\dots \log_e \frac{(P - P^+)}{(P_0 - P^+)} = -t/RC$$

$$(12) \dots\dots\dots P = (P_0 - P^+)e^{-t/RC} + P^+$$

$$(13) \dots\dots\dots P = (P_0 - P_{ss}^+)e^{-t/RC} + P_{ss}^+$$

$$(14) \dots\dots\dots \omega = \frac{P_0 P(2) - P(1)^2}{P_0 + P(2) - 2P(1)}$$

$$(15) \dots\dots\dots Q = \frac{\pi R^4}{\mu} \cdot \frac{M}{\alpha^2} \cdot M \sin (\omega t - \phi + \Sigma)$$

$$(16) \dots \dots Q = \frac{\pi R^4}{\mu} \cdot \frac{1}{8} \cdot \frac{P_1 - P_2}{l}$$

$$(17) \dots \dots (P - P^+) \cdot \frac{1}{R} = -C \cdot dP/dt$$

$$(18) \dots \dots F = (P - P^+) \cdot \frac{1}{R} + C \cdot dP/dt$$

$$(19) \dots \dots F = (P - P_{ss}^+) \frac{1}{R}$$

$$(20) \dots \dots f_R = (P - P^+) \cdot \frac{1}{R}$$

$$(21) \dots \dots f_C = C \cdot dP/dt$$

$$(22) \dots \dots \frac{(P_1 - P^+)}{f_{R1}} = \frac{(P_2 - P^+)}{f_{R2}}$$

$$(23) \dots \dots \frac{(P_1 - P^+)}{aF_1} = \frac{(P_2 - P^+)}{aF_2}$$

$$(24) \dots \dots P_{ss} = \frac{P_1 \cdot P_3 - P_2^2}{P_3 + P_1 - 2P_2}$$

$$(25) \dots \dots C = \frac{F}{dP/dt}$$

$$(26) \dots \dots dP/dt = \frac{1}{RC} \cdot P_0 e^{-t/RC}$$

$$(27) \dots \dots Q_t = Q_C + Q_R$$