CIRCULATORY RESPONSES TO STATIC MUSCULAR EXERCISE WITH OBSERVATIONS ON THEIR REFLEX NATURE

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Thesis presented for the degree of Doctor of Philosophy
of the University of Edinburgh in the Faculty of Medicine

September, 1966.

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INTRODUCTION

Our present knowledge of cardiovascular reflexes largely derives from studies on the mechanism whereby an ideal resting circulatory state is maintained. It is therefore natural that the effects of complex manoeuvres such as exercise are still ill-described and but imperfectly understood. Much of the barrier to research into the reflex effects of exercise has been methodological and it has been in only comparatively recent times that one is equipped to accurately measure, in intact conscious subjects, the rapidly induced changes.

The story of cardiovascular reflexes has been one of animal studies. The first definitive evidence of nervous control in a circulation was provided in 1845, when Weber, while stimulating the vagus nerve, stopped a frog's heart in diastole. Shortly afterwards, Claude Bernard (1852) demonstrated vasocontriction in the rabbit's ear on stimulation of the cervical sympathetic. Marey (1863), anticipated in physiological terms the baroreceptor mechanism when proposing what later became known as "Marey's Law", namely, that there existed an inverse relationship between heart rate and blood pressure. The first evidence of reflex action within the circulation appeared in 1866, when de Cyon and Ludwig demonstrated the cardiac depressant effect of stimulation of an afferent branch of the vagus. Both vagi constituted the efferent limb and the reflexly evoked effect was slowing of the heart. The finding by Dittmar (1873) of a vasomotor centre established that the circulation was profoundly influenced by the nervous system. The idea that there was a finely adjusted nervous mechanism in relation to the cardiovascular system which allowed it to monitor its own changes and counteract unsteadying influences was thus put on some sort of functional and anatomical basis.

There were some further advances in methods in the late nineteenth and early twentieth century, but the next outstanding contribution to reflex circulatory control was by Hering (1924), who unequivocally demonstrated the baroceptor function of the carotid sinus. Less important reflexogenic areas had already been demonstrated in the aortic arch (Koster and Tschermak, 1902). Other areas were described, which may include thoracic aorta, the ventricles, and the coronary and pulmonary vessels (de B. Daly and Verney, 1926, 1927). Monographs appeared over the following decade on control of the circulation by Hering (1927), Heymans (1929) and Koch (1931). From 1927 to 1930-31, Heymans and his colleagues discovered the chemoreceptor function of the aortic and carotid bodies. A complete analysis of the role of the baroreceptor and chemoreceptor reflexogenic areas in the control of breathing and the circulation was published in 1933 by Heymans, Bouckaert and Regniers.

Much of the foregoing were subtle animal experiments with considerable control over many variables. Exercise was studied, as will be described, but the available techniques imposed great limitations. Since exercise, as we normally understand it, is volitional, it requires a conscious subject and detailed studies were therefore difficult to perform on animals. This obstacle has been surmounted in some degree for rhythmic work by the use of trained animals on a treadmill, though one cannot study discrete muscle groups in this type of activity. Static exercise requires an even higher degree of subject co-operation, which more or less necessitates study of the human.

The circulatory effects of static exercise have nevertheless been investigated in some degree by previous workers. The Scandinavian and German precision studies on the respiratory and cardiovascular systems in the human subject were developed in the early half of this century. Among these workers

Krogh and Lindhard (1912) first introduced, for instance, the nitrous oxide method of measuring total blood flow. By about 1915 the ventilation, oxygen uptake, cardiac output and arterial-mixed venous blood oxygen difference (A - V difference) could be measured in a given subject. Many of these variables could not, however, be measured simultaneously and acute changes were also difficult, if not impossible, to follow. Lindhard (1920), did, nevertheless, apply his techniques to the study of static exercise. It is interesting that this original work was published four years before Hering's contribution on the carotid sinus. In other words, he was studying the effects of an induced change in a system whose control at rest was not fully understood.

Lindhard's study was a comprehensive one of the effects on the respiration and circulation of sustained muscular contractions in four healthy subjects. In his experiments the subjects performed the exercise of hanging, with arms bent, from a horizontal bar for a period lasting roughly one minute. Alveolar ventilation was found to increase two to three times during the exercise, but there was invariably a further increase immediately after its cessation, and the level remained increased for some time. Oxygen metabolism increased during the work performance, with a further large increase on relaxation. It then gradually fell to resting levels in about three minutes. In addition the oxygen utilization or A-V difference (calculated from the oxygen uptake and cardiac output), actually decreased during work, increasing afterwards sometimes markedly. Cardiac output, measured by the nitrous oxide technique, was roughly doubled during the exercise. As with the oxygen uptake, it increased further on its cessation, reaching a peak in the first minute of recovery, declining thereafter to normal. He made few observations on pulse rate changes, but those he did make suggested that increases were large in proportion to the increase in oxygen

uptake and unlike the cardiac output, rapidly returned to normal. The pH (blood sampled from finger, ear lobe or occasionally vein) fell during the working period and did not return to normal within the first two minutes of the recovery period. From his results Lindhard was led to postulate that (i) the small increase in oxygen uptake and decrease in A-V difference during the course of the exercise was explained by the proposal that the statically contracted muscles set up a mechanical obstruction to blood flow; (ii) the large increase in oxygen uptake immediately on cessation of exercise was an expression of the oxygen debt created by such a circulatory obstruction; (iii) the fall in pH was the result of the lactic acidosis caused by the anaerobic metabolic state.

It is felt that Lindhard's flow measurements should be accepted with some caution. The nitrous oxide method of measuring cardiac output, originally reported by Krogh and Lindhard (1912), was further described, with a discussion of errors, by the same authors on other occasions (Lindhard, 1916; Krogh and Lindhard, 1917). Lindhard (1916) stated the uncertainty of a single determination, including technical errors and physiological variation, to be 10 per cent. During the particular type of exercise performed here (hanging from a bar), however, incomplete mixing of the gas might be suspected. Lindhard does not state the allowed mixing time precisely, but this has been elsewhere criticised by other investigators (Grollman and Marshall, 1928; Marshall and Grollman, 1928). An apnoeic period due to thoracic fixation would be the most likely cause of incomplete mixing in these experiments. Lindhard states, however, that where the first inspiration was 'too small'*, the experiment was abandoned. If there was a large error involved in the

*translation

exercise period measurements, it is nevertheless significant that there was a further increase in the measured cardiac output (i.e. a change in the same direction) after the cessation of work, when the apnoeic or hypoventilation period had presumably ceased. A further difficulty with the nitrous oxide method was the gas's characteristic of incomplete elimination from the body for about fifteen minutes. The cardiac output determinations could not, therefore, be arranged in immediate chronological series. Hence resting, exercise and recovery values do not relate to the same actual experiment, but are compilations from numerous performances of the same experiment. Repeatability of results was, however, demonstrated.

Cathcart, Bedale and McCallum (1923) disagreed with Lindhard, finding no evidence of a post-exercise increase in oxygen uptake. They investigated three types of static work: (i) continuous maintenance of a 15 Kilogramme weight against gravity; (ii) intermittent maintenance of a 10 Kilogramme weight against gravity, exercise periods alternating with resting periods and (iii) 'gradually increasing static effort' involving the alternate extension and relaxation of a spring. These authors did note a rise in pulse rate and blood pressure (more especially the diastolic pressure) during these forms of exercise. Dusser de Barenne and Burger (1928) also found no post-exercise increase in oxygen uptake in subjects who performed the static exercise of standing with knees at 130° and heels elevated for 3 minutes. The considerable differences in the exercise may explain the disparity between the findings of these authors and those of Lindhard. The main point of difference would appear to be the greater level of work (as judged by the oxygen uptake) chosen by the latter author. Rein and Tolbett (1935) claimed Lindhard's thesis regarding mechanical obstruction to flow to be incorrect in that they demonstrated

increased flow (using a Rein flowmeter) in animal experiments, through tetanically contracted muscles. These views need not, however, conflict, for an increase in flow is not at all incompatible with a relative ischaemia and lactic acidosis if the rate of muscular work is proportionately greater. Marschak (1931) and Assmussen and Hansen (1938) supported Lindhard's findings. The latter pair, in an extensive study on one subject, repeated Lindhard's work with some modifications. The work consisted of pushing both feet against a lever. Two different levels of exercise were studied, at oxygen uptake rates of 266 and 494cc/O_2/minute respectively. Cardiac output was measured by the acetylene method. Pulse rate was recorded by means of an arm cuff with a Boulitte double capsule, while a Pachon oscillometer was employed for blood pressure measurements. These authors confirmed Lindhard's findings in nearly every respect and subscribed to the view that static contractions hindered blood flow through the involved muscles. Assmussen and Hansen also found a considerable rise in both pulse rate (circa 30 and 60 beats/minute at O_2 uptake rates of 266 and 494cc/O_2/minute respectively) and blood pressure (systolic - 60 and 80 mm.Hg. respectively: diastolic 40 and 40 mm.Hg. respectively) with an immediate return to normal on relaxation. The promptness of this drop in the pulse rate and blood pressure differed from the changes in oxygen uptake and cardiac output during recovery. Grant (1938) showed by water bath plethysmography that statically contracted forearm muscles did indeed hinder blood flow. Barcroft and Millen (1939) later suggested that blood flow through the muscle was occluded at a contraction tension of less than 20 per cent of maximum. As we shall see, later work by Lind and others contradicts this.

Circulatory changes during static exercise had been previously studied

by White and Moore (1925), who recorded changes in pulse rate, blood pressure and hand venous pressure. The work performed was the maintenance in the horizontal position of both lower limbs without external support while sitting in a chair. There occurred a rise in pulse rate and blood pressure with a return to normal within the first two minutes of relaxation (range of increase in systolic pressure = 12-40 mm.Hg: range of increase in diastolic pressure = 2-23 mm.Hg.). There was usually a greater rise in the systolic than the diastolic component of the blood pressure. Venous pressure usually rose by 2 - 3 cm.H_2O. The authors also inferred from the product of pulse pressure and pulse rate that there occurred an increase in cardiac output during the exercise performance. They made the further inference that the rhythmic squeezing action of the muscles was not a pre-requisite for the maintenance of filling pressure during exercise.

In 1937 Alam and Smirk first reported their work on the relationship between muscular work, albeit dynamic, and blood pressure. These workers closely related three observed events and crystallized many of the thoughts of former workers. The three events were (i) muscular work; (ii) ischaemia and (iii) circulatory changes. They considered the last event to be the result of the former two. They originally noticed that vascular occlusion of dynamically working lower limbs resulted in a rise in blood pressure, whereupon they made a more systematic study of the pulse rate and blood pressure changes during exercise of the upper and lower limbs. They observed small rises in blood pressure during the dynamic activity of alternately squeezing and relaxing the rubber bulb of a sphygmomanometer. The lower limb activity, which produced similar effects, consisted of alternately raising and lowering the knees with a weight across the thighs. These authors

found that vascular occlusion greatly potentiated the blood pressure response and that the blood pressure remained above normal, after the cessation of work, for so long as the circulation remained occluded. The pressor response was less with activity of the lower limbs but was, unlike the upper limb activity, accompanied by a rise in pulse rate (Alam and Smirk, 1938a). They suggested that the muscle mass involved determined the pulse rate response. Alam and Smirk (1938b) also demonstrated that, while ischaemic pain may have contributed to the response, the latter was not just due to a non-specific painful stimulus. They were led to postulate a reflex arising from voluntary muscle, possibly triggered by factor P of Lewis, Pickering and Rothschild (1931). This view was partly supported by the study of a subject with no sensation in one lower limb below the knee. It was shown that even with total vascular occlusion, the blood pressure returned to normal on cessation of the work with the affected lower limb, while exercise of the healthy limb led to the standard type response. The authors do not comment on why the blood pressure rose at all while working with the affected lower limb. These authors are again referred to at a later stage.

Knox (1951) demonstrated increases in heart rate during alternate extension, followed by holding in extension, and relaxation, of two "Terry" springs. The static component was separated from the dynamic before conclusions were drawn as to the effect of the former. Tuttle and Horvath (1957) made a comparative study of the effects of dynamic and static exercise on the heart rate and blood pressure. Dynamic exercise consisted of bicycle ergometry at a rate of 1250 Kg.m. for one minute, while the static variety involved squeezing a grip dynamometer at maximum effort for one minute. They showed that there occurred in dynamic exercise a rise in systolic pressure

with no change or decrease in diastolic pressure. During the static exercise there was a rise in both systolic (mean rise = 51 mm.Hg.), and diastolic (mean rise = 44 mm.Hg.). They also found that the dynamic exercise was accompanied by a mean oxygen debt of 1200 cc., while during static exercise the subject invoked only a slight oxygen debt. This odd observation is probably explained by the smaller muscle mass used in the hand gripping. Tuttle and Horvath went on to suggest that the blood pressure effects were a consequence of reflexes which were modified by the metabolic changes associated with the work load.

Clarke, Hellon and Lind (1958) demonstrated, by means of mercury in rubber strain gauge plethysmography, an increase in blood flow through muscle during sustained contractions. They also showed that the increase in blood flow was greater at high muscle temperatures (e.g. 42°C). The degree of work was 33 per cent of maximum, and this work therefore contradicts Barcroft and Millen's suggestion that blood flow was suppressed at a tension between 10 and 20 per cent of the maximum. Clarke and his colleagues attributed the disagreement to different methods of establishing maximum tension. Humphreys and Lind (1963) later studied blood flow through muscles during sustained contractions of graded intensity. They found an increase in the amount of blood flowing into the forearm at tensions from 30 to 60 per cent of the maximum. The rate of rise in blood flow during the contraction increased with tension, but the actual values at the end of contraction decreased as tension rose. They suggested that vascular occlusion would not be complete until a tension exceeding 70 per cent of maximum was reached. They also commented on rises in systolic and diastolic blood pressure during sustained contractions, the degree of rise being proportional to the degree

of contraction.

A more complete study of the haemodynamic effects of graded hand grip contractions has recently been made by Lind, Taylor, Humphreys, Kennelly and Donald (1964). The experimental methods were similar to those used by the author. The object of the study was to record the effects on the systemic circulation of hand grip contractions (performed on a strain gauge dynamometer) at, in turn, 10 (5 min. contraction),20 (5 min. contraction) and 50 (1 or 2 min. contraction) per cent of the maximum voluntary contraction (M.V.C.). There was, in all subjects studied, at 10 per cent M.V.C. a rise in systolic and diastolic pressure and heart rate. In all but one subject a steady state (for blood pressure and heart rate) was achieved after about three minutes. The rise in systemic arterial pressure was brought about by an increase in heart rate and cardiac output. Baseline levels were re-achieved within one minute of relaxation. At 20 per cent M.V.C. the response was qualitatively similar but quantitatively greater and continuously increasing. At 50 per cent M.V.C., which could be sustained for only 1 or 2 minutes (depending on the subject), the response, which increased throughout, was yet again greater in magnitude. Changes in systemic vascular resistance were slight, only one of the four subjects (the oldest) contributing to the pressor response by an element of vasoconstriction. Forearm blood flow was increased in the working limb in all instances, the increase being less marked at 50 per cent M.V.C.

This presentation commences, (i) with a more complete study of the quality of the haemodynamic response to hand grip. Events within the pulmonary circuit are described in addition to changes in the systemic circulation. Ventilation is also studied. (ii) the influence of ischaemia

of the working muscle is then examined and (iii) the levels of certain chemicals in the effluent blood from the working muscle are estimated, establishing the presence of anaerobiosis and a high local potassium concentration during such activity. More applied aspects are then described: (iv) the response of hypertensive subjects to hand grip and the effect of drug sympatholysis on the circulatory response are examined; (v) the effects of hand grip on the heart rate and blood pressure during the performance of dynamic exercise by large muscle groups during treadmill exercise are also studied and (vi) the haemodynamic changes induced by ischaemic dynamic exercise of the lower limbs are reported. There is a final discussion.

The presentation is divided into sections. Each section commences with a short introduction and ends in a discussion. The purpose of these discussions has been to recreate the continuity of thought which obtained during the performance of the project, and to provide, where necessary, rational connecting links between sections.

METHODS

INTRAVASCULAR PRESSURES

Systemic arterial pressure was recorded through a 55 cm. nylon catheter (bore 0.80 mm.) which was introduced into the brachial artery by a modified Seldinger technique and advanced into the aortic root. Pressure was transduced by a Statham P23Db strain gauge manometer. The catheter manometer system was critically damped to give a virtually flat frequency response to 20 cycles per second. The square wave response of the system was 95 per cent within 0.03 second, with less than 5 per cent overshoot. The electrical output from the manometer was arranged to allow synchronous recording of both pulsatile and mean aortic pressures. Zero reference level of the arterial pressure was 10 cm. above the plane of the x-ray table. The systemic arterial calibration was arranged to extend approximately 10 mm.Hg. on either side of the pressure wave to allow the maximum recording precision with least electromechanical distortion. The saline-filled calibration pressure heads for the system were maintained by specially calibrated Reckla Aneroid manometers. The frequency response of the galvanometers was 90 cycles per second at 95 per cent of true fidelity. The systemic arterial pressure was measured as the average of the values extending for 15 or 20 seconds about the point of determination.

Pulmonary-artery wedge, pulmonary arterial, and right atrial pressures were taken through a nylon triple lumen catheter. These pressures were transduced by Statham P23Db strain gauge manometers. For calibration purposes reference levels of 0 and 30 or 40 mm.Hg. were chosen, 0 being taken by exposing the system to atmosphere, and 30 - 40 mm.Hg. being recorded from a calibrated water manometer.

Zero reference level for all pressures was 10 cm. above the plane of the x-ray table. All pressure traces were recorded simultaneously on an ultra-violet recorder (New Electronic Products Ltd. Type 1185).

CARDIAC OUTPUT

The cardiac output was in all instances measured by the indicator dilution technique. This method had been previously developed for the Department of Medicine, The Royal Infirmary, Edinburgh, and subjected to a comparison with the Fick method (Taylor, Kenelly, MacKenzie, Sutherland, Hutchison, Staunton and Donald, in preparation). As the indicator dilution technique is not yet standardized its method of application varies in different laboratories. Each laboratory using such a technique must therefore validate it. A short discussion of the theoretical basis of the method will follow. An account will be given of the method as here applied. A dye-Fick comparison performed in this laboratory will then be discussed.

THEORETICAL BASIS AND BACKGROUND OF THE INDICATOR DILUTION TECHNIQUE IN MEASURING CARDIAC OUTPUT

A dye or other indicator which does not diffuse out of the vascular system, will, when injected into the venous tributaries, the right side of the heart, or pulmonary artery, appear in arterial blood. The time course of its concentration may be measured by analysing separate timed samples or by a continuous monitoring device. The indicator will appear after a delay (appearance time), build up to a peak concentration, and then fall in concentration in exponential fashion. The exponential decline has been shown in model systems to be decided by the presence of a mixing chamber

between the injection and sampling sites (Hamilton, Moore, Kinsman, and Spurling, 1932). In the mammal, when an injection is made into the pulmonary artery, the left side of heart serves as a mixing chamber, i.e. the amount of dye washed out per unit time is proportional to the concentration in the left heart reservoir. The decline of a time-concentration curve will therefore be exponential and the prolongation of the downslope past the point of recirculation will, with the preceding part of the curve, enclose an area that will describe the changing concentration of all the indicator on its first circulation. It will also eliminate that which is recirculating.

Flow (F) is calculated from the time-concentration curve by the formula:

$$F = 60\ I/cf.$$

where I = amount of indicator injected

c = average concentration of indicator during its first circulation.

f = the time of passage of the indicator on its first circulation.

Various indicators have been used and these include salt (Stewart, 1897; Wiggers, 1944), cold saline (Fegler, 1954), dyes (Hamilton, 1932) and radioactive material (MacIntyre, Pritchard, Eikstein and Friedell, 1951). Stewart (1897) originally used a constant salt infusion method. The artery was one side of a wheatstone bridge and an alternating current signalled a change in conductivity due to the passage of the infused salt solution. Since then the bolus type of injection has become universally used.

There was a patent disadvantage in using diffusible substances which could escape in some degree into interstitial pulmonary fluid. There was, therefore, an attraction in a dye such as brilliant vital red (Hamilton et al, 1932), which attaches itself to the plasma proteins. Subsequently Evans Blue

(T 1824) became more popular because of its different spectral properties to haemoglobin, which allowed it to be measured in the presence of haemolysis. Continuous recording of approximate dye concentration was later made possible by the use of the oximeter (Wood, 1950). "Coomassie blue' was suggested to be as accurate with an ear oximeter as other work with a cuvette oximeter (Taylor and Thorp, 1959; Taylor and Shillingford, 1959). More recently indocyanine green ('cardio-green') has been introduced by Wood and co-workers (1957). This dye has been used in this study in association with a cuvette oximeter. It absorbs light at 800 u., at which both oxygenated and reduced haemoglobin have the same absorption. It is measured with the infra-red cell of the cuvette oximeter. Bolus injections were made.

TECHNIQUE OF MEASURING CARDIAC OUTPUT

Method of Dye Injection

Small, known, amounts of indocyanine green dye were injected into the right atrium or pulmonary artery (usually the latter) from a glass-barrelled syringe which was driven by an electrically activated, high-speed, compressed-air driven ram. The syringe automatically reloaded from a central dye reservoir. The injectate volume was constant for each individual study, though it varied between 1.055 and 1.569 ml. (average 1.450 ml.) in different studies. The volume was measured after each study by injecting separate boluses into four flasks, and re-weighing. The stroke of the ram activated an electric time marker on the recorded dye base-line. A compressed-air driven three-way tap was so arranged that activation of the injector ram was associated with communication between the syringe and catheter, while completion of the stroke resulted in communication between the syringe and central dye reservoir.

The syringe thus reloaded after each injection .

Haemolysis was not observed, despite the high expenditure of kinetic energy in the injection.

Method of Arterial Sampling

Continuous arterial sampling was performed through a 55 cm. nylon catheter (bore 0.80 mm.) whose tip had been advanced into the aortic root. Constant rate of sampling was performed not alone during each cardiac output measurement, but also for all determinations in any one experiment. This precluded velocity-dependant changes in spectral transmission of blood passing through the cuvette (Wood, 1950; Zijlstra, 1953). Summit 80 ml. syringes and a Harvard Apparatus Co. Inc. pump were used for withdrawal. Sampling speed was not affected by changes in haemoglobin concentration. The rate of withdrawal was, for most experiments, 38 ml. per minute. Such a high velocity was chosen because of the decrease in distortion of the concentration-time curve accompanying high flow rates (Milnor and Jose, 1960). The tap system was machined as one assembly (Ole, Dich, Copenhagen), thereby reducing the number of connections whereby air might be introduced with the high negative pressure involved. Whenever air did appear, it was immediately apparent and the problem could be eliminated by the tightening of connections.

The distance between catheter tip and cuvette was 58 cm. This was the shortest distance which would still allow a high aortic sampling site. The average sampling time for the entire transcription of a dye curve during a resting cardiac output determination was of the order of 20 seconds. Following inscription, the sampled blood was re-infused into the subject and the system was flushed, under pressure, with warm, heparinized saline.

Transduction

The dye curves were transduced by a Waters X 300 densitometer cuvette. This cuvette consisted of two cadmium-selenium photocells, one of which had a maximum filter sensitivity at 800 u., while the other cell gave minimal transmission at this wave length. The passage of dye through the cuvette therefore created an imbalance in the Wheatstone bridge of which the photocells were two limbs. The resultant signal was fed via an attenuator into the input of a six-stage, balanced, direct-coupled amplifier. The input stage of the amplifier consisted of a twin-triode valve employed in a long-tailed pair configuration which had high stability and low drift characteristics. This was followed by two pentode valves, similarly connected, which provided the main amplification. These, in turn, were coupled with a twin-triode cathode follower which gave a low impedance balanced output which supplied the morror galvanometer in an ultraviolet recorder (New Electronic Products Ltd. Type 1185).

The employment of a sensitivity gain control allowed the height of dye curves to be kept to levels suitable for analysis.

Linearity of the System

The deflections at different dye concentrations in whole blood ranging from 0-60 mg./1., have been studied elsewhere (Taylor et al, in preparation). It has been shown that the linearity of the system is good up to concentrations of about 25 mg./1. Blood concentrations during cardiac output determinations reach a peak of approximately 6 mg./1.

Method of Calibration

Calibration was performed by a whole blood, in vitro, technique. Before the start of any study, 130 ml. of blood were removed with dry syringes and run into a siliconed flask containing 1.5 ml. of 25,000 units/ml. heparin, with constant agitation to assist mixing. The flask was then stored at body temperature and the calibration carried out at the end of the study. The exact method was as follows. 1 ml. of dye was pipetted into a 25 ml. flask which contained whole blood. From this dyed blood samples of 1 ml., 2 ml., and 3 ml. were pipetted into other 25 ml. flasks which again contained undyed whole blood. The remaining 25 ml. of whole blood was reserved to provide a zero base line. The blood was then withdrawn through the cuvette at the same rate as that obtaining during the study, in ascending order of concentration. A typical calibration is shown in fig. 1. The average of the three deflection values was taken as the calibration factor.

Method of Measurement

The baseline was extrapolated beneath the inscribed curve. Pulsatile curves were smoothed freehand. The area under the curve was then found by dividing the baseline into equal intervals of 0.5 second and measuring the height of the curve at each interval. The downslope was then re-plotted on semilogarithmic paper and extrapolated. All readings down to 1 mm. were then summed. The cardiac output was then calculated from the formula:

$$C.O. = \frac{I \times 60}{c/_2 \times f}$$

when I = injectate in ml.

c = sum of the heights, in centimetres, of the dye curve at half second intervals

f = Calibration factor in ml./cm.

The output was, in all instances, finally expressed per square metre body surface area.

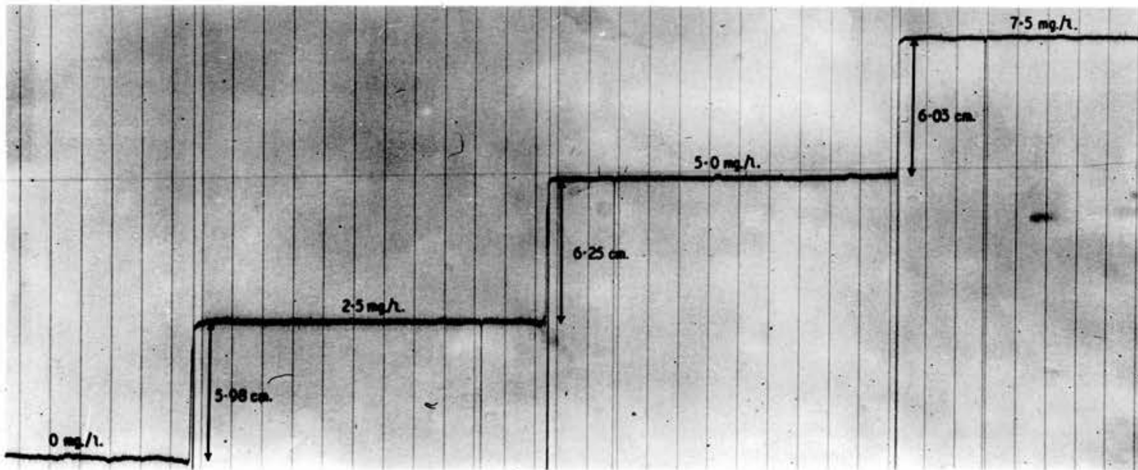


Figure 1. A Typical Dye Calibration

VALIDITY OF ABOVE METHOD OF CARDIAC OUTPUT DETERMINATION

The method described here has been compared to the hitherto standard method of measuring the cardiac output, namely, that based on the Fick principle. 39 subjects were studied. These subjects comprised a wide range of pathophysiological states. Hypertensive subjects with dilated ventricles were chosen. Others had aortic or mitral valve disease. Some had isolated atrial fibrillation. Subjects with low output states (myxoedema) and high output states (anaemia) were also studied. Following placement of the catheters in the pulmonary artery and brachial artery an initial resting output was determined by the standardised Fick method, the blood being sampled from the pulmonary artery. During this period five dye output determinations were made. Supine leg exercise sufficient to raise the total body oxygen uptake into the region of 400 ml./sq.m./minute was performed and a further Fick determination made between the fourth and sixth minute of such exercise. During this same period three dye determinations were made. The exercise level was then increased, bringing the oxygen uptake up to about 800 ml./sq.m./ minute. Again a Fick determination and three dye measurements were made between the fourth and sixth minute. Following a recovery period of 30 minutes seven consecutive Fick outputs were made, each over a four-minute period. During each of these determinations five dye outputs were performed.

Results of Dye-Fick Study

For analysis the Fick outputs were compared to the mean of the relevant dye output values. The complete results of this study are being described elsewhere (Taylor et al). The technique has been shown to be valid. Briefly, the following results emerged. Within the range of 1.5 to 25 l./minute

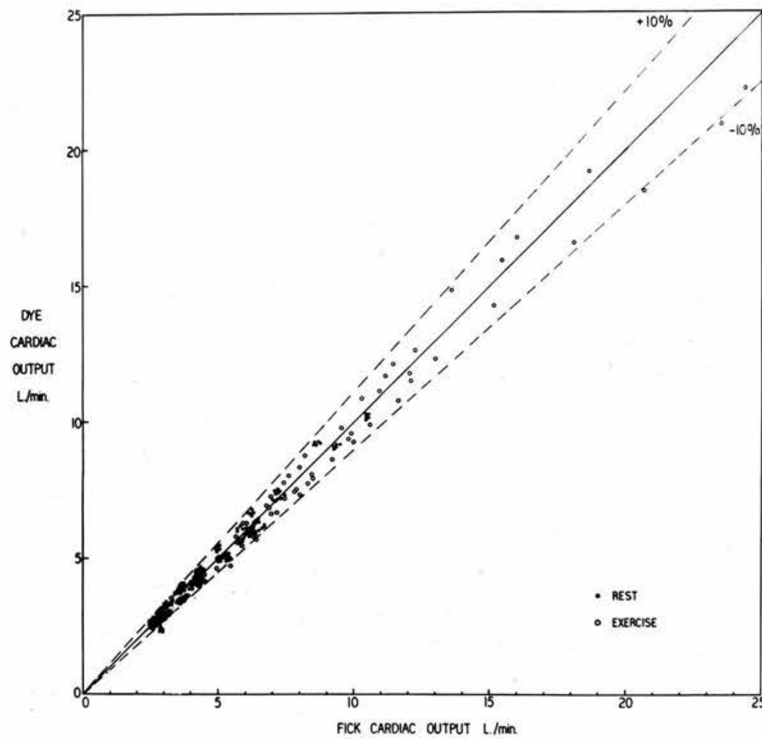


Figure 2. Dye - Fick Correlation

nearly all cardiac output values fall within 10 per cent of the median line when the methods are plotted against one another (fig. 2). The correlation coefficient was 0.993. 70 per cent of all values were within 5 per cent of the median line. There is no systematic error. The dye method does, however, in the presence of mitral incompetence, give a systematically lower value than the Fick method.

Reproducibility

Certain subjects showed a variation in pulse rate of not greater than three beats/minute between two consecutive estimations. They were considered to be in a stable state. The correlation line between such consecutive outputs is plotted in fig. 3. There was a maximum difference of 8 per cent. 95 per cent differed by less than 7 per cent. 70 per cent differed by less than 4 per cent.

MEAN TRANSIT TIME was calculated according to the formula:

$$\text{M.T.T. secs.} = \frac{C_1 t_1 + C_{2} t_2 \text{ ------------ } Cntn}{C_1 + C_2 \text{ ------------ } Cm} + \text{A.T.} - 0.8$$

M.T.T. = mean transit time

C = height of y axis of dye curve

t = time or x axis of curve

A.T. = appearance time (in seconds)

-0.8 = time delay (in seconds) in catheter cuvette sampling system

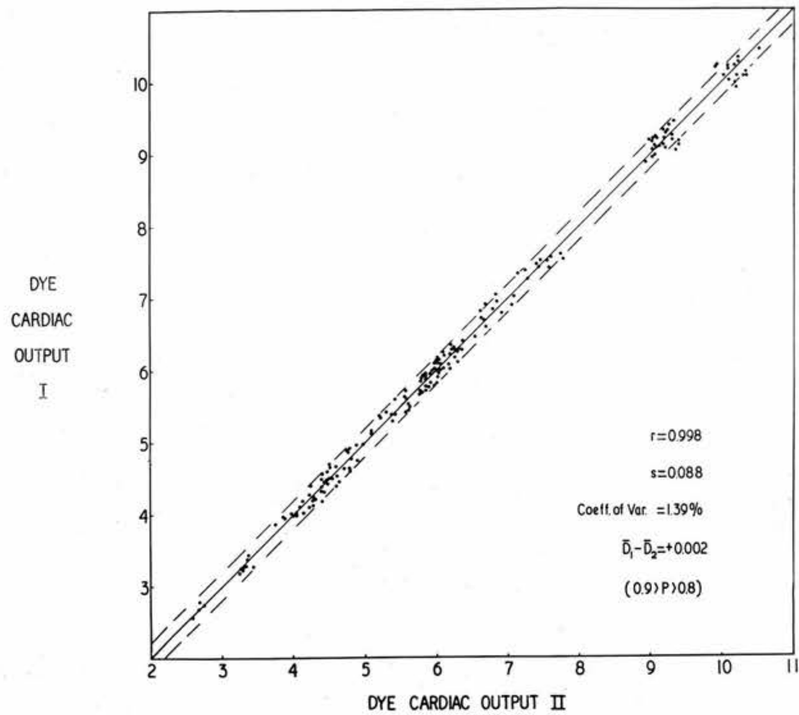


Figure 3. Correlation Between Consecutive Cardiac Outputs estimated by the Indicator Dilution Technique during a Stable State

CENTRAL BLOOD VOLUME

The calculation of central blood volume, using the techniques described, is open to criticism. This is discussed elsewhere (page 31) The calculated quantity is taken to represent the volume of blood between the injection site (usually pulmonary artery) and sampling site (aortic root). It has been calculated according to the formula:

$$C.B.V. = \frac{C.O.}{60} \times M.T.T.$$

when C.B.V. = central blood volume

C.O. = cardiac output

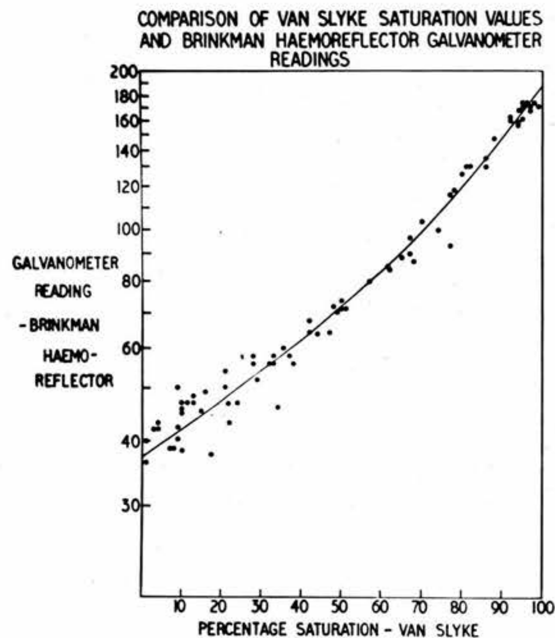
M.T.T. = mean transit time

The final value was in all instances expressed per square metre body surface area.

VENTILATION

Ventilation was measured in a Tissot spirometer with a pen and ink recorder. Before any estimations were made the Tissot spirometer was washed out with a volume of over 20 litres of expired air.

BLOOD OXYGEN SATURATION was measured on a Kipp haemoreflector. Reference to fig. 4 will show that without using a corrected calibration, this method is inaccurate when compared with the manometric Van Slyke method. It was therefore standardized against the latter method. Fig. 4 shows that with a corrected calibration, the correlation is good for higher values, but poorer for values under approximately 30 per cent saturation.



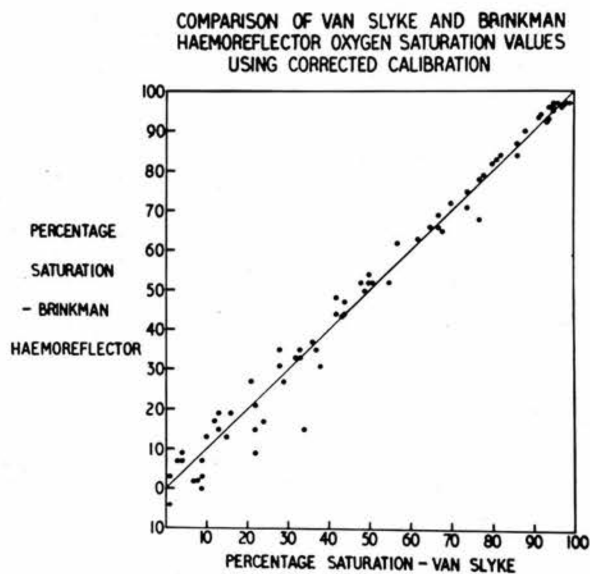


Figure 4. Correlation between Kipp haemoreflector (uncorrected and corrected) and monometric van Slyke method in the measurement of oxygen saturation.

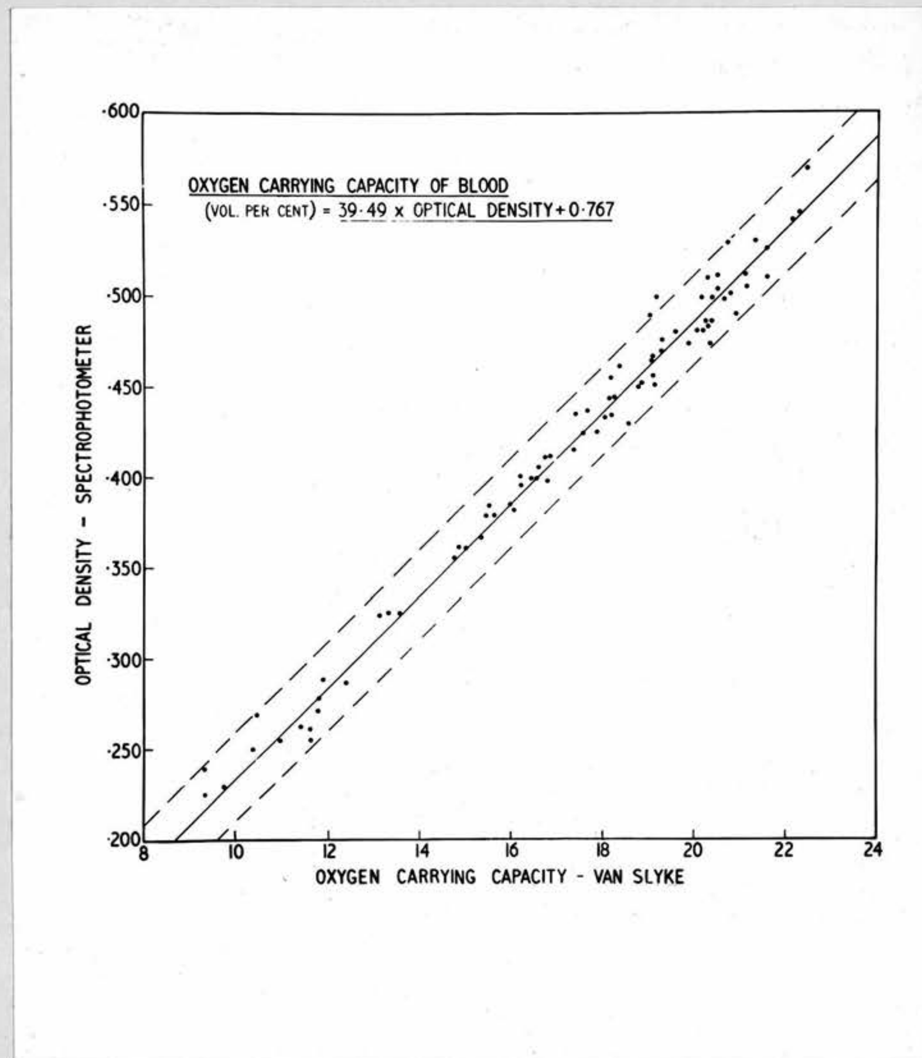


Figure 5. Comparison of spectrophotometric haemodilution and van Slyke manometric method in the estimation of blood oxygen carrying capacity.

OXYGEN CARRYING CAPACITY OF BLOOD

The method employed for the measurement of blood oxygen carrying capacity was based on a spectrophotometric haemodilution technique which was standardized against the Van Slyke manometric method (see fig. 5).

BLOOD pH

Arterial blood pH was measured by means of an E.I.L. (Electronic Instruments Limited) capillary electrode. Calibration was performed with a 7.416 phosphate buffer. pH is expressed to the nearest 0.01 pH units. The temperature of the water bath surrounding the electrode was 38° C. The accepted variation in an individual blood sample was 0.004 pH units.

SERUM ELECTROLYTES

Serum potassium was measured by means of an E.E.C. (Evans Electroselenium Ltd.) flame photometer (normal range 3.6 - 5-/m.Eq./l).

SERUM LACTATE

Serum lactate was determined by the Boehringer method. This method involved the conversion of all the serum lactate in a blood sample to pyruvate and measuring the degree of reduction of diphosphopyridine nucleotide which takes place during the reaction (Varley, 1962).

HAND GRIP DYNAMOMETER

The machine employed (illustrated in fig. 6) was based on a photo cell system.

A measuring gauge with sensitivity control was employed to set the galvanometer needle for a maximal voluntary contraction (M.V.C.) at 100. Thereafter a contraction bringing the needle to 10, 20 or 50 on the gauge represented 10, 20 or 50 per cent of the maximal voluntary contraction. A controlling device (vide infra) was used to activate a white light that would shine only when the required percentage was attained, so that the tension exerted during the sustained contraction could be accurately monitored by the subject. A red light would shine when the tension was too great and a green light when too little, about 2 per cent being allowed on either side of the desired level.

The machine employs two photo transistors and two low-voltage torch bulbs.(see fig. 7). Between them is a metal vane, painted matt black, attached to the steel bar. The position of the simple optical system can be adjusted so that when the bar is at rest (i.e. not being gripped) an equal amount of light falls on the two photo cells, and the output is balanced. A zero adjustment control enables the meter needle to be brought to zero at this point. Gripping of the bar will produce an imbalance in the output. Beyond the meter circuit, the lamp level selector varies the degree of imbalance with regard to the meter reading and so determines the currents flowing in the base circuits of two transistors connected as emitter followers which, in turn, drive a zero-sensing moving-coil relay. Another two relays, one of which is energised when the emitter follower circuit is unbalanced, are wired to give the following conditions:

Zero sensing relay	Relay 1	Relay 2	Lamp
Zero	not energised	not energised	white
negative current	" "	energised	green
positive current	energised	not energised	red

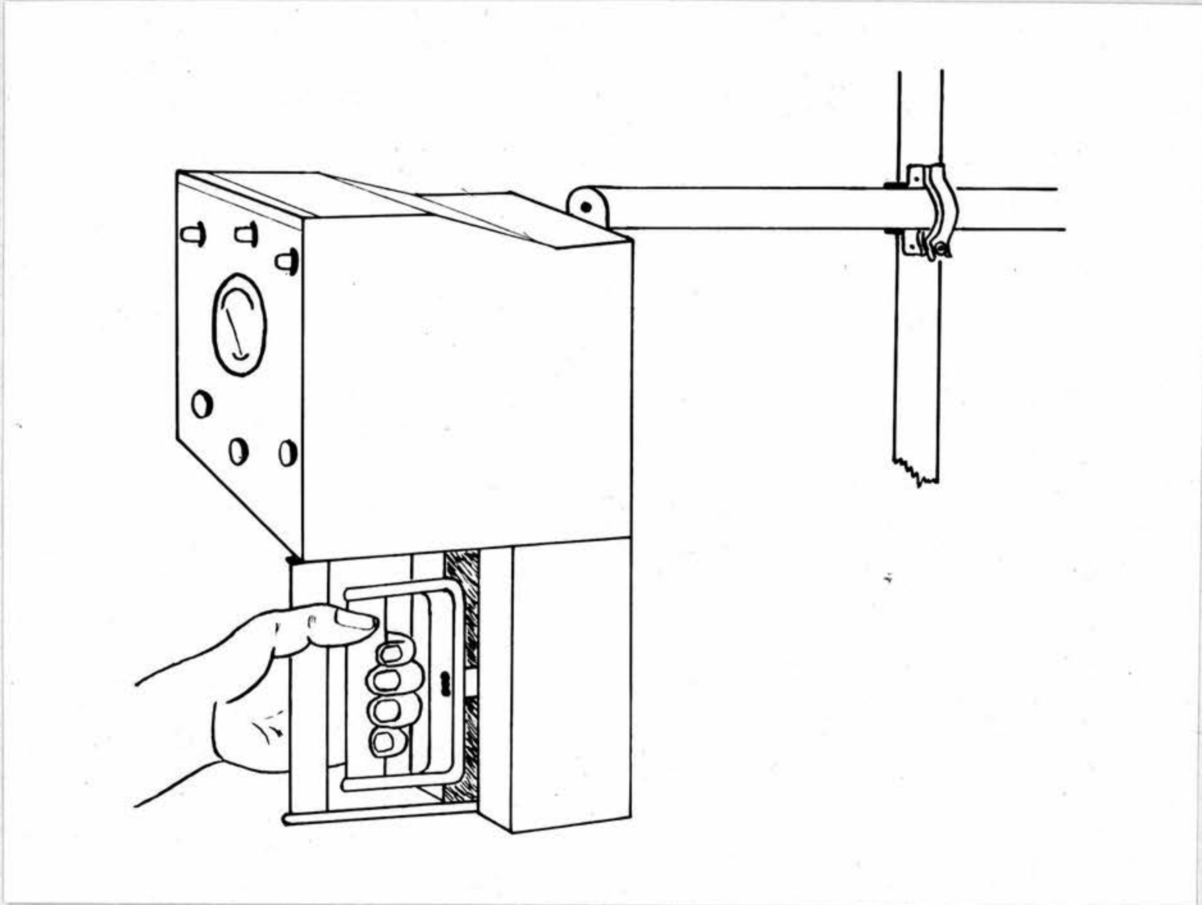


Figure 6. Hand grip dynamometer.

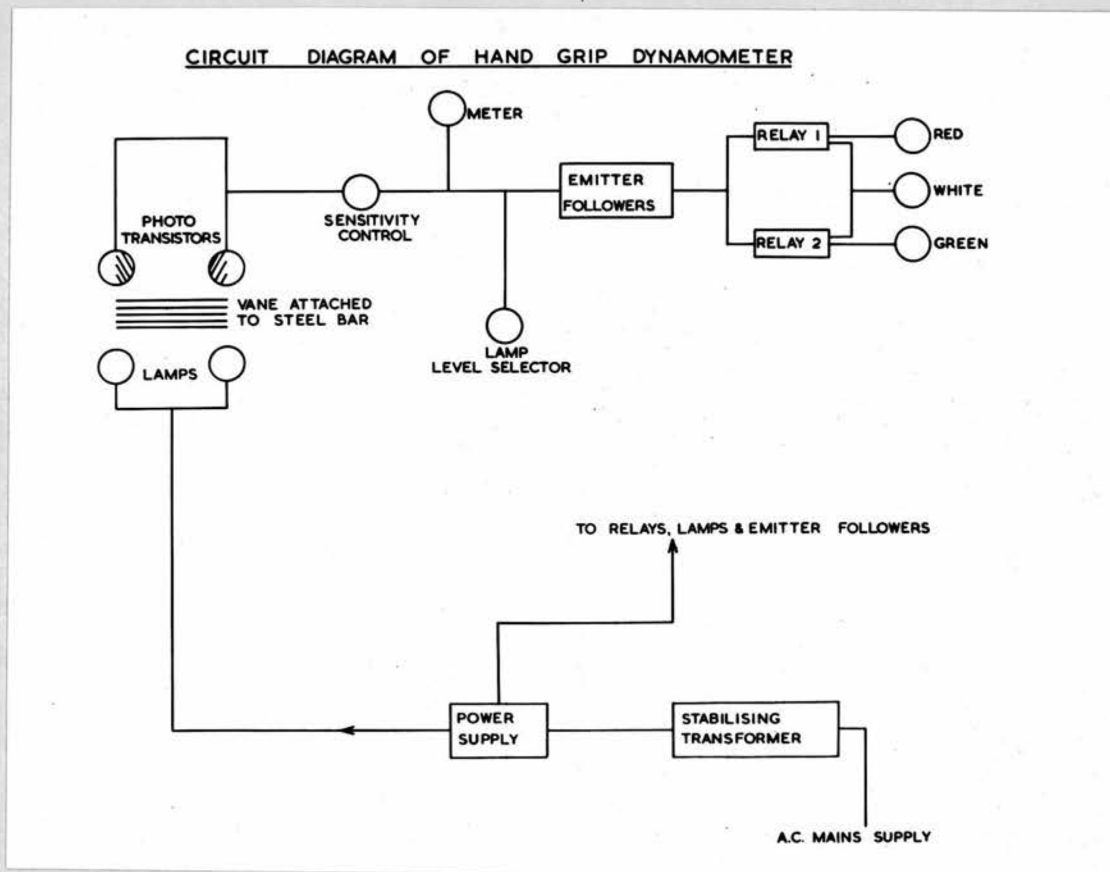


Figure 7. Dynamometer circuitry.

The lamp level selector can be adjusted so that the white lamp lights at any meter reading between 5 and 60.

All power supplies are obtained from the A - C mains via a stabilising transformer in order that the system will be inherently insensitive to mains voltage fluctuations.

The response of this system is not fully linear, due partly to the photo-cell sensing system and partly to the fact that the bar was not heat-treated. Hysteresis tended to occur, but this effect was minimised by re-calibration during the experiments.

THE SIMULTANEOUS EFFECTS OF HAND GRIP ON THE SYSTEMIC AND PULMONARY CIRCULATIONS IN FOUR NORMAL SUBJECTS

The simultaneous effects of static forearm muscular work on the systemic and pulmonary circulations are described below. The behaviour of the pulmonary circulation during what has already been shown to be a systemic pressor stimulus was considered to be of particular interest. A level of exercise was chosen which, it was felt, would definitely elicit the systemic pressor response, and yet allow a contraction time of five minutes. Because of previous observations (Lind et al, 1964), thirty per cent of the maximal voluntary contraction (30 per cent M.V.C.) was chosen as the degree of hand grip.

TECHNIQUES:

A triple lumen venous catheter was introduced through the median basilic vein, passed centrally through the right side of the heart, and fixed in the pulmonary wedge position. Pulmonary wedge pressure was taken through the lumen at the catheter tip, pulmonary artery pressure through a second lumen 15 cms. proximal to the tip, and dye injections were made through a third lumen 20 cms. proximal to the catheter tip. A 55 cm. nylon catheter was introduced into the brachial artery of both right and left arms. These were passed centrally into the aortic root. Continuous phasic and mean arterial pressures were recorded through one of these catheters. Blood was sampled through the other catheter during the cardiac output determinations.

PLAN OF INVESTIGATION:

Observations were made on four healthy young males.

Prior to the day of study all subjects were trained in the full

experimental protocol on two occasions. They were also familiarised with the laboratory surroundings. The subjects were studied in the fasting state. Prior to the beginning of the study, the subjects were required to make two maximal hand-grips, separated in time by one minute, on the dynamometer. During this the gauge on the dynamometer dial was set at 100 per cent. The subject then carried out some light non-fatiquing leg exercise for a period of three minutes. It has been shown (Donald, Bishop, Cumming and Wade, 1955) that this helps to achieve a more basal and steady state. Twenty minutes after the cessation of this dynamic exercise the study was begun.

Observations were carried out during a control period of six minutes. Cardiac output and mixed venous saturation determinations were made on alternate minutes. Apart from intermittent sampling through one of the pulmonary artery lumens, and less frequent sampling from the arterial pressure catheter, all pressures were recorded continuously. Following the control period, the subject was required to grip the dynamometer at 30 per cent M.V.C. for five minutes. Minute by minute cardiac output and mixed venous saturation determinations were made throughout the exercise period. This procedure was continued through the first two minutes of the recovery period and thereafter on alternate minutes to the sixth minute. In one subject (J.F.) more frequent flow and saturation determinations were made. Cardiac output measurements are however, incomplete in this subject owing to sampling difficulties during the latter half of the recovery period.

RESULTS

EFFECTS ON THE SYSTEMIC CIRCULATION:

The results are presented in tables 1 - 4 and fig. 8.

J.H.: There was, in this subject, a marked rise in systemic arterial pressure (fig. 8 - rise in mean pressure = 28 mm.Hg.). This was associated with a rise in heart rate (9 beats per minute), accompanied by an increase in cardiac output (0.899 l./sq.m./minute). Cardiac output and blood pressure rapidly reverted to normal with cessation of the work. This recovery was interrupted by a further temporary increase in flow in the second minute of the recovery period.

R.B.: This subject also had a definite pressor response (fig. 8 - rise in mean pressure = 10 mm.Hg.). Here, however, there was no sustained increase in heart rate. Similarly, the cardiac output, with the exception of the first minute, showed no increase during exercise. The rise in blood pressure was brought about, therefore, solely by an increase in systemic vascular resistance.

J.B.: This subject experienced a marked rise in systemic arterial pressure (fig. 8 - rise in mean pressure = 21 mm.Hg.). There was an associated increase in heart rate (8 beats per minute), and a rise of a modest order in cardiac output (0.256 l./sq.m./minute). Stroke volume fell slightly, thus explaining why the tachycardia did not bring about a greater output response. There was also an increase in systemic vascular resistance (241 dyne.sec.cm.$^{-5}$sq.m.) during the work performance. The increase in

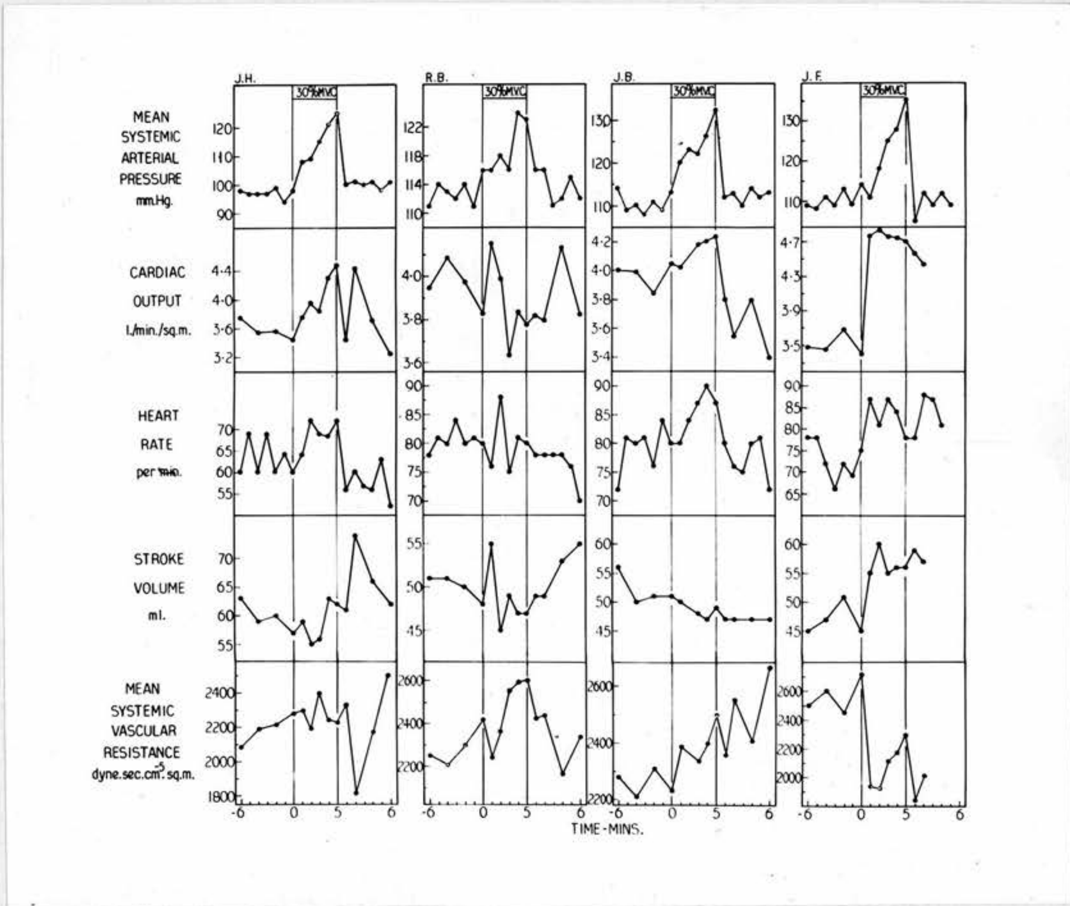


Figure 8. The effects of hand grip contraction at 30% M.V.C. on the systemic circulation in 4 normal subjects.
M.V.C. = maximum voluntary contraction

blood pressure was brought about, therefore, both by an increase in cardiac output and peripheral resistance. In the post-exercise phase a fall in cardiac output to below resting levels was observed. This was associated with a further drop in stroke volume, which did not return to pre-exercise levels. There was, over this period, a simultaneous increase in systemic vascular resistance, thereby keeping the blood pressure at around pre-exercise levels.

J.F.: In this subject hand-grip was associated with a large increase in systemic arterial blood pressure (fig. 8 - rise in mean systemic arterial pressure = 25 mm.Hg.). There was a simultaneous increase in heart rate (11 beats per minute) and cardiac output, the latter being of a large order (1.216 l./sq.m./minute). There was, in addition, a considerable rise in stroke volume. The stroke volume and cardiac output remained at above resting levels during the first two minutes of the recovery phase. As mentioned, the latter half of the recovery period is not fully documented.

THE EFFECTS ON THE PULMONARY CIRCULATION

It is felt that, before proceeding to a description of the effects of hand grip on the pulmonary circulation, the validity of one's measurements should be firstly discussed, changes in the lesser circulation being difficult to analyse.

Possibly the greatest advantage of the techniques described here is that simultaneous measurements were made of heart rate, pulmonary arterial and wedge pressures, and of cardiac output. This meant that over the 15 - 20 second period that a cardiac output determination was made, these other variables

could be measured at one point, allowing a calculation of pulmonary vascular resistance to be made for that same point in time. The measurement of the cardiac output by the indicator dilution technique can be performed rapidly enough to make this possible. On the other hand, the making of a single cardiac output determination by the Fick method would necessitate normally an expired air collection time of at least one minute (Donald et al, 1955). The Fick method would have the added disadvantage of requiring the use of a valve and mouth-piece.

For the calculation of pulmonary vascular resistance, nevertheless, one has no true record of the drop in pressure across the pulmonary vascular bed, as the catheter was in neither the left atrium nor one of the pulmonary veins, but in the pulmonary-artery wedge position. The pulmonary-artery wedge pressure was originally described by Hellems (1948) as the pulmonary "capillary" pressure. Because of doubt as to its validity in representing pulmonary capillary pressure the term pulmonary-artery wedge pressure was later introduced by Connolly, Kirklin and Wood, 1953. It is now accepted by most that under ideal conditions there is a static column of fluid between the wedged catheter tip and the pulmonary veins, which are in turn reflecting left atrial pressure changes. Varied reports have been made on its value as an index of left atrial pressure. They have varied from the extremely favourable (Connolly, Kirklin and Wood, 1953 and Hamer and Dow, 1961) reporting differences in simultaneously measured pulmonary-artery wedge and left atrial pressures of less than 1 mm., to the unfavourable (Bernstein, Fierer, Laszlo, Samet and Litwak, 1960), reporting complete lack of correlation on occasions. Theoretical objections have been made. It has been suggested, for instance, on both anatomical (Burch and Romney, 1954)

and physiological (Eliakim and Aviado, 1961) grounds that sphincters may exist between the pulmonary veins and left atrium. Most reports have, however, demonstrated that the pulmonary wedge pressure, when satisfactorily recorded, provides a reasonable index of left atrial pressure changes and therefore allows calculations to be made of changes in pulmonary vascular resistance. Pulmonary vascular resistance has been calculated by the formula:

$$\frac{\text{P.A. pressure (mm.Hg.) - P.W. pressure (mm.Hg.) x 1332}}{\text{blood flow (ccs per second)}}$$

where P.A. = pulmonary artery

P.W. = pulmonary artery wedge

It is accepted that in such a low pressure system, this formula is inadequate, no account being taken of the loss of energy in overcoming viscous resistance and generating turbulence. In addition compliance within the pulmonary circulation is high, allowing the system to be dilated with but little expenditure of energy. Changes in resistance will not therefore necessarily signify changes in vessel tone. Because of the low resistance in the pulmonary circuit pulmonary artery pressure runs off greatly in diastole and one has seen occasions where it has become equal to the pulmonary-artery wedge pressure, allowing a calculation of pulmonary vascular resistance to equal zero in the presence of a measurable blood flow.(as one measures the pulmonary pressures over the same 15 - 20 seconds that a flow determination is made, there is definitive evidence that a measurable blood flow does exist). No record has been made of intra-thoracic pressure (e.g. oesophageal pressure), or of ventilation, so that interpretation of intraluminar pressure in specific terms may be difficult. Static work of small muscle groups has been shown before, however, to affect ventilation but little (Dejours, 1963). In the subjects

studied here changes in pulmonary arterial pressure have therefore been considered to represent genuinely specific changes in intraluminar pressure.

In the discussion of changes in pulmonary vascular pressures, reference will be made to pulmonary blood flow. If one brings about a rise in pulmonary artery pressure such as by, for example, acute hypoxia, and finds that flow did not change the rise in pulmonary vascular resistance which is found almost certainly represents a definite change in vessel calibre. It is more difficult however to decide this in the presence of a significant flow increase such as is shown to occur in the experiments being described.

The central blood volume was calculated by the Stewart-Hamilton method (1932 : 1953). The injectate entered the blood stream in the pulmonary artery, so that the figures derived do not include the volume contained in the right side of the heart. No correction has been made for the error introduced by the choice of sampling site, namely, the aortic root rather than left atrium. Whatever doubt may exist as to what volume one is exactly measuring, the choice of injection and sampling sites will have systematic effects.

RESULTS

The results are illustrated in fig. 9 and tabulated in tables 1 - 4.

J.H.: In this subject, in whom there was a marked increase in flow, there was an initial small rise in pulmonary arterial pressure with no change in wedge pressure. There was a simultaneous slight rise in pulmonary vascular resistance. Thereafter, while flow continued to increase, the

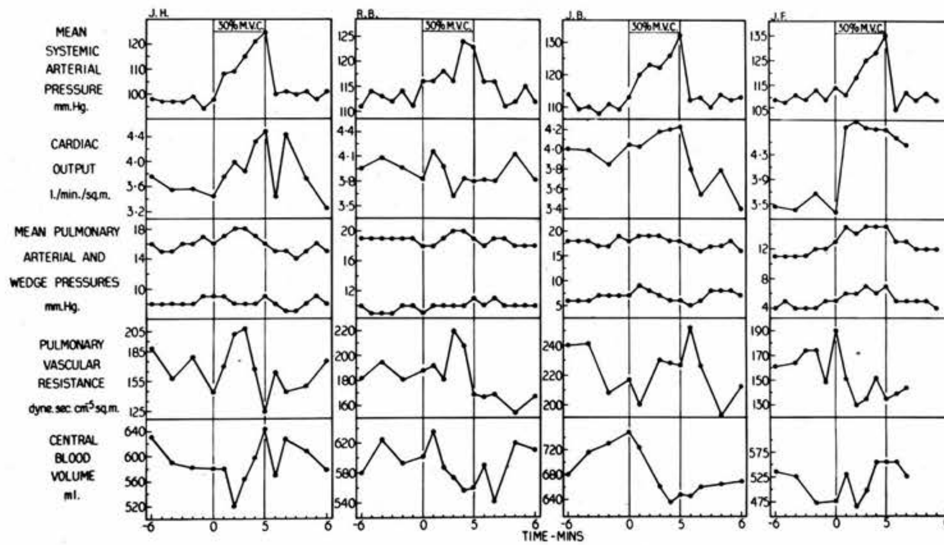


Figure 9. The effects of hand grip contraction at 30% M.V.C. on the pulmonary circulation in 4 normal subjects.

pulmonary arterial pressure dropped to pre-exercise levels, thereby expressing either vasodilatation in the pulmonary arterial bed, probably passive, or the opening up of fresh channels to accommodate the increased flow. This is graphically expressed in the fall in pulmonary vascular resistance. The initial fall in central blood volume illustrates that one need not necessarily have an increase in the presence of an increase in pulmonary blood flow. This initial drop, when considered in conjunction with the initial increase in vascular resistance despite the flow increase, suggests that there may have been some initial pulmonary vasoconstriction.

R.B.: The interesting feature about this subject was that his rise in systemic blood pressure, which was marked, was mediated solely by an increase in systemic vascular resistance. In examining the pulmonary circulation the pulmonary arterial-pulmonary wedge pressure gradient ($\triangle$ P) was noted to increase slightly in the presence of a decrease in flow (see minute 3 of the exercise period). This would suggest mild pulmonary vasoconstriction. Central blood volume fell slightly as the exercise progressed.

J.B.: There was a moderate increase in flow in this subject which was unaccompanied by significant changes in either pulmonary arterial or wedge pressure. The pulmonary vascular resistance remained unchanged despite the flow increase. This is signified by the slight increase in $\triangle$ P. Central blood volume fell during the exercise period.

J.F.: This subject, who also had a marked increase in cardiac output, exhibited a concomitant rise in pulmonary arterial and wedge pressures, keeping $\triangle$ P at pre-exercise levels. Calculated pulmonary

vascular resistance varied inversely with flow, probably representing passive dilatation or the opening up of fresh channels to accommodate the flow increase.

EFFECT ON OXYGEN UPTAKE:

There was a significant increase in oxygen uptake in those three subjects who experienced an increase in cardiac output (J.H., J.B. and J.F.) (fig. 10, tables 1, 3 and 4). The average increase in these subjects was 47 mls./sq.m./minute (range 41 - 51). The exceptional subject (R.B.) showed at first a slight fall, with a gradual return to pre-exercise levels during the work performance. At no stage did this subject show an increase. This was the exceptional subject who experienced no increase in cardiac output.

ARTERIO-VENOUS OXYGEN DIFFERENCES:

Two subjects (J.H. and J.B.) showed small increases in A - V difference of 0.10 and 0.74 vols. per cent respectively. The other two subjects (R.B. and J.F.) one of whom had experienced a large increase in cardiac output were each found to have lowered their A - V difference by 0.17 vols. per cent.

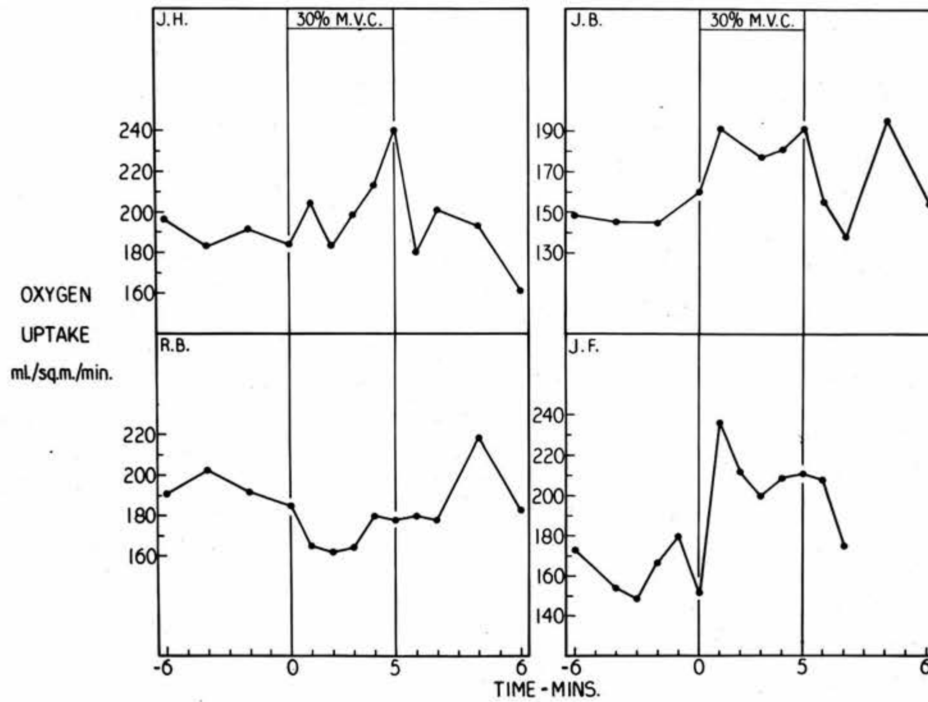


Figure 10. **The effects of hand grip contraction at 10% M.V.C. on the oxygen uptake in 4 normal subjects.**

COMMENT:

These experiments were considered to have shown that:

(i) In four normal subjects sustained isometric contraction of the forearm muscles at 30 per cent M.V.C. resulted in marked rises in systemic arterial pressure.

(ii) In two of the four subjects this pressor response was mediated solely by an increase in cardiac output associated with a tachycardia. In one subject the pressor response was mediated by both an increase in cardiac output associated with a tachycardia and an increase in systemic vascular resistance. An increase in systemic vascular resistance solely accounted for the increase in pressure in the fourth subject.

(iii) There is no strong evidence for the occurrence of active changes within the pulmonary circulation. In the subject (R.B.) whose systemic vascular response was due to arteriolar vasoconstriction, there is some evidence that some mild pulmonary vasoconstriction occurred.

(iv) Three subjects were found to increase their oxygen uptake by an average of 47 ml./sq.m./minute, while one subject showed no increase. Two subjects increased their A - V oxygen difference slightly while the other two subjects decreased it slightly.

THE EFFECT OF STATIC FOREARM MUSCULAR EXERCISE ON VENTILATION

The subjects initially studied by Lind et al (already referred to in Introduction) were chosen to undergo this experiment. One of the subjects (P.H.) however, found it impossible to work with a mouthpiece. The findings in the other three subjects are reported. Ten, twenty and fifty per cent M.V.C. were the levels of hand grip tension which they performed.

TECHNIQUES:

Ventilation was measured in Tissot spirometers, two of which were connected in series in order to obviate any interruption for emptying. Thus, minute by minute monitoring of a 20-minute period was made possible. Following the tracing precluded unnoticed effort apnoea.

PLAN OF INVESTIGATION:

Each level of hand grip was studied on a different day. All subjects were studied in the fasting state. Prior to the experiment the subjects underwent a short period of non-fatiguing supine leg exercise on a bicycle ergometer. Resting measurements were begun 20 minutes afte the cessation of the exercise. Measurements were made during a control period of five minutes, following which time the subject performed the required hand grip level. The first ten minutes of recovery after exercise were also documented.

RESULTS:

The results are tabulated in tables 5 - 7.

The mean increase in ventilation for the three subjects (for the total exercise period), at 10 per cent M.V.C., was zero (range 1.0 - +0.7/ sq.m./minute). The mean increase at 20 per cent M.V.C. was 1.2 1/sq.m./minute. (range 0.5 - +3.8). The mean increase at 50 per cent M.V.C. was 0.9 1/sq.m./minute (range +0.5 - +1.2). Changes were therefore slight. Reference to tables 5 to 7 also shows that there is no post exercise increase in ventilation.

COMMENT:

Hand grip is associated with but slight increases in ventilation.

For further confirmation of this finding, particularly because the range was somewhat wide, ventilation during hand grip was studied in a further four normal subjects.

THE EFFECT OF HAND GRIP AT 10, 20 AND 50 PER CENT M.V.C. ON THE VENTILATION IN FOUR FURTHER NORMAL SUBJECTS

TECHNIQUES:

These were as for the preceding study.

PLAN OF INVESTIGATION:

All subjects were studied in the fasting state. Prior to the exercise a short period of dynamic exercise was undergone on a bicycle ergometer. Thereafter the subject was studied according to the protocol described for the preceding study. All three levels of hand-grip were, however, performed during one session.

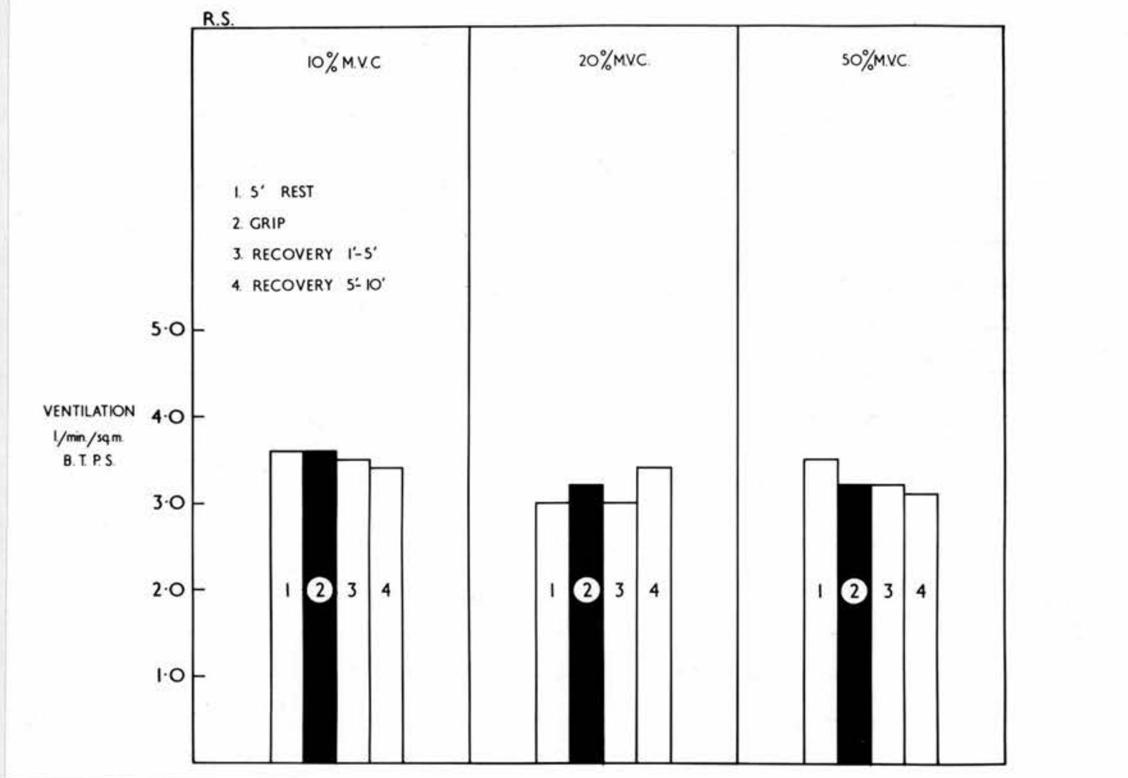


Figure 11. The effect of graded hand grip contractions on pulmonary ventilation.

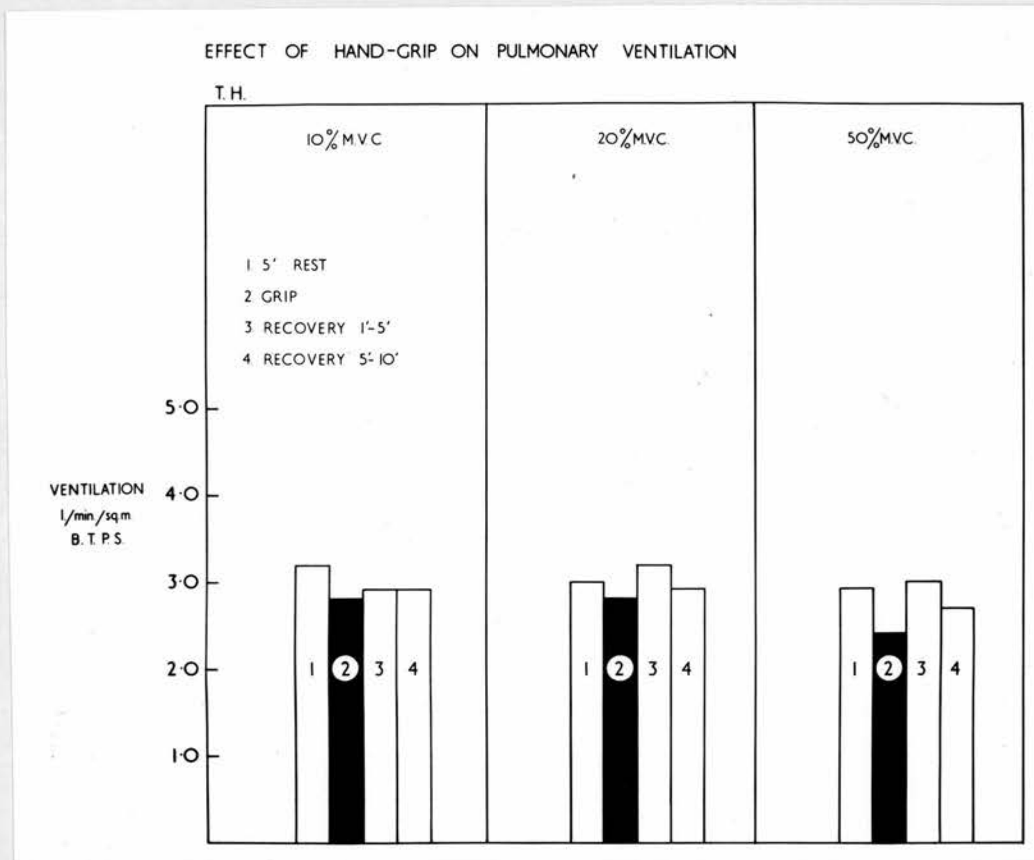


Figure 12. The effect of graded hand grip contractions on pulmonary ventilation.

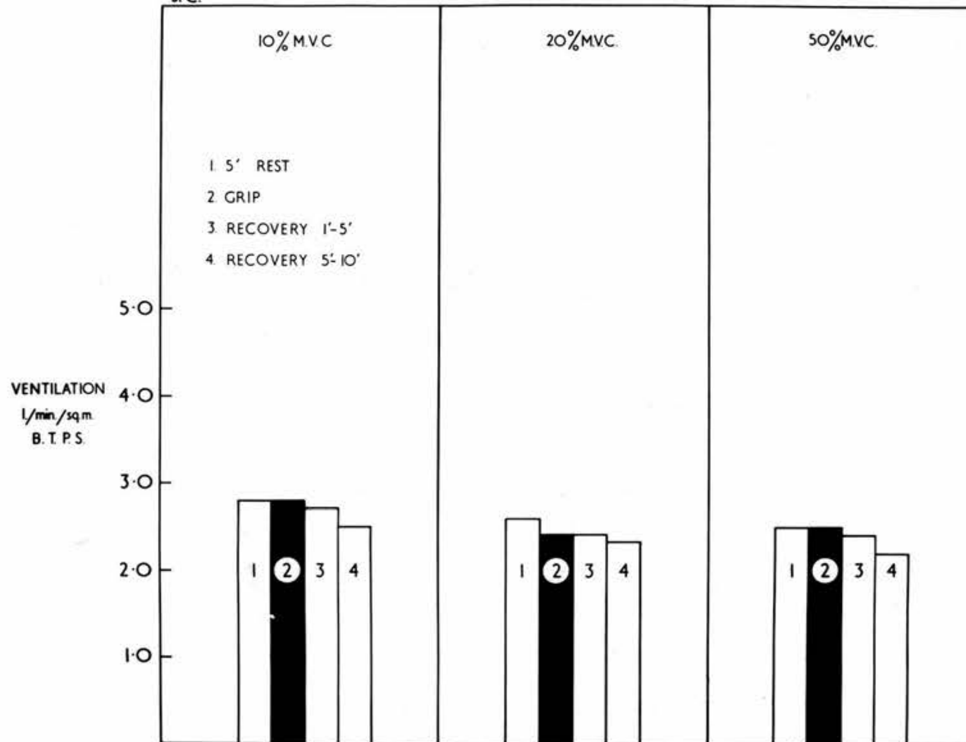


Figure 13. The effect of graded hand grip contractions on pulmonary ventilation.

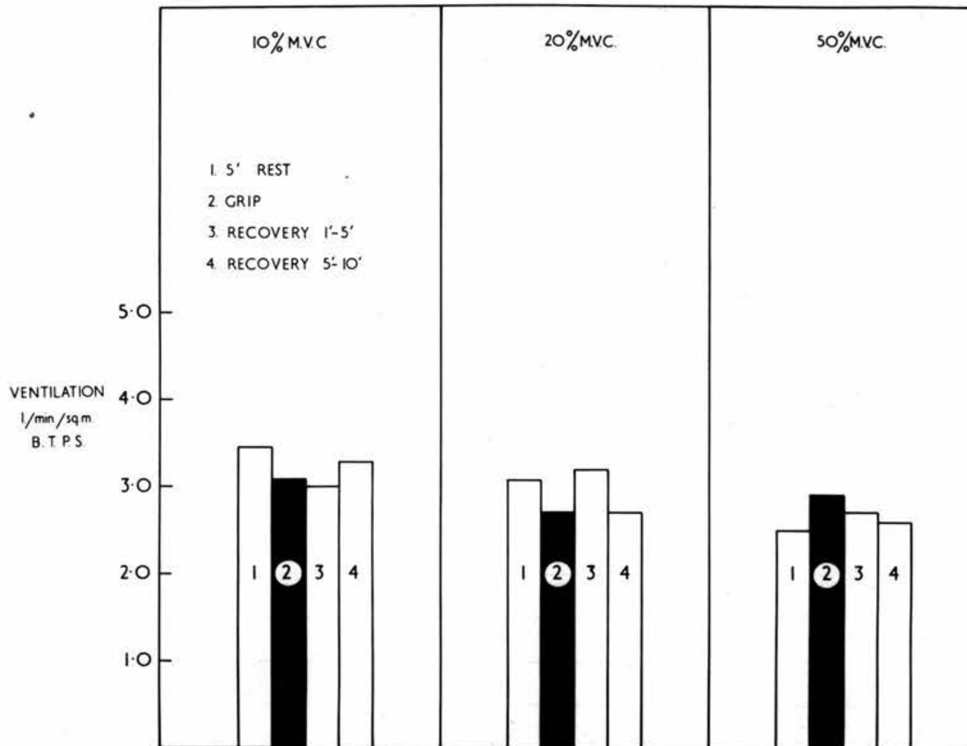


Figure 14. The effect of graded hand grip contractions on pulmonary ventilation.

RESULTS:

There was little or no significant increase in ventilation at any of the three levels of work studied (fig. 11-14, tables 8-11).

DISCUSSION:

Rushmer has described in detail a non-specific circulatory response, which occurs at the start of exercise, eating, or on being startled (Anzola and Rushmer, 1956; Rushmer, Smith and Franklin, 1959). It includes a prompt tachycardia, reduction in ventricular dimension, increased systolic and end-diastolic pressures in the left ventricle, greater rate of change in diameter, greater peak power, greater peak rate of change in pressure, and increase in accumulated stroke work. During continuance of the activity changes were prolonged. Similar responses could be produced by sympathetic stimulation and stimulation of discrete areas in the hypothalamic and subthalamic regions. Simulation of the changes could not be achieved by the creation of other conditions known to occur at the start of exercise, such as (i) the production of an increase in filling pressure, (ii) increasing heart rate with a pacemaker, (iii) the infusion of catecholamines. Rushmer suggested that the circulatory response as the start of exercise is due to a centrally determined sympathetic discharge. It is not unlikely that a similar non-specific response is evoked at the start of static exercise. In some of the situations such as postural changes and startling, the initial changes described above are somewhat of an overshoot, since there is no continued biological demand. A rapid reversion to normal therefore occurs. In static work, however, performed by small muscle groups, the heart rate,

cardiac output and systemic arterial pressure, systolic and diastolic, remain elevated or, more usually, continue to rise. The response has become specific. It is important to consider how the haemodynamic changes are maintained. It has been suggested that there may be a cortical influence at the start of activity giving rise to a non-specific sympathetic discharge. It is unlikely, however, that a specific discharge for static work, unlike that for other forms of exercise, is emitted from this point onwards. If this is so the increasing pressor response must be an expression of the particular type of work involved and it is likely that it is brought about by some influence, humoral or neural, from the working limb. Evidence will be presented later which is in favour of the view that the maintained pressor response is in fact reflexly dependant on the working limb.

A further point of specificity is that relatively large haemodynamic changes are associated with biologically slight muscular work. If one accepts the oxygen uptake as the biological index of work then an interesting point emerges from the foregoing studies. In dynamic work there is a fairly constant relationship between cardiac output and oxygen uptake (Donald et al, 1955). If one compares the relationship as defined by Donald et al for mild dynamic work (average oxygen increase per sq. m. = 163 ml.s) with that for static work one finds that for a given cardiac output increase one has disparate increases in oxygen uptake. The average oxygen uptake increase per sq.m. per litre increase in cardiac index in the series by Donald is 173 mls. (range 163 - 204) as compared with 59 mls. (range 39 - 160) in the present study. This difference is clearly decided by the working lower limbs with unimpeded circulation in the Donald series. It must then

be decided whether the haedynamic response in static work is geared quantitatively to the metabolic requirements of the tissues, or to something else. The absence of measurable oxygen debt suggests the latter to be true. This proposal is further supported by the data on arterio-venous oxygen differences. In Donald's series the average increase in A - V difference per litre increase in cardiac index was 2.76 vols. per cent (range 2.41 - 4.12 vols.). In this study the average increase was 0.28 vols. per cent (range -0.14 - 2.89). As can be seen from the range, one subject actually lowered his A - V difference during the performance of static work. Since the organism does not use the oxygen delivered, and since there is no oxygen debt created, there is therefore not a quantitative relationship between the work performed by the body and the increase in cardiac output. The increase in cardiac output would therefore appear to be in the nature of a phenomenon related to the degree of static tension of the hand grip.

The only common response to hand grip has been the increase in systemic arterial pressure. Increases in heart rate and cardiac output usually, but do not invariably (see fig. 8, subject R.B.) occur. It should be remembered that all subjects studied were relatively young. Older subjects would be those most likely to respond by vasoconstriction. Studies in this laboratory on dynamic exercise have certainly suggested that vasoconstriction is resorted to by older subjects during fatiguing treadmill exercise as a means of maintaining perfusion pressure.

There were no marked signs of active changes within the pulmonary circulation (fig. 9). It is accepted that events may have occurred which the limitation imposed by the techniques concealed. It should be noted, however, that only one subject responded solely by systemic vasoconstriction

(and probably also vasoconstricted within the pulmonary circulation). Essentially the same increase, therefore, occurs in each circulation, namely, an increase in blood flow. This results in an increase in pressure in the systemic circulation, but not in the highly compliant pulmonary circulation.

It may be wondered why the baroreceptors are not stimulated by the rise in systemic arterial pressure to reflexly bring about cardiac slowing and peripheral vasodilatation. It is clear, however, that since the baroreceptors will under normal circumstances keep the blood pressure around a certain mean level, they are here over-ridden by a different and even more powerful stimulus.

It has been proposed, therefore, that there is an initial response to static muscular work which may be closely akin to that non-specific response described for the beginning of dynamic exercise, startling reactions and changes in posture. It is also proposed that from this point onwards the response to static work is specific, and that the continued change within the circulation during its performance is dependant on some influence from the working limb. An attempt will now be made to delineate this influence and illustrate its character.

RESPONSES TO VASCULAR OCCLUSION

Reflexes arising from ischaemic tissues have been commented upon in the past. Latschenberger and Deahna (1876), for instance, found that a fall in blood pressure resulted in reflex local vasodilatation. The tissue hypoxia resulting from the fall in pressure was claimed by Zunta (1878) to be the stimulus bringing about this reflex. Hess (1930) commented on rises in systemic blood pressure which followed blockage of an artery to many individual parts. These areas which, when ischaemic, led to rises in pressure, included brain, the territory of the external carotid, kidney, and hind legs. Schneider (1934), using a Rein stromuhr, demonstrated an increase in flow in one femoral artery if circulation through the other were occluded. This response was abolished by section of the femoral nerve and by intravenous nicotine. The concept of a mechanism whereby asphyxiated tissue brought about increased local perfusion by general as well as local events was clearly attractive and led to the term 'nutrition reflex' (Hess, 1930; Fleisch, 1935).

Ludwig (1931) failed to demonstrate a rise in blood pressure in normal men if the circulation to three limbs was shut off. Alam and Smirk (1937) reported a marked pressor response to dynamic forearm muscular work, however, if the circulation to the working limb was occluded. They also noted that the blood pressure remained elevated after the cessation of work provided the circulation remained occluded. Similar work under conditions of free circulation resulted in but small changes. It was considered that the type of work was not so important as the circulatory conditions under which it was operating.

The following investigations were therefore devised to:

(i) define the change in magnitude of the pressor response in static work when done under conditions of total vascular occlusion;

(ii) note the effect on the heart rate and blood pressure of total vascular occlusion to a resting arm;

(iii) note the effect on the heart rate and blood pressure of continued total vascular occlusion after the cessation of static work.

THE EFFECT OF VASCULAR OCCLUSION ON THE PRESSOR RESPONSE TO STATIC MUSCULAR WORK

TECHNIQUES:

One 55 cm. catheter was introduced into the brachial artery and passed centrally. Continuous pressure was recorded.

PLAN OF INVESTIGATION:

The object of the study was to compare the changes in systemic arterial pressure and heart rate during hand grip at 10, 20 and 50 per cent of a maximum voluntary contraction (M.V.C.) before and after complete vascular occlusion of the working forearm and hand.

The study was carried out on four subjects (J.L., G.R., A.H. and D.S.). Personal data are contained in table 12. All subjects were trained beforehand in the experimental protocol on three occasions.

Following an initial control period the subject was required to grip the dynamometer at 10 per cent M.V.C. for five minutes. Observations were continued throughout the subsequent five minute recovery period. After a rest period of twenty minutes, the same procedure was exactly repeated, but with the circulation to the limb completely occluded during the working period by a sphygmomanometer cuff round the upper arm inflated to 240 mm.Hg. The occluding cuff was abruptly inflated and deflated at the onset and end of work respectively. Following a further recovery period of twenty minutes this entire procedure was repeated at hand grip tensions of 20 and 50 per cent M.V.C. Due to the earlier onset of fatigue at these higher working levels the contraction was required to be maintained at 20 per cent M.V.C. for only three minutes and at 50 per cent M.V.C. for two minutes. Heart rate and systolic, diastolic and mean systemic arterial pressures were recorded throughout the entire procedure.

RESULTS:

SUBJECTIVE EFFECTS:

Repeated preliminary trials had shown that none of these hand grip contractions caused any pain either with or without vascular occlusion. It was, in fact, on this basis that the tension-time programme was decided.

EFFECTS OF HAND GRIP ON THE SYSTEMIC ARTERIAL PRESSURE:

The effects of hand grip on the systemic arterial pressure in the four normal subjects at 10, 20, and 50 per cent M.V.C. are detailed in tables 13 - 16, and illustrated in figs. 15 - 19. It will be observed that

the increments in the pressor responses are approximately proportional to the increments in rate of work.

During the control study, prior to vascular occlusion, at 10 per cent M.V.C., the mean arterial pressure increased in all four subjects by an average of 5 mm.Hg., the range of increase being 3 - 9 mm.Hg. In all subjects this increase in pressure occurred within one minute of the onset of the contraction and thereafter did not increase further. At the completion of the contraction the pressure promptly returned to normal levels.

At 20 per cent M.V.C. without vascular occlusion, the increase in the mean arterial pressure was progressive in three of the four subjects studied. At the end of three minutes of hand grip the blood pressure had increased by an average of 10 mm.Hg., the range of increase being 3 - 15 mm.Hg. Again the blood pressure rapidly returned to control values on relaxation.

At 50 per cent M.V.C. the mean arterial pressure rapidly and progressively increased in all four subjects during the two minutes of the contraction. The average increase at the end of this period of contraction was 27 mm.Hg., the range of increase being 17 - 36 mm.Hg. Relaxation was associated with a rapid return of the blood pressure to normal levels.

There was no significant change in pulse pressure in any of the four subjects at any level of hand grip tension.

EFFECTS OF VASCULAR OCCLUSION ON THE SYSTEMIC ARTERIAL PRESSURE RESPONSE TO HAND GRIP

The changes in blood pressure described above were remarkable potentiated by vascular occlusion; in all subjects the degree of potentiation

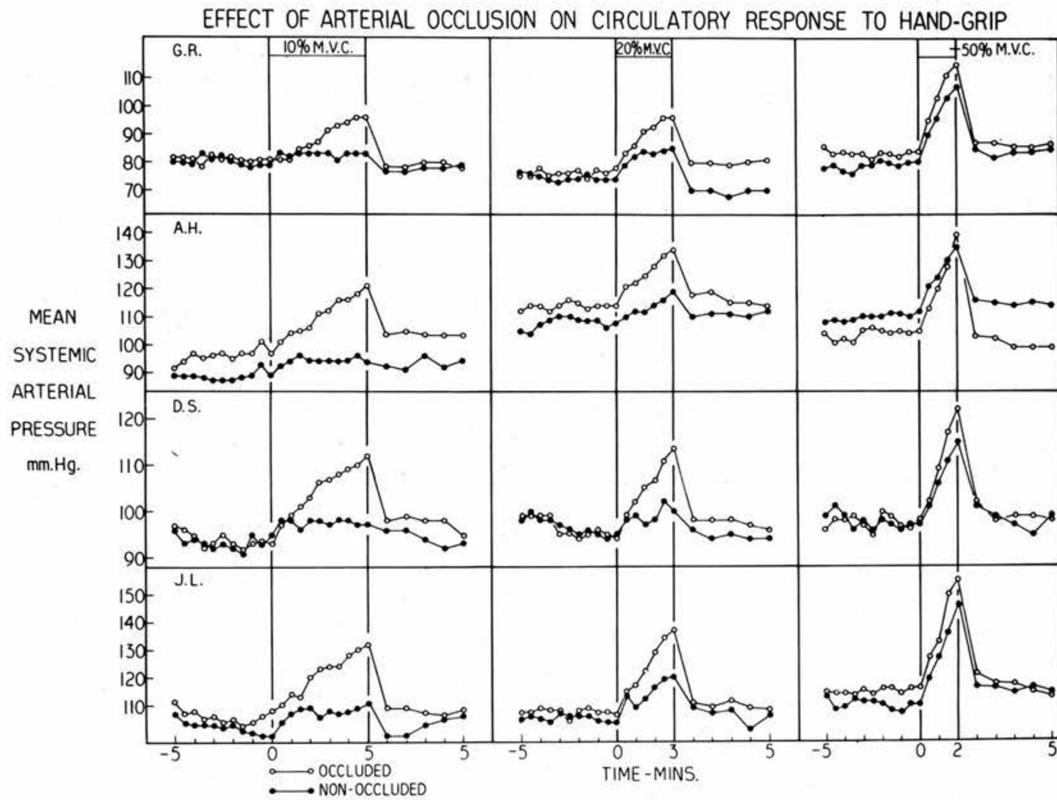


Figure 15. The pressor effect of graded hand grip contractions under conditions of free circulation and during total vascular occlusion of the working limb.

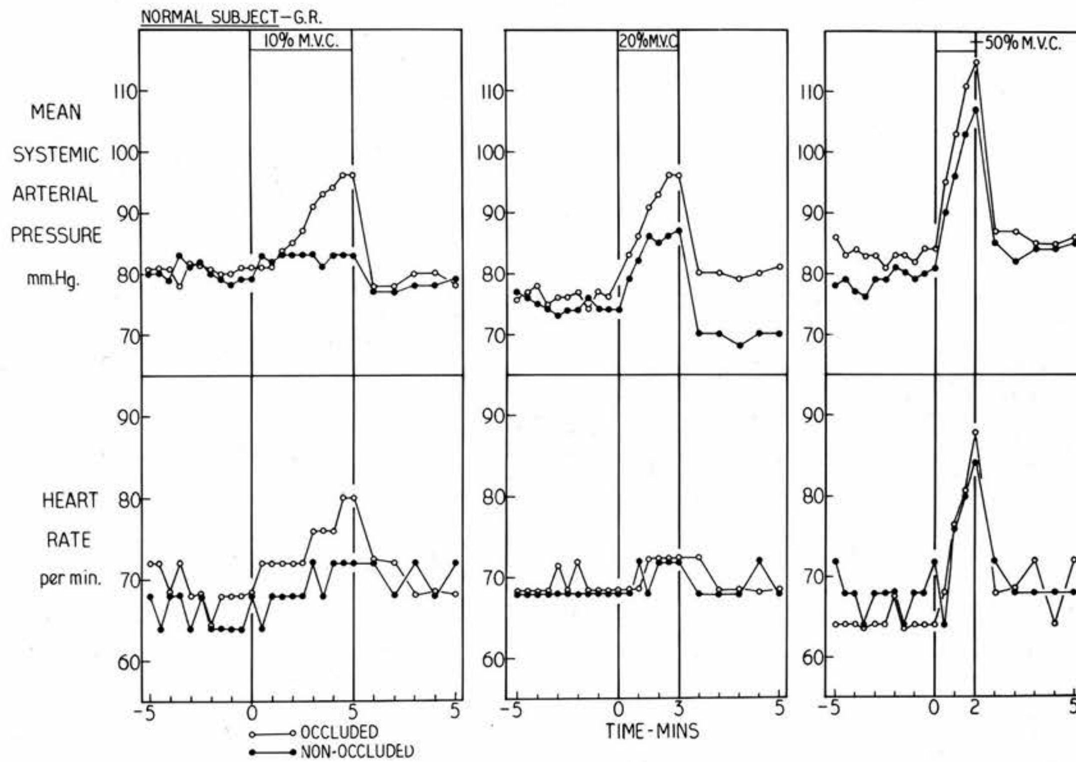


Figure 16. The effect of graded hand grip contractions on the blood pressure and heart rate.

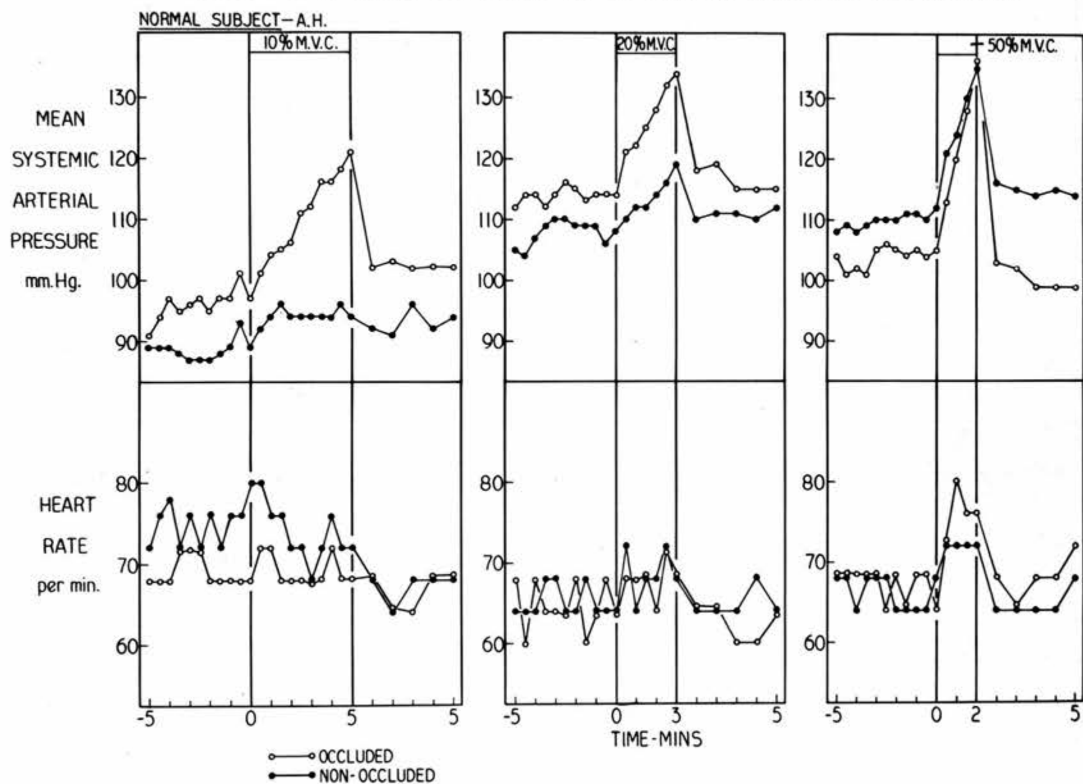


Figure 17. The effect of graded hand grip contractions on the blood pressure and heart rate.

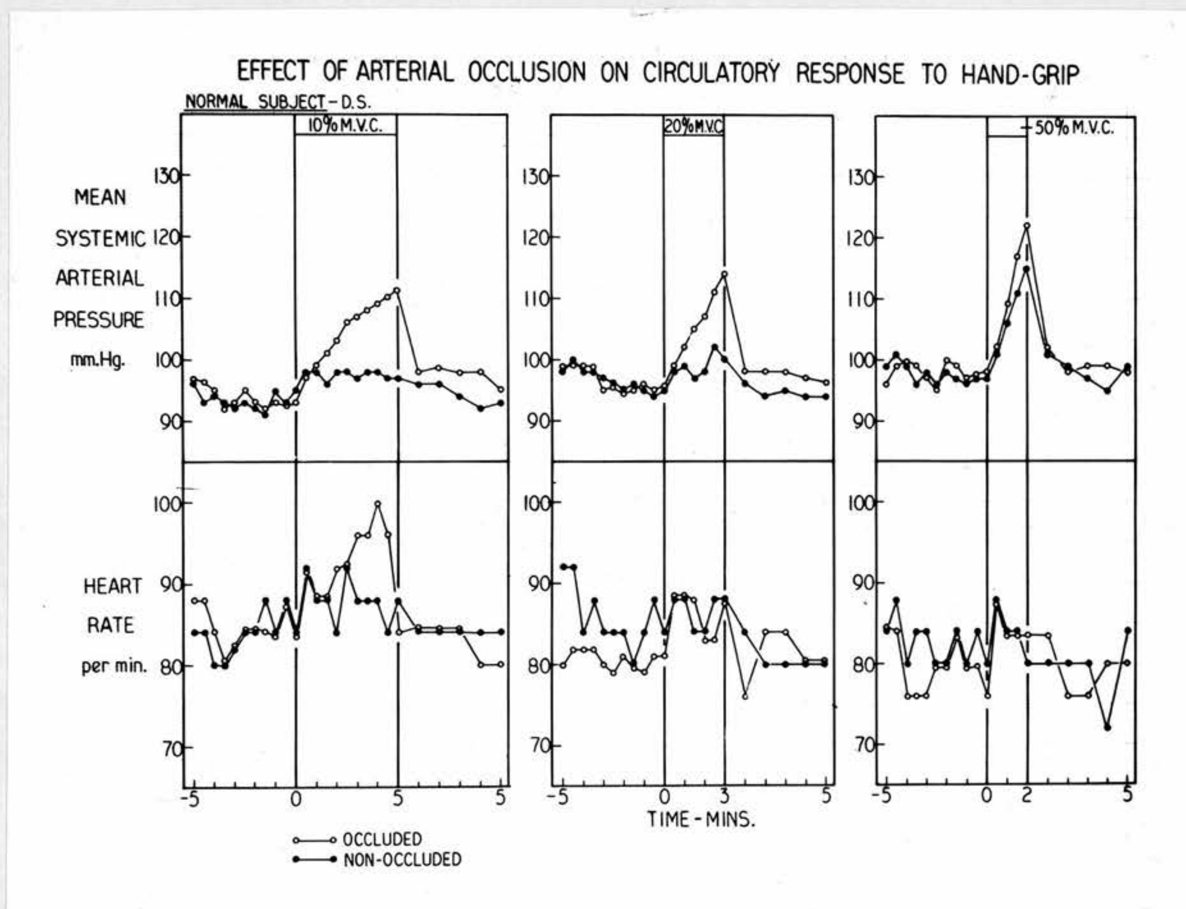


Figure 18. The effect of graded hand grip contractions on the blood pressure and heart rate.

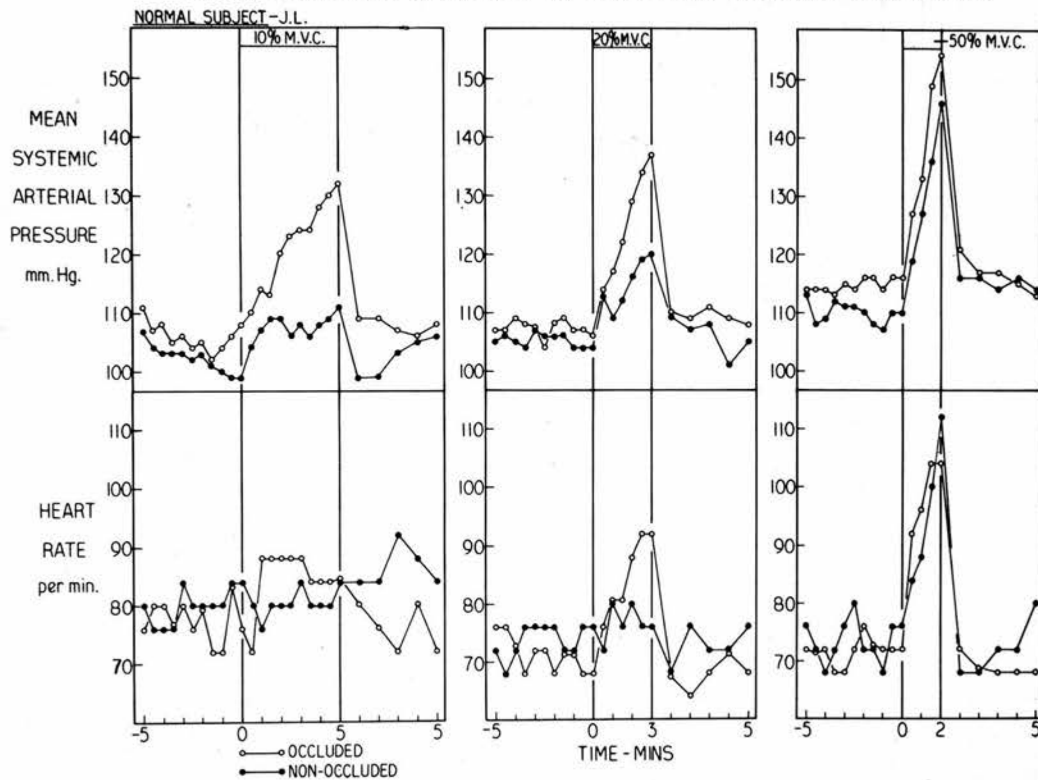


Figure 19. The effect of graded hand grip contractions on the blood pressure and heart rate.

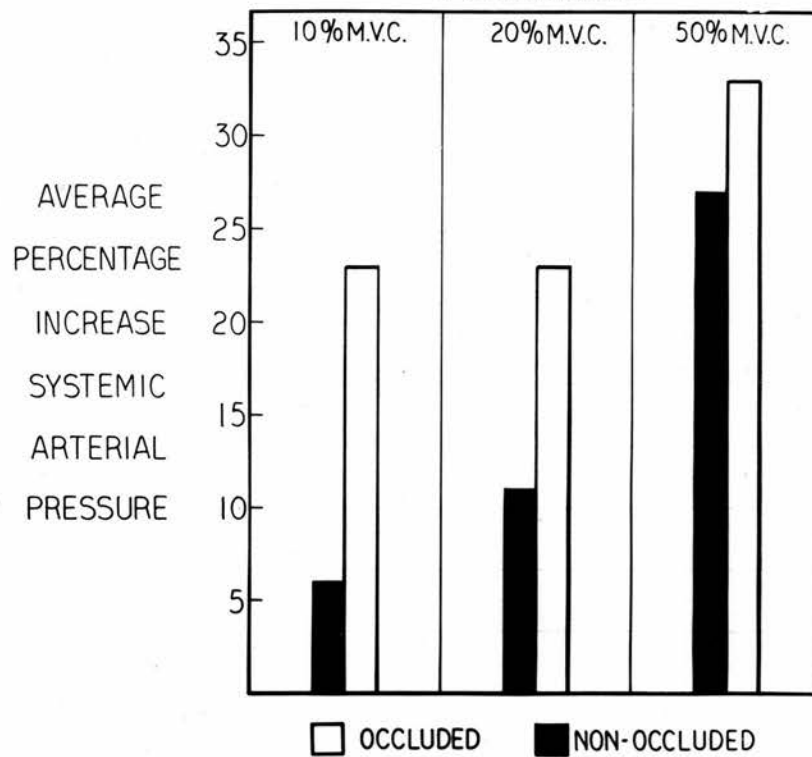


Figure 20. The pressor effect of graded hand grip contractions under conditions of free circulation and during total vascular occlusion of the working limb.

was greatest at 10 per cent and least at 50 per cent M.V.C. (figs. 15 - 20).

The addition of complete vascular occlusion at 10 per cent M.V.C. converted the plateau of increased blood pressure observed in the control study to a continuously rising curve in all four subjects. Whereas, prior to vascular occlusion, the average rise in blood pressure was 5 mm.Hg. at the end of five minutes of hand grip contraction, the addition of vascular occlusion of the working muscles produced an average increase of 21 mm.Hg., the range of increase being 16 - 26 mm.Hg.

During the control study, 20 per cent M.V.C. for three minutes without vascular occlusion was associated with a progressive increase in blood pressure, the average increase being 10 mm.Hg. This pressor response was significantly increased by vascular occlusion in all four subjects, the average increase now being 22 mm.Hg., and the range of increase 17 - 20 mm.Hg.

At 50 per cent M.V.C. the potentiation of the pressor response by vascular occlusion was much less marked. During the control study the average increase in blood pressure at the end of two minutes of hand grip was 27 mm.Hg. After two minutes of similar work during vascular occlusion the average increase in pressure was 32 mm.Hg., the range of increase being 24 - 40 mm.Hg.

Although there were individual variations in the response of the pulse pressure to hand grip during vascular occlusion, these followed no consistent trend.

EFFECTS OF HAND GRIP ON THE HEART RATE

The results are detailed in tables 13 - 16 and illustrated in figs. 16 - 19.

Although the changes in heart rate during hand grip both before and during vascular occlusion were quite variable, certain similarities to the changes in blood pressure were observed. At 10 per cent M.V.C. the heart rate response during vascular occlusion was significantly increased over that which obtained in the control study in three of the four subjects. Before vascular occlusion was superimposed on the working, 10 per cent M.V.C. was associated with an average increase in heart rate, comparing the fifth minute of work with the mean of the control values, of five beats per minute (range of increase 4 - 6) in the three subjects J.L., G.R. and D.S. During complete vascular occlusion the same degree of hand grip produced an average increase in heart rate of nine beats per minute (range of increase 6 - 11) in these three subjects. At 20 per cent M.V.C. the heart rate in the control study increased by an average of three beats per minute (range of increase 2 - 4) in the four subjects. However, at this level of hand grip only one subject (J.L.) demonstrated potentiation of the heart rate response during vascular occlusion, although the systemic arterial pressor response was potentiated in all four subjects. In this subject (J.L.), 20 per cent M.V.C. before and after vascular occlusion was associated with increases in heart rate of two and 21 beats per minute respectively. 50 per cent M.V.C. was associated with a marked increase in heart rate in all but one subject (D.S.) during the control contraction. The average increase in heart rate in the three subjects J.L., A.H. and G.R. was 20 beats per minute (range of increase 6 - 38). The addition of vascular occlusion during the hand grip caused little or no change in this response in any of the four subjects studied.

THE EFFECT OF VASCULAR OCCLUSION OF THE RESTING FOREARM AND HAND ON THE HEART RATE AND SYSTEMIC ARTERIAL PRESSURE

TECHNIQUES:

One 55 cm. nylon catheter was introduced into the brachial artery of a resting limb and passed centrally. Continuous pressure was recorded. Skin electrodes were placed over the forearm to be occluded and attached to an electromyograph so that even minor movements by fingers were recorded synchronously with the vascular trace.

PLAN OF INVESTIGATION:

The objective of the study was to measure the effects, if any, of vascular occlusion of the resting forearm and hand over a period of twenty minutes.

The study was carried out on two subjects, one male and one female (W.R. and M.R.) whose personal data are contained in tables 17 - 18. Following recovery from an initial period of stabilizing supine leg exercise, the subject was required to lie quietly without movement of the arms for a control period of ten minutes. The sphygmomanometer cuff was then rapidly inflated to 240 mm.Hg. and kept so for a total period of twenty minutes, the arterial pressure being recorded from the opposite arm. Recovery observations were made for a further period of five minutes.

RESULTS:

The results are contained in tables 17 - 18. In subject M.R., in whom there was practically no movement of the forearm muscles as checked electromyographically, there was no change in systemic arterial pressure or

in heart rate. In the other subject W.D., in whom there was electromyographic evidence of slightly more movement, the mean systemic arterial pressure increased slightly after ten minutes. This was unaccompanied by any change in heart rate.

THE EFFECT OF CONTINUED VASCULAR OCCLUSION ON THE PRESSOR RESPONSE TO STATIC MUSCULAR WORK

TECHNIQUES:

One 55 cm. nylon catheter was introduced into the brachial artery of the resting limb and passed centrally. Continuous pressure was recorded.

PLAN OF INVESTIGATION:

The objective of the study was to observe the changes in heart rate and systemic arterial pressure of continued vascular occlusion following the performance of hand grip undergone under ischaemic conditions. Two normal subjects were studied. Personal data are contained in tables 19 to 20. Following an initial control period of five minutes a sphygmomanometer cuff round the upper arm was abruptly inflated to 240 mm.Hg. After three minutes the subject was required to grip the dynamometer at 30 per cent M.V.C. with the circulation to the working forearm and hand still totally occluded. One subject (H.S.) gripped for a period of three minutes while the other subject (M.L.) did so for five minutes. Following cessation of hand grip the cuff was kept inflated for a further three minutes. Measurements were then continued for a recovery period of five minutes.

RESULTS:

SUBJECTIVE EFFECTS:

One subject (M.L.) experienced some pain towards the end of the gripping period, while the other subject (H.S.) experienced none. Fatigue was the predominant subjective effect on both.

EFFECTS ON SYSTEMIC ARTERIAL PRESSURE AND HEART RATE:

The results are illustrated in fig. 21 and tabulated in tables 19 - 20.

In both of the subjects studied there were slight increases in mean systemic arterial pressure during the three minute period of vascular occlusion alone (fig. 21). There were, during hand grip under the same conditions of circulatory obstruction, rises of 36 per cent (H.S.) and 46 per cent (M.L.) in mean blood pressure (percentage increase of final measurement during gripping period over the mean of the control measurements). On relaxing the hand grip, but with the circulation still occluded, 52 per cent of the increase was maintained by one subject (H.S.) and 90 per cent by the other subject (M.L.). In the final recovery period after cessation of occlusion one subject (H.S.) approached pre-exercise levels within five minutes, while the other subject (M.L.) still had not done so.

Both subjects showed an increase in heart rate during the gripping period. This, however, immediately returned to normal on cessation of grip. There was no maintenance of the tachycardia by vascular occlusion alone.

The preceding experiment has since been repeated in four further subjects in the Department of Medicine, The Royal Infirmary, Edinburgh, with exactly similar results. The findings are illustrated in fig. 22 (subject M.L. is included in figs. 21 and 22).

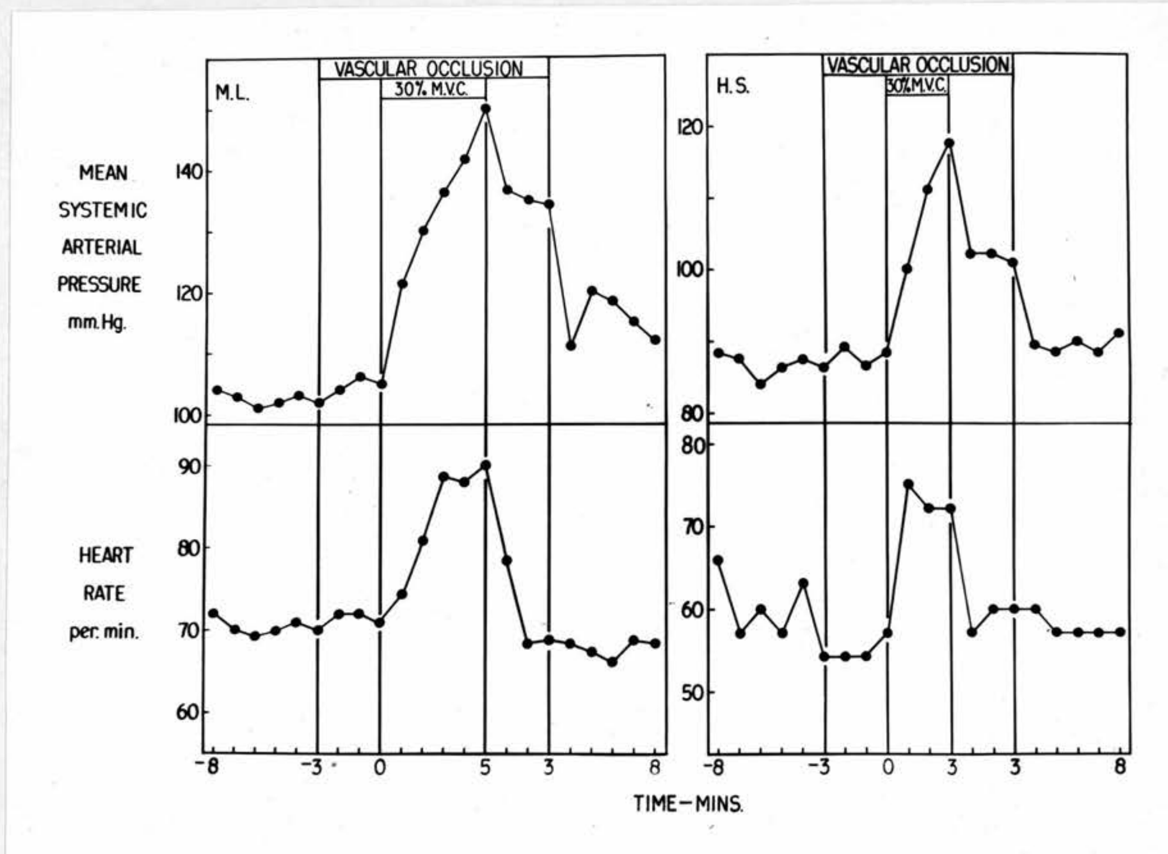


Figure 21. The effect of maintained vascular occlusion after cessation of exercise by the ischaemic limb.

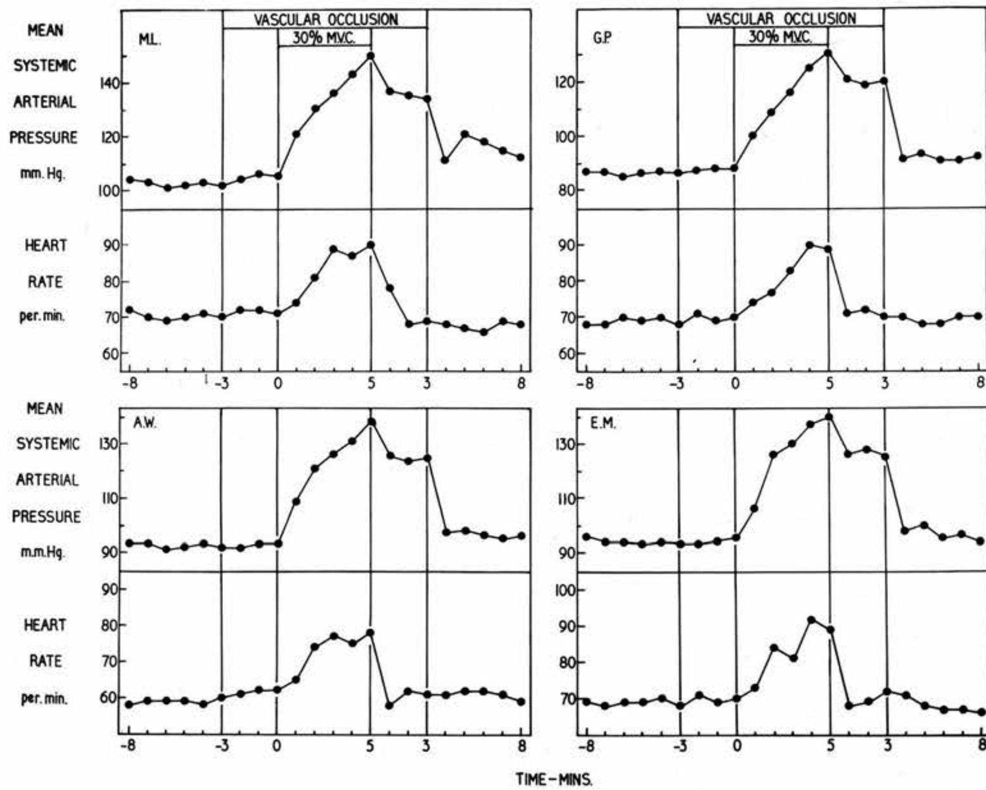


Figure 22. The effect of maintained vascular occlusion after cessation of exercise by the ischaemic limb.

DISCUSSION:

Evidence has already been cited (see Introduction) to establish that static contractions, if strong enough, can prejudice the blood flow through working muscles. Whether this is effected by the high intramuscular pressure or by 'nipping' of the blood vessels is uncertain.

If circulatory obstruction plays a central role in the elicitation of the pressor response to static work, then the potentiating effect of total vascular occlusion should be far more marked at lower levels of contraction where circulatory obstruction under natural conditions will be minimal. This was found to be so, the pressor response being greatly potentiated at 10 per cent M.V.C. Similarly, the potentiation by vascular occlusion at 50 per cent M.V.C. was observed to be very much less, with the response at 20 M.V.C. lying somewhere between the other two levels (figs. 15 - 20). The very slight or absent potentiations at 50 per cent M.V.C. are interpreted as an expression of the greater obstruction to flow at this level of sustained contraction in the non-cuffed limb.

The foregoing provided strong evidence that the stimulus from the limb in static work is closely related both qualitatively and quantitatively to circulatory obstruction in the presence of muscular contraction (albeit near - isometric). It also provided strong, though not definitive, evidence that there is a stimulus from the limb. In the final series of the three preceding experiments, however, it is clearly demonstrated that the blood pressure, though initially dropping slightly at the cessation of work, is nevertheless maintained at abnormally high levels for so long as the cuff remains inflated. Here the unpredictable effects of mental concentration

on the work performance have been removed. In one of these subjects (H.S.) pain was absent. In the other subject (M.L.), while there was some pain, fatigue was the predominant symptom. In addition we have established that the psychological effects of total vascular occlusion of a resting limb for twenty minutes, with its associated discomfort, did not result in a significant change in heart rate or blood pressure (tables 17 - 18). There is therefore more or less conclusive evidence for the existence of an influence operating at the periphery. This influence could only be mediated, in the occlusion experiments, via the neural connections between the limb and the rest of the soma. The pressor response must be therefore considered to be reflexly determined. The pulse rate changes are different in that they are not maintained by vascular occlusion alone following cessation of exercise. This might suggest that there is a central element concerned in their production. We have indeed shown in all of these experiments that the heart rate response is more erratic than the rise in blood pressure.

The reflex must of necessity be activated by one of two mechanisms, or by a combination of both. These are (i) mechanical distortion of nerve endings, which endings are more sensitive to distortion under ischaemic conditions, or (ii) chemical stimulation of some receptors in or near the muscle.

The type of contraction involved in our experiments is near-isometric and static. The difficulty of having a purely isometric contraction is appreciated and it is freely admitted that some slight degree of muscle shortening will occur. This shortening, and therefore mechanical distortion will be, however, slight, and certainly much less than during dynamic work.

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In addition the blood pressure remains elevated after the cessation of work and therefore after the cessation of mechanical distortion, if the cuff remains inflated. To support the mechanical distortion hypothesis further necessitates the proposition that the local environmental changes induced by ischaemia have created a favourable situation for the maintenance of a discharge sink initially created by the mechanical distortion of sensitive nerve endings.

Because of its possible clear relationship to ischaemia, the second suggested mechanism, that of chemical stimulation of receptors in or near the muscle, is more attractive. We have shown that the performance of muscular work under conditions of circulatory obstruction is the main factor deciding the pressor response. For a receptor to interpret this event, it must be presented with a stimulus in some definite form such as, for instance, by a low pO_2, pH, or by an abnormally high local concentration of the products of anaerobic metabolism. The appearance of the latter substances will of course be greatly accelerated under the ischaemic conditions. The potentiation brought about by total vascular occlusion would then contribute to the stimulation in two ways. It would, firstly, increase the ischaemia. Secondly, the associated venous occlusion would cause an almost complete retention in the limb of any substances which are produced. Many of these substances, which, under conditions of normal blood flow are present in only minute amounts, and which during dynamic work with unimpeded circulation will be washed out of the limb, will now accumulate. Such substances might be suspected of stimulation of local receptors, especially under the influence of a low pH (evidence for which will be later presented).

It is well known that sufficient stimulation of almost any afferent nerve in the body will lead to a pressor response. This response is usually vasoconstrictor in the animal. Many areas are tabulated below, which when stimulated, lead to rises in blood pressure.

Central end of almost any afferent nerve	v. Bezold (1863) Grützner and Heidenhain (1875)
Post. roots,	Asp (1867)
Splanchnic	Mall (1890)
Dura Mater	Howell and Austin (1900)
Spinal Cord	Gray (1912)
Post. auricular	Lovén (1866)
Radial, median, ulnar.	Grossman (1897)
Optic and facial	Martin and White (1922)
Carotid nerve	Tournade and Malméjac (1930)
Post. roots	Bradford (1889)

Pressor responses may be seen in spinal animals (Dittmar, 1870), and we know that autonomic reflexes have been elsewhere demonstrated in the spinal cord (Guttman and Whitteridge, 1947). On the other hand the sympathetic discharge in response to stimulation of N. ischiadicus and brachialis in the cat has been shown to be dependent on an intact spinal cord (Sell, Erdelyi and Schaefer, 1958). It has been demonstrated by Ranson and Billingsley (1916) that the impulses from somatic muscle bringing about pressor responses pass up the spinal cord via the tract of Lissauer. Johannsson (1962) has shown that weak or slow stimuli to the sciatic nerve in the chloralosed cat bring about depressor reflexes, but that a certain critical frequency or strength of current will convert this response into a pressor one. The afferent fibres subserving this reflex, when separated out by means of strength

duration curves, appeared to be non-medullated c-fibres. These are fibres known to conduct under ischaemic conditions.

The pressor response in these animal experiments has usually been vasoconstrictive in type and is therefore not directly analogous to the human experiments under discussion where a heart rate dependent increase in cardiac output is the main cause of the rise in blood pressure. The attempt is not being made, however, to relate the two so closely. The attempt is being made to show that there are possible pathways over which a pressor reflex could travel. It would be probably rewarding to investigate this subject more closely in humans with certain neurological deficits.

THE EFFECT OF HAND GRIP ON OXYGEN SATURATION, pH, LACTATE AND POTASSIUM CONCENTRATION OF FOREARM VENOUS BLOOD

Because it is reflex dependant, the pressor response to static muscular work must be brought about by the physico-chemical stimulation of some sensitive nerve receptor site. This will create an action potential which will then be propogated as a nerve impulse. The substance which initially causes stimulation may be a metabolic end-product only produced during ischaemic muscular work. There may be, alternatively, a change in the local concentration of some substance already present, such as, for instance, hydrogen ions. Changes are known to occur in the concentration of certain substances (see below) during muscular work. It was therefore decided to study this subject. The substances selected for study and the reasons for their choice are considered below.

Retrograde catheterisation of the median cubital vein was the method chosen to obtain representative samples of blood issuing from the working muscle area. There can be little doubt that, with this technique, the sample will contain an admixture of hand and forearm skin venous blood (Coles, Cooper, Mottram and Occleshaw, 1958). It is almost certain, however, that such dilution would not conceal changes in concentration of the substances chosen for study (see later reference to studies by Barcroft, Greenwood and Whelan, 1963, and Fukudu, 1951).

In the experiment about to be described, oxygen saturation, pH, lactate and potassium concentration were measured before, during and after hand grip. Reasons for choice of these substances are given below:

Oxygen Saturation: We have already shown that prejudice of vascular supply is related both qualitatively and quantitatively to the pressor reflex. The degree of desaturation by the muscle at different work levels and its choronological relationship to the pressor response would therefore yield information of considerable value. A similar study has been recently made (Barcroft et al 1963).

pH: The excitability of tissues is known to be related to the pH of their environment. It was therefore decided to note whether there existed a chronological relationship between pH changes and the pressor response. It was to be expected, a priori, that there would occur a fall in pH during the performance of work by muscles with an inadequate blood supply.

Lactate: The fall in pH under anoxic condition would be almost certainly due to an accumulation of lactic acid, for with lack of oxygen, on which the citric acid cycle is dependant, a considerable proportion of the pyruvic acid will be reduced to lactate. Again, the chronological relationship between changes in lactate concentration and the pressor response is of major importance.

Potassium: Potassium is known to flow out of muscles during a contraction, or to be more precise, during the action potential which precedes the chemico-mechanical coupling leading to a contraction. It is also known to be present in a higher concentration in blood sampled from the cubital fossa after ischaemic muscular work by the forearm muscles (Broome et al, 1964; Ladé and Brown, 1963; Farber, Pellegrino, Conan and Earle, 1951).

These changes are measurable despite the dilution in such a site by skin venous blood. The dilution in our chosen sampling site, which is deeper and more proximal to the muscle, might be expected to be much less. Potassium was also considered to be of especial interest since it is a known depolarizing agent.

TECHNIQUE:

A 12 cm. nylon catheter was introduced by a modified Seldinger method into the median cubital vein and passed peripherally and deeply. This catheter was considered to be sampling mainly muscle venous blood, though there was a probable admixture of skin and hand venous blood (vide supra). A 55 cm. nylon catheter (bore 0.75 mm.) was introduced into one brachial artery and was used for sampling arterial blood.

The methods used in determination of blood hydrogen ion, lactate, oxygen and potassium concentration are already referred to (see Methods).

PLAN OF INVESTIGATION:

Four subjects were studied. These were the same subjects as in the study by Lind et al (1964).

Initially, two maximum contractions, separated in time by one minute, were performed. Twenty minutes later control observations were made for a period of five minutes. The subject was then required to perform a hand grip at 10 per cent M.V.C. for five minutes. Following relaxation the recovery period was documented for ten minutes. This entire procedure was repeated at 20 per cent. At 50 per cent the period of contraction was reduced

to one minute, but the experiment was otherwise similar. During control periods, venous blood oxygen saturation was determined minute by minute, while pH, lactate and potassium concentration were determined on alternate minutes. During exercise all of these parameters were measured at intervals of one minute, except at 50 per cent M.V.C., when they were measured at intervals of half a minute. During recovery periods, venous blood oxygen saturation was again determined minute by minute, while pH, lactate, and potassium determinations were made on the 1st, 2nd, 3rd, 5th and 10th minutes. Arterial blood measurements were made less frequently (see figs. 23 - 26).

RESULTS:

The results are tabulated in tables 21 - 24.

Blood Oxygen Saturation: In fig. 23 the changes in blood oxygen saturation are illustrated. There was, at 10 per cent M.V.C., in all instances, a considerable fall in forearm venous oxygen saturation. The average drop in percentage saturation for the four subjects was 26.8 (range 18.8 - 33.6). The average final value achieved during work was 38.9 per cent (range 32.2 - 50.7). The average increase in A - V difference, was, for the same period 5.45 vols per cent (range 3.85 - 6.80). In all instances these variables returned to pre-grip levels within one minute of relaxation.

There was, at 20 per cent M.V.C., a yet greater fall in oxygen saturation, the average percentage drop being, on this occasion, 36.7 (range 34.7 - 39.3). The average final value achieved after five minutes exercise was 27.4 per cent (range 24.8 - 30.8). Similarly, there occurred a greater increase in A - V difference than at 10 per cent M.V.C. Here the

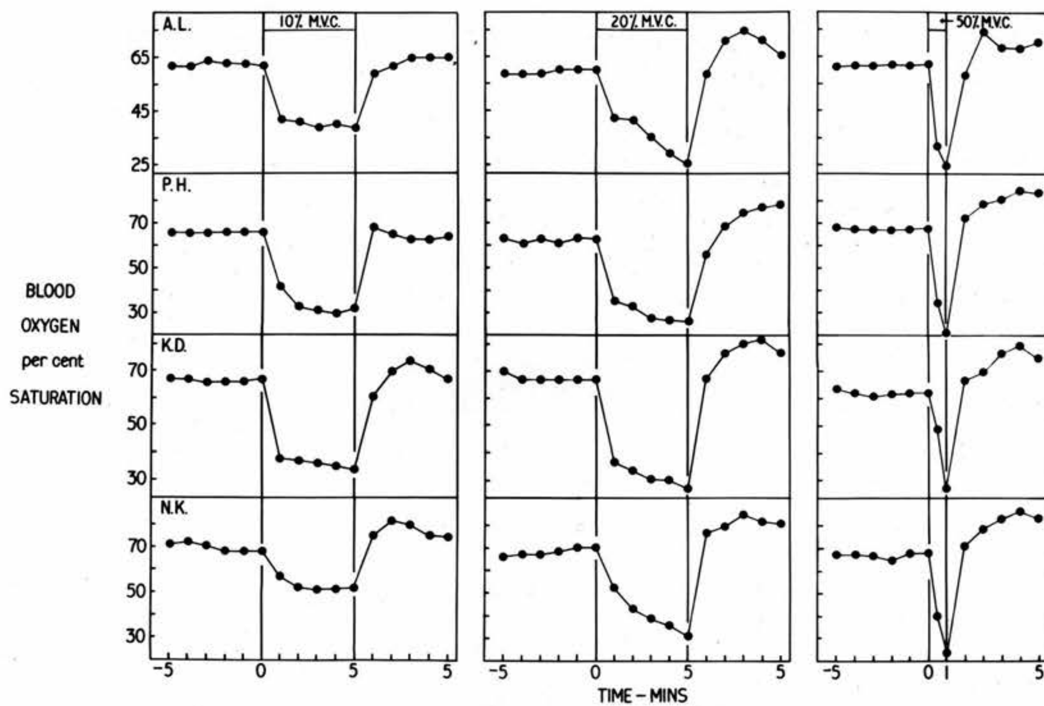

Figure 23. The effect of graded hand grip contraction on forearm venous blood oxygen saturation.

average increase was 7.78 vols. per cent (range 7.10 - 8.27). Again the oxygen saturation returned to around pre-grip levels within one minute, but then, in all instances, rose slightly, usually achieving a level rather greater than in the control observations. Similarly, the A - V difference quickly returned to normal, and then fell below control levels. This phenomenon is readily attributable to the accompanying reactive hyperaemia.

At 50 per cent M.V.C. the exercise period lasted for one minute only. Despite this, however, the fall in oxygen saturation was greater at the end of exercise than at the end of a five minute period at 20 per cent M.V.C. The average percentage fall was 40.1 (range 34.6 - 44.8). The average actual value achieved was 24.0 (range 22.2 - 27.3). The increase in A - V difference was also yet greater again than at 20 per cent M.V.C. The average rise was 8.31 vols. per cent (range 6.88 - 9.52). Again venous oxygen saturation and A - V difference rapidly returned to normal, then increased and decreased, respectively, during the recovery period. It was here also thought to be due to the reactive hyperaemia which is a constant feature in this phase.

pH: In fig. 24 are represented the changes in forearm venous blood pH during hand grip contractions at 10, 20, and 50 per cent M.V.C.

There was, at 10 per cent M.V.C., in all four subjects, a slight fall in pH (average 0.03 pH units; range 0.02 - 0.05). During the exercise the pH did not continuously fall, but settled in three of the four subjects; the exception was P.H. In all instances the pH did not return immediately to normal on relaxation and at least five minutes invariably elapsed before pre-grip levels were again reached.

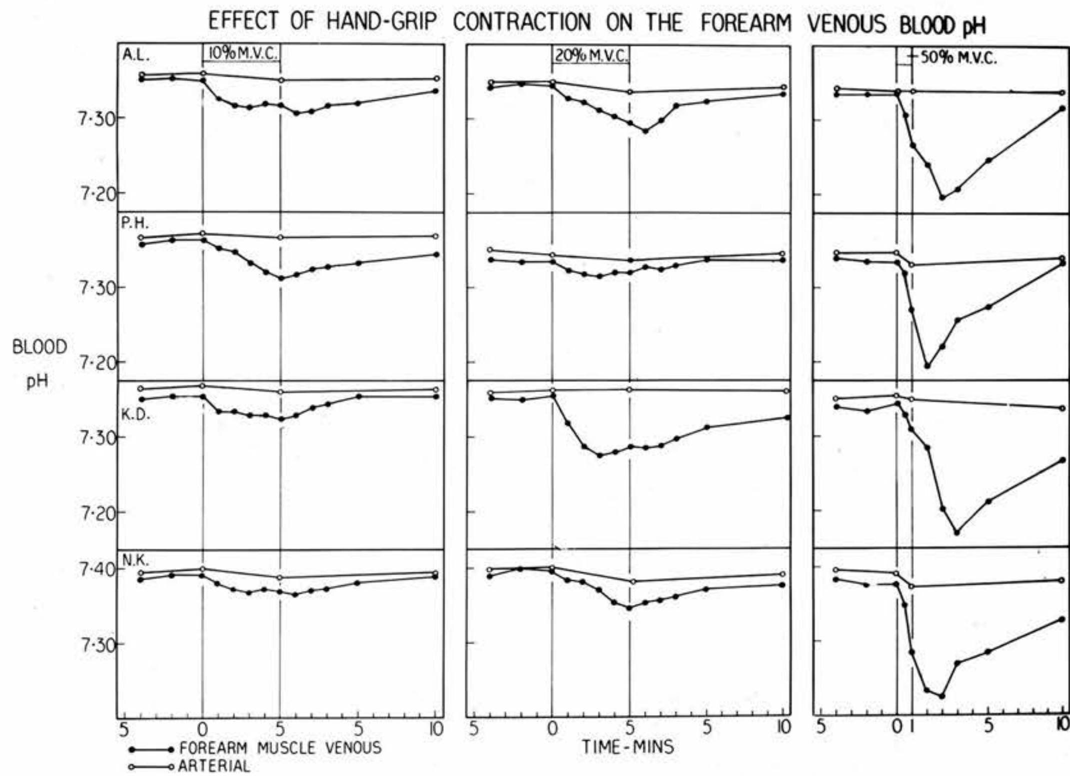

Figure 24. The effect of graded hand grip contraction on forearm venous blood pH.

The average fall in pH was, at 20 per cent M.V.C., somewhat greater, namely 0.05 pH units (range 0.02 - 0.06). On this occasion it continued to decrease during the exercise in two of the four subjects (A.L. and N.K.) while the other two subjects achieved steady levels. Again at least five minutes elapsed in all instances before a return to around resting levels.

At 50 per cent the average fall in pH at the end of a one-minute exercise period was 0.07 (range 0.03 - 0.09) and was thus greater than that achieved after a five minute period at 20 per cent M.V.C. The most significant feature about the changes here, however, was the further drop in pH after the cessation of exercise in all subjects. The lowest overall figure was finally achieved in the 1st, 2nd, or 3rd minutes of the recovery period. The lowest pH figures achieved in this phase were as follows:

A.L. - 7.198; P.H. - 7.194; K.D. - 7.170; N.K. - 7.224.

Resting levels were re-achieved by the 10th minute in only one subject (P.H.).

Lactate: The changes in lactate concentration are illustrated in fig. 25.

There was a slight rise in blood lactate at 10 per cent M.V.C. This rise was quickly checked and the level stabilized in all cases after one to two minutes of exercise. The average rise at the 5th minute was 0.12 m. moles/l.(range 0.04 - 0.24). There was, in two instances, (P.H. and K.D.) a further slight rise in the 1st and 3rd minutes, respectively, of the recovery period. Otherwise there was a gradual decline to normal.

There was a greater rise in concentration at 20 per cent M.V.C. The average increase at this level was 0.60 m.moles/l. (range 0.28 - 0.97). There was in all instances, a still further rise after the cessation of exercise, a peak being reached in the 1st minute. There was then a gradual

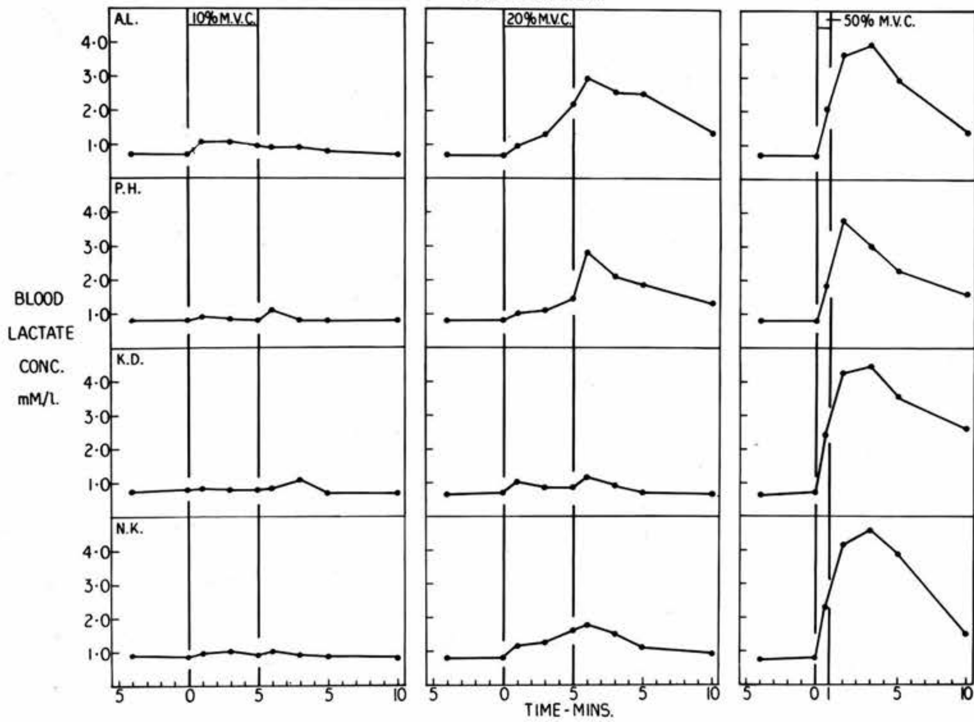

Figure 25. The effect of graded hand grip contraction on forearm venous blood lactate concentration.

decline towards resting levels. In only two of the four subjects (K.D. and N.K.) had pre-grip concentrations been re-achieved by the 10th minute of the recovery period.

The increase in lactate concentration was greatest at 50 per cent M.V.C., the average rise being 1.81 m.moles/l. (range 1.46 - 2.16). There was again a further large increase following relaxation, a peak being finally achieved in the 1st (P.H.) or 2nd (A.L., K.D. and N.K.) minutes of the recovery period. In no subject were pre-grip levels re-achieved during the period of documentation.

It will be noted that, at 10 per cent M.V.C. the highest level in lactate concentration was achieved during the exercise and not during the relaxation phase. It may be, however, that the dilution due to the reactive hyperaemia was great enough to offset the small rise in absolute quantity, thereby lowering concentration.

The pattern of change in lactate concentration was exactly similar to that in pH and the chronology was clearly related.

Changes in pH and lactate concentration do not chronologically parallel those known to occur in blood pressure.

Potassium: Changes in forearm venous potassium concentration are illustrated in fig. 26.

There was at 10 per cent M.V.C. an average increase in potassium concentration of 0.5 m.Eq./l. (range 0.4 - 0.7). In all subjects the concentration had returned to normal by the first minute of the recovery period.

At 20 per cent M.V.C. there was a yet greater rise in concentration, the average increase being 1.0 m.Eq./l. (range 0.6 - 1.3). The concentration

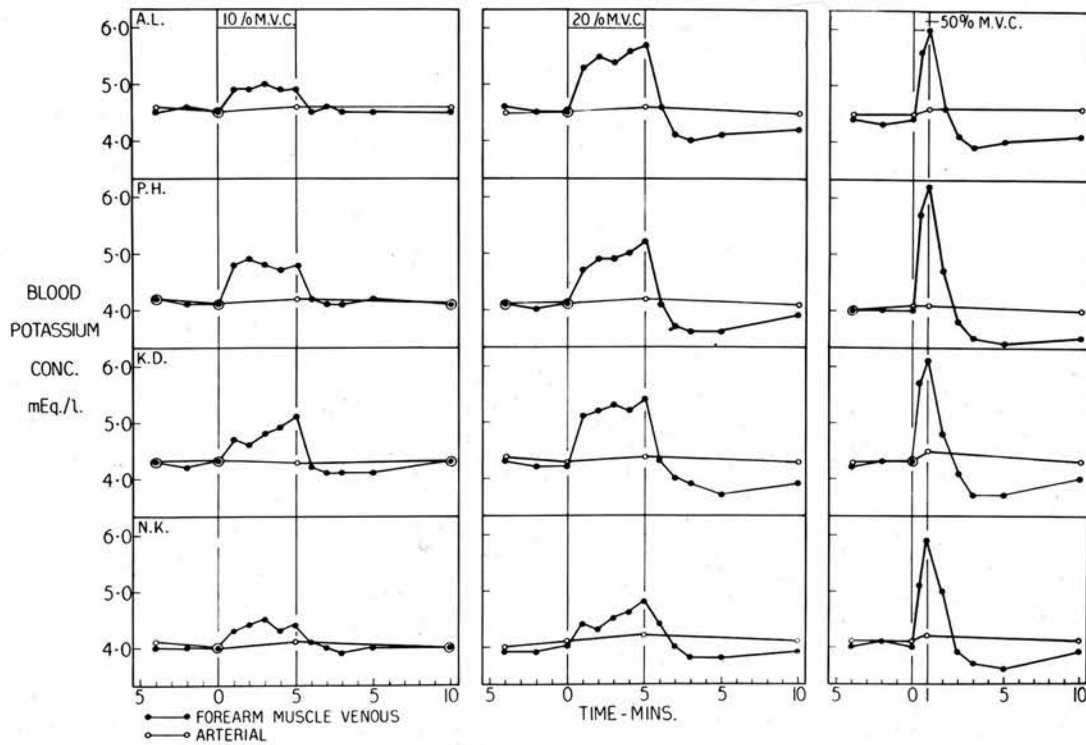

Figure 26. The effect of graded hand grip contraction on forearm venous blood potassium concentration.

continued to rise throughout the exercise period. In all subjects but one (N.K.) the concentration returned to normal within one minute. There was then a further fall to below pre-grip levels. This may be explained by dilution due to reactive hyperaemia, coupled with the disappearance of potassium ions back into the cells. In no instance did a further rise occur in concentration on relaxation.

The average increase in concentration at 50 per cent M.V.C. was 1.9 m.Eq./1. (range 1.6 - 2.5). This was roughly double the response at 20 per cent M.V.C. which was in turn roughly double the response at 10 per cent M.V.C. The peak concentrations achieved (again all during the exercise period) were as follows:

A.L. - 6.0 m.Eq./1; P.H. - 6.4 m.Eq./1; N.K. - 5.9 m.Eq./1; K.D. - 5.9 m.Eq./1.

Again, there was a rapid return to normal, though this was not usually achieved within one minute. There was then, as at 20 per cent M.V.C., a yet further drop during the recovery period to below control levels.

It is clear that the rapid changes in potassium concentration bear a fairly clear chronological relationship to those which occur in blood pressure. As with the potassium, the peak blood pressure level is invariably achieved at the end of the exercise, but never after its cessation. There is also an extremely rapid return to normal. On the other hand, the changes in pH and lactate, though quantitatively holding the same type of relationships between different grades of work, are not so similar in their time course.

DISCUSSION:

The findings of a fall in oxygen saturation, with a post-exercise increase, the latter accompanied by a fall in A - V difference, are not original. Love (1955) found similar results with rhythmic exercise on sampling mixed (median cubital vein) or deep (retrograde catheterization of the deep branch of the median cubital vein) forearm venous blood. He also found substantially similar results (though not so consistently so) with sustained muscular contractions. Love's observations during exercise were, however, few, and he did not study different work levels. The post-exercise increase in oxygen saturation reflected, he felt, an increase in oxygen tension and therefore was evidence against the stimulus to reactive hyperaemia being anoxic. It may be that, instead, the desaturated blood mixes with the arterialized blood from the reactive hyperaemia and therefore becomes diluted.

Donald, Wormald, Taylor and Bishop (1957) had already demonstrated that a remarkable degree of desaturation could be performed by working muscles of the lower limbs, even sufficient to reduce the saturation to as low as 1 and 2 per cent in femoral venous blood.

Barcroft, Greenwood and Whelan (1963), made a comprehensive study of venous oxygen saturation changes during sustained muscular contractions of graded degrees. These authors studied the effects of strong, medium and weak contractions, which cannot be standardized against our three levels of work except in so far as the strong contraction reflects a maximal hand-grip on a water-filled rubber bulb. Their results were substantially similar to our own, though the degree of desaturation less. They were as follows:

Contraction	Average oxygen saturation percentage and range	
	Before Exercise	End of Exercise
Strong	54 (45 - 65)	27 (3 - 41)
Medium	49 (38 - 65)	34 (25 - 38)
Weak	49 (36 - 65)	44 (28 - 66)

Our results, treated in the same fashion, are as follows:

Contraction	Average oxygen saturation percentage and range	
	Before Exercise	End of Exercise
50 per cent M.V.C.	64 (61 - 67)	24 (22 - 27)
20 " " "	64 (60 - 68)	28 (25 - 31)
10 " " "	66 (61 - 67)	39 (32 - 51)

Both experiments agree that the degree of desaturation is proportional to the degree of work. The differences in absolute figures may be explained by the experimental differences. Surprise has been expressed before that the desaturation process does not proceed further. Indeed, the fact that blood from fatiguing muscle does not usually have a saturation below 10 per cent, despite the fact that we know the capability of muscle to extract all available oxygen (Donald et al, 1957), has led some to say that ischaemia is not the cause of fatigue (Scherrer and Monod,1960). Barcroft et al (1963) do not subscribe to this view and suggest that the contracting human muscle, supplied with normal vessels, cannot desaturate blood completely during strong sustained effort. Certainly we know the work performed is ischaemic and we also know that our samples contain mainly muscle venous blood. Yet complete desaturation does not occur.

It is to be expected that, under ischaemic conditions, with insufficient oxidation, much lactic acid will be formed from pyruvic acid

during the exercise performance. Its accumulation can be taken to account for the local fall in pH. It will take some time to be either washed out of the limb or reconverted into pyruvic acid after the cessation of exercise, Hence the lactate concentration and pH do not return immediately to normal. One may possibly explain the post-exercise peak by the contention that maximal production is at the end of exercise, when the environment is at its most ischaemic, and that diffusion must then occur to a vein and catheter at some finite distance from the muscle membrane.

We have shown that a peak occurs in lactate concentration in the post-exercise phase (at 20 and 50 per cent M.V.C.). This is clearly out of phase with the blood pressure which, consistently reverts to normal within one minute of relaxation. Hence it is impossible to invoke lactic acid or hydrogen ions as the sole afferent stimulus to the pressor reflex. It could, however, provide a medium which facilitates the depolarizing action of some other chemical agent. It is not inconceivable that a low pO_2 might be such a stimulus. It is significant that the venous oxygen saturation, like the blood pressure and unlike the pH and lactate concentration immediately returns to normal. This, in the presence of a low pH, means that the pO_2 also quickly returns to normal.

Fukudu (1951), in an investigation of rhythmic forearm muscle contractions, showed that there occurred, during such exercise, a rise in the potassium content of blood sampled from the cubital fossa. The concentration immediately fell to normal on relaxation. This was followed by a further drop to below pre-exercise levels. Keys (1937) had originally shown somewhat similar results. These authors considered the sudden drop to

be due to re-entry of potassium into the cells. The findings already described (see Results) are in complete agreement with these of Fukudu, and one would like to emphasize, in particular, the sudden fall in potassium concentration. This fall has probably two causes: (i) the entry of potassium into the muscle cells, and, less importantly, (ii) dilution during the hyperaemic phase and washing out from the limb. Fukudu, interestingly, in a small study of lactate concentration changes, noted, as we have here described, the delay in return in concentration of this chemical to normal during the recovery period.

The pattern of change in potassium concentration during static work has been shown to be identical to that in blood pressure in the following points: (i) there is generally a 'plateau-type' response at 10 per cent M.V.C., (ii) there is a continuous rise in concentration at 20 and 50 per cent M.V.C., (iii) the degree of increase is proportional to the degree of contraction and (iv) there is a rapid decline to normal levels. It could be legitimately enquired therefore, as it could not be in the case of lactate or hydrogen ions, whether the increase in potassium concentration could be the depolarizing agent providing the reflex trigger. Let us examine the theoretical basis of this assumption.

The resting potassium membrane potential of the assumed receptor nerve can be given by the Nernst equation:

$$Ek = \frac{RT}{F} \times \log e \frac{(K)_1}{(K)_o}$$

where Ek = potassium equilibrium potential

$(K)_1$ = intracellular potassium concentration

$(K)_o$ = extracellular potassium concentration

R = gas constant

T = absolute temperature

F = Faraday

Let us assume $\frac{RT}{F}$ to be a constant and examine the effect of changing the extracellular potassium concentration. In one of the subjects in our study (P.H.) the venous potassium concentration rose from 3.9 to 6.4 m.Eq./l. If one assumes a normal intracellular concentration in the nerve of 140 m.Eq./l., then:

$$\frac{E_1}{E_2} = \frac{K \times \log e \frac{140}{3.9}}{K \times \log e \frac{140}{6.4}}$$

$$= 1.16$$

$$\therefore \quad \frac{E_2}{E_1} = \frac{1.00}{1.16} = 0.86$$

$\therefore$ Percentage fall from E_1 to E_2

$$= (1 - 0.86) \times 100$$

$$= 14 \text{ per cent.}$$

Therefore, by increasing K_o from 3.9 to 6.4 m.Eq./l. it can be calculated that there would occur a reduction of 14 per cent in the membrane potential provided other factors remained constant. Similarly, with another subject (N.K.) the reduction would be 11 per cent. These are admittedly the two subjects with the largest increases, but when one considers that the samples were derived from a vein in which lay a relatively large-bore catheter at some distance from the source of ion efflux, it might be easily imagined that the extracellular concentration near working muscle cell membrane is considerably higher. Huxley and Stämpfli (1951) have experimentally confirmed the inverse relationship between potassium concentration and resting membrane potential. Now a fall in resting membrane potential of about 15 per cent will cause an action potential to fire (Eccles, 1957).

It is therefore a conceivable possibility that potassium could be a stimulating agent in certain circumstances during the performance of hand grip. An attempt has been made here only to examine the physical possibility of such an occurrence. The presented data may help to formulate a hypothesis, but the response to administration of potassium under controlled conditions will be the definitive experiment to decide this matter.

THE EFFECT OF HAND GRIP ON THE SYSTEMIC AND PULMONARY CIRCULATIONS IN HYPERTENSIVE SUBJECTS

It has been claimed in the past (Hines and Brown, 1932; 1933-34) that the response to cold pressor stimuli is of greater magnitude in hypertensive subjects than in a normal population. This was contradicted by Pickering and Kissin (1936), who failed to demonstrate a difference. At the same time the latter authors showed that the degree of response was related to age. Alam and Smire (1938), supported, however, the findings of Hines and Brown and invoked disparity of age between the hypertensive and normal groups studied by Pickering and Kissin to explain their negative findings. Alam and Smirk also found, in subjects with essential hypertension, a greater pressor response to ischaemic muscular work.

Baráth (1928) had already shown greater rises in blood pressure resulting from emotional stimuli in essential hypertensives than in normal controls. He also showed that the performance of dynamic muscular work raised the systolic pressure to a greater extent in this pathological state than in health. Hejl (1957), using stressful mental arithmetic as a pressor stimulus, showed that the rise in blood pressure may be due to an increase in cardiac output, systemic vascular resistance, or both. He found a greater incidence of the 'resistance type' response in hypertensive subjects. This supported the findings of Wolf and Wolff (1951). These authors had also concluded that hypertensive subjects responded more commonly than normal controls to pressor stimuli by an increase in systemic vascular resistance. Brod (1959; 1960) could not confirm these findings. He demonstrated the similarity between the circulatory response to stressful mental arithmetic and the state of mental preparedness for muscular exercise, and postulated that hypertensives had a greater liability to this state, in which occurred elevation in cardiac output and blood pressure, splanchnic and renal

vasoconstriction, and vasodilatation within muscle. He also declared the impossibility in predicting the change in systemic vascular resistance, since it was, in any individual, the algebraic sum of such changes.

The following study describes the effects of static muscular work on the systemic and pulmonary circulations in eight hypertensive subjects.

Two separate experiments have been performed:

(i) Four subjects were studied at one level of hand grip (30 per cent M.V.C.)

(ii) Four subjects were studied at three levels of hand grip (10, 20 and 50 per cent M.V.C.).

The pulmonary circulation was studied in all four subjects in group (i) and in three subjects in group (ii).

THE EFFECTS OF HAND GRIP CONTRACTION (30 per cent M.V.C.) ON THE SYSTEMIC AND PULMONARY CIRCULATIONS IN FOUR HYPERTENSIVE SUBJECTS

TECHNIQUES:

A triple lumen venous catheter was introduced through the median basilic vein, passed centrally through the right side of the heart, and fixed in the pulmonary-artery wedge position. Pulmonary-artery wedge pressure was taken through the lumen at the catheter tip, pulmonary arterial pressure through a second lumen 15 cms. proximal to the tip, and dye injections were made through a third lumen 20 cms. proximal to the catheter tip. A 55 cm. nylon catheter was percutaneously introduced into the brachial artery of both right and left arms. These were passed centrally into the aortic root. Continuous phasic and mean systemic arterial pressures were taken through one of these catheters. Blood was sampled through the other catheter during the cardiac output determinations.

PLAN OF INVESTIGATION:

Observations were made on four hypertensive subjects. Their personal data is presented in tables 26 to 29. Brief clinical details are provided in table 25. Prior to the study, all subjects were trained in the experimental protocol on at least two occasions.

Following placement of the catheters in position, the subject was required to make two maximal hand grips, separated in time by one minute, on the dynamometer. During this procedure the sensitivity was set at the correct level. The subject then performed some light, non-fatiguing leg exercise for a period of three minutes. Twenty minutes after the cessation of this dynamic exercise the study was begun. Observations were made during a control period of six minutes, cardiac output and mixed venous saturations being determined every two minutes. Minute by minute cardiac output and mixed venous saturations were made during a five-minute exercise period at 30 per cent M.V.C. This procedure was continued through the first two minutes of the recovery period and thereafter on alternate minutes to the tenth minute. Systemic arterial and pulmonary artery-wedge pressures were recorded continuously throughout and, apart from sampling time, the same applied for the pulmonary arterial pressure.

RESULTS:

EFFECTS ON THE SYSTEMIC CIRCULATION

The results are tabulated in tables 26 to 29, and illustrated in fig. 27.

There was a marked and sustained rise in systolic, diastolic and mean arterial pressure in all four subjects (mean rise = 27 mm.Hg. or 17 per cent of resting value). In only one subject (A.A.) did the pressure continuously rise during hand grip. In all subjects the pressure returned to around pre-grip levels within the first minute of the recovery period.

All subjects exhibited a definite rise in heart rate (mean rise = 16 beats per minute or 19 per cent) and this was accompanied by, in all instances, an increase in cardiac output (mean rise = 0.431 l./sq.m./minute or 15 per cent). This was not, in two subjects (J.R. and C.C.), however, the sole mediator of the pressor response, there being in these cases a simultaneous and moderate (J.R.) to quite marked (C.C.), increase, in systemic vascular resistance. These two subjects exhibited small falls in stroke volume. One subject (R.T.), in whom heart rate remained elevated after exercise, continued to have an increased cardiac output after relaxation. Systemic arterial pressure, however, settled, thus expressing the fall in resistance presumably brought about by baroreceptor stimulation. The cardiac output, in the other three subjects, continued to fall throughout the recovery period, just as did the systemic vascular resistance continue to rise, thereby keeping the blood pressure at pre-exercise levels.

In summary, therefore:

(i) All of four hypertensive subjects exhibited a marked rise in systemic arterial blood pressure during hand grip at 30 per cent M.V.C.

(ii) In all cases there was an increase in heart rate and cardiac output. In two of the four cases this was the sole mediator of the pressor

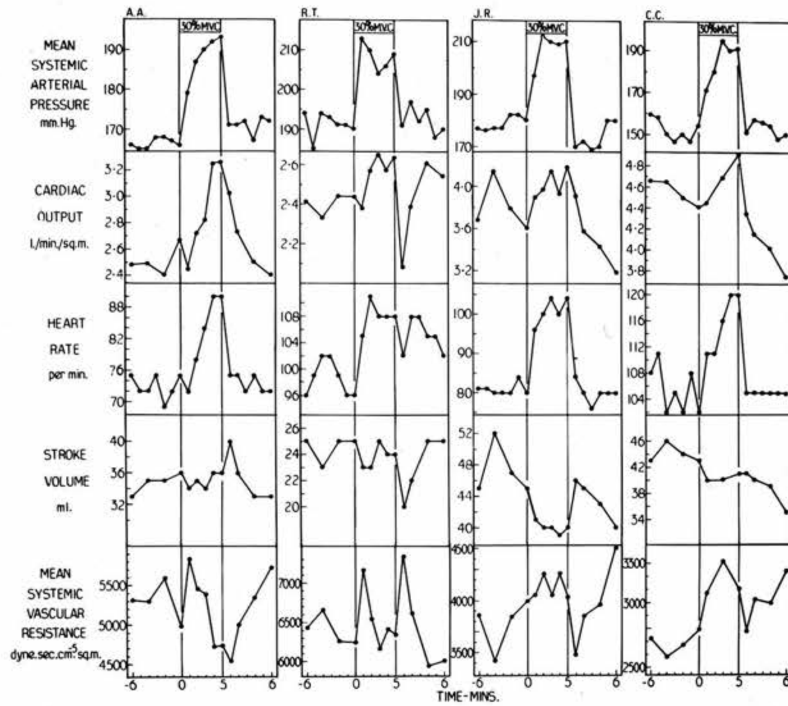

Figure 27. The effects of hand grip contraction at 30% M.V.C. on the systemic circulation in 4 hypertensive subjects.

response. In the other two cases there was an associated increase in systemic vascular resistance, and moderate fall in stroke volume.

(iii) In the recovery period the cardiac output continued to drop throughout the entire six minutes in three of the four subjects, though blood pressure and heart rate remained constant.

EFFECTS ON THE PULMONARY CIRCULATION

The results are tabulated in tables 26 to 29, and illustrated in fig.28.

There was, as already discussed, an increase in systemic arterial pressure and cardiac output in all four subjects.

A.A.: This subject experienced a continuous rise in pulmonary arterial pressure (fig. 28) without any change in wedge pressure. Pulmonary vascular resistance remained constant. The large increase in flow may solely account for the increase in pulmonary pressure, though the increase in Δ P and the absence of a fall in pulmonary vascular resistance might suggest resistance to passive dilatation and therefore slight increase in vasomotor tone. In the presence of such a flow increase, however, one cannot decide that vasoconstriction occurred.

R.T.: This subject, whose systemic pressor response was also brought about by an increase in cardiac output, exhibited initially a marked rise in pulmonary arterial (8 mm.Hg.) and pulmonary-artery wedge (6 mm.Hg.) pressure. These pressures gradually fell during the course of the exercise. Pulmonary vascular resistance showed no change, while there was a continuous rise in central blood volume. It is concluded that no active changes occurred here.

J.R.: This subject, whose systemic pressor response was partly contributed to by an increase in cardiac output and partly by an increase in systemic vascular resistance, showed overall modest rises in pulmonary arterial and pulmonary-artery wedge pressures with little or no definite change in a varying pulmonary vascular resistance. Central pulmonary blood volume dropped during the exercise. This subject only, showed such a fall. It was concluded that the pulmonary circulation behaved passively here.

C.C.: This subject also brought about the systemic pressor response by a combination of an increase in cardiac output and systemic vascular resistance (see fig. 27). He had a moderate rise in pulmonary arterial pressure (fig. 28), with a considerable and disproportionate rise in pulmonary-artery wedge pressure, with a fall in ΔP. This was associated with a marked fall in pulmonary vascular resistance. Central blood volume was elevated considerably during the work. It is concluded that the pulmonary circulation behaved passively here and that the rise in wedge pressure was a pathophysiological phenomenon suggestive of left ventricular decompensation. This subject had electrocardiographic evidence of left ventricular strain.

In summary, therefore:

(i) Of four hypertensive subjects studied during hand grip at 30 per cent M.V.C.:- one subject probably exhibited pulmonary vasoconstriction; the pulmonary circulation behaved passively in three of the four subjects; one subject sustained a disproportionate rise in wedge pressure which was probably a sign of left ventricular decompensation.

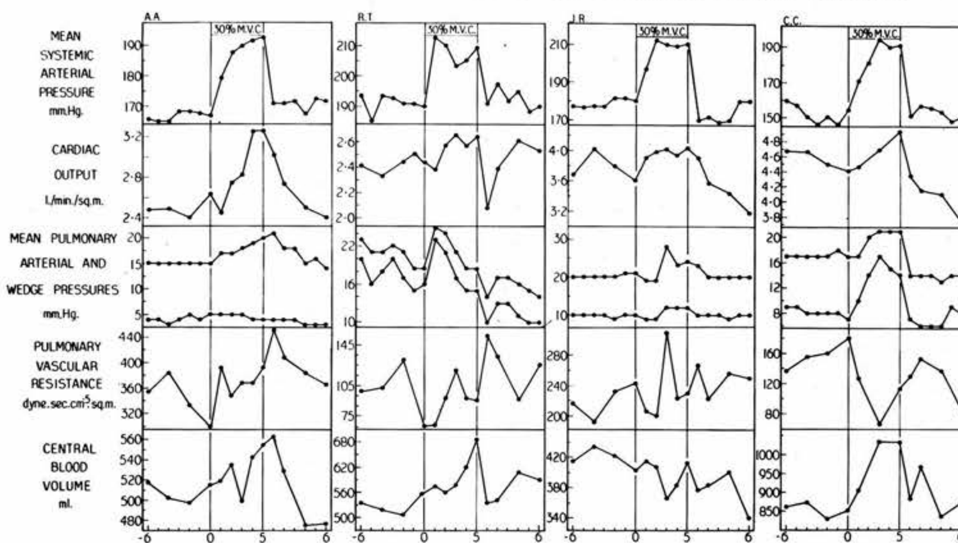

Figure 28. **The effects of hand grip contraction at 30% M.V.C. on the pulmonary circulation in 4 hypertensive subjects.**

(ii) The central blood volume increased in three of the four subjects and decreased slightly in one.

THE EFFECTS OF GRADED HAND GRIP CONTRACTIONS (10, 20, and 50 per cent M.V.C.) ON THE SYSTEMIC AND PULMONARY CIRCULATIONS IN FOUR HYPERTENSIVE SUBJECTS

TECHNIQUES:

These were as for the preceding study, except for one subject (C.P.), in whom pulmonary pressures were not studied.

PLAN OF INVESTIGATION:

Observations were made on four hypertensive subjects. Personal data is presented in tables 30 to 33. Brief clinical details are provided in table 25. The preliminaries were as for the preceding experiment.

The method of study was as described for the preceding experiment. Three exercise levels were studied. A 10 per cent M.V.C. was performed for five minutes, 20 per cent M.V.C. for three minutes, and 50 per cent M.V.C. for two minutes. As the changes induced by a 10 per cent M.V.C. contraction tend to be slight, it was decided, in two instances (J. MacK. (i) and (ii)) to accept the end of the ten minute recovery period after that level of contraction as part of the control for the 20 per cent M.V.C.

RESULTS:

EFFECTS ON THE SYSTEMIC CIRCULATION:

The results are tabulated in tables 30 to 33 and illustrated in figs.29-32.

(i) 10 per cent M.V.C.: There was, at this working level, a slight rise in systolic, diastolic and mean arterial pressure in three of the four subjects (J. MacK. (i) and (ii) and C.P.) In these subjects the pressure exhibited a

plateau type response or even dropped somewhat before the cessation of exercise.

Heart rate showed no detectable change.

Two subjects showed no change in cardiac output (C.P. and J.MacK. (i)), both bringing about a pressure increase by a slight increase in systemic vascular resistance. One subject (T.D.) who did not have a pressor response, experienced an increase in cardiac output brought about by a change in stroke volume. This was, however, offset by a fall in resistance, thereby keeping his blood pressure constant. One subject (J.MacK. (ii)) had a continuous fall in cardiac output of small but definite proportions. This continued throughout most of the recovery period. It is difficult to invoke as the explanation for this, absence of a basal state during the control period, for, as is shown in fig.30 at no stage was his heart rate faster than 68 per minute. Despite the fall in cardiac output a modest rise in systemic arterial pressure was brought about by an even greater than proportional increase in systemic vascular resistance. This continued to rise afterwards, presumably either in response to, or providing the stimulus for, the fall in cardiac output.

(ii) <u>20 per cent M.V.C.</u>: At this level three of the four subjects (J.MacK. (i) and (ii) and C.P.) showed, during the three minute exercise period, rises in systolic, diastolic and mean systemic arterial pressure of a greater order than at 10 per cent M.V.C. In two of these subjects (J.MacK. (i) and (ii)) the pressure underwent a marked increase and appeared to be continuously rising. In one of the subjects (C.P.), whose response at 10 per cent was so small as to be doubtful, the pressure increase here was still unimpressive (see fig. 32). The fourth subject (T.D.) was on a falling blood pressure baseline during the control period. This, after an initial drop, was partly

checked in the exercise period, and thereafter resumed its downward path for part of the recovery period. Again it is noted that there was no such erratic behaviour by a heart rate which was slow and steady throughout.

There were no definite changes in heart rate.

Two subjects (J.MacK. (i) and (ii)) exhibited a definite rise in cardiac output. This was very marked in (J.MacK. (ii)), in whom it was associated with a fall in systemic vascular resistance, which attenuated the pressor response. In the other subject there was no change in systemic vascular resistance. In both the flow response was brought about by an increase in stroke volume. The other two subjects showed slight changes in cardiac output and systemic vascular resistance without the emergence of a marked trend.

(iii) <u>50 per cent M.V.C.</u>: At the highest working level all four subjects experienced a continuously rising blood pressure.

All subjects brought this about solely by an increase in cardiac output. In two of the subjects (J.MacK. (ii) and T.D.) there was, if anything, a fall in systemic vascular resistance (figs. 30 and 31).

In all subjects there was a marked increase in heart rate during the exercise period, this being the main mediator of the flow increase. There was, in two subjects, however, (J.MacK. (ii) and T.D.), a sudden increase in stroke volume in the first minute which soon settled back to near pre-exercise levels.

<u>SUMMARY OF FINDINGS IN SYSTEMIC CIRCULATION</u>

(i) There were, at 10 per cent M.V.C., in four hypertensive subjects, slight increases in blood pressure in three subjects, which was

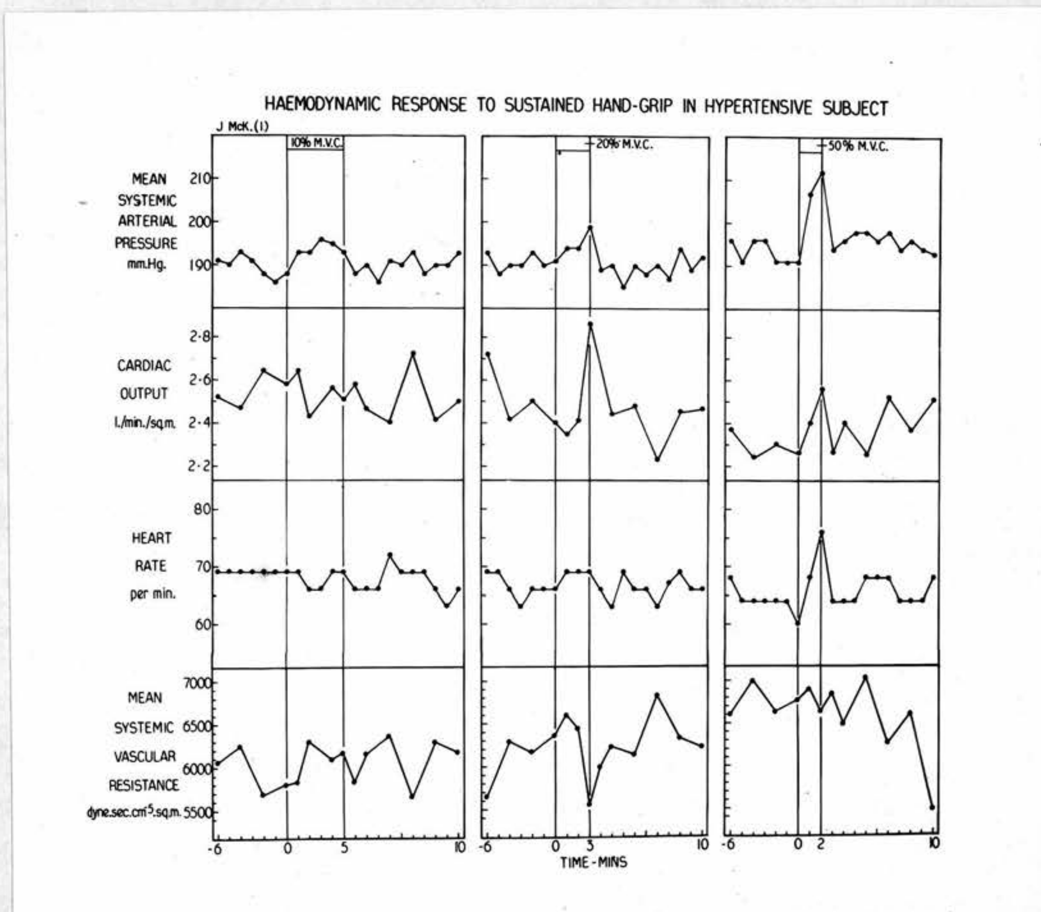

Figure 29. **The effects of graded hand grip contractions on the systemic circulation in hypertensive subject.**

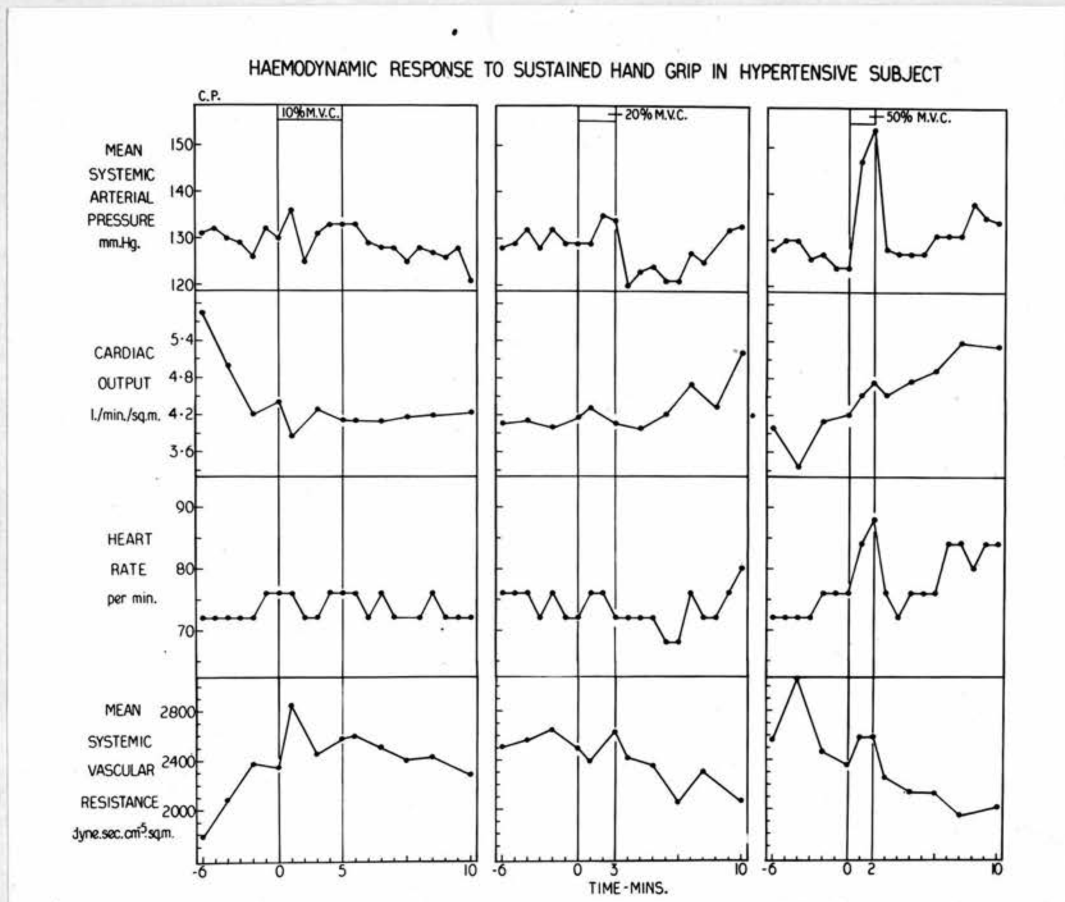

Figure 30. The effects of graded hand grip contractions on the systemic circulation in hypertensive subject.

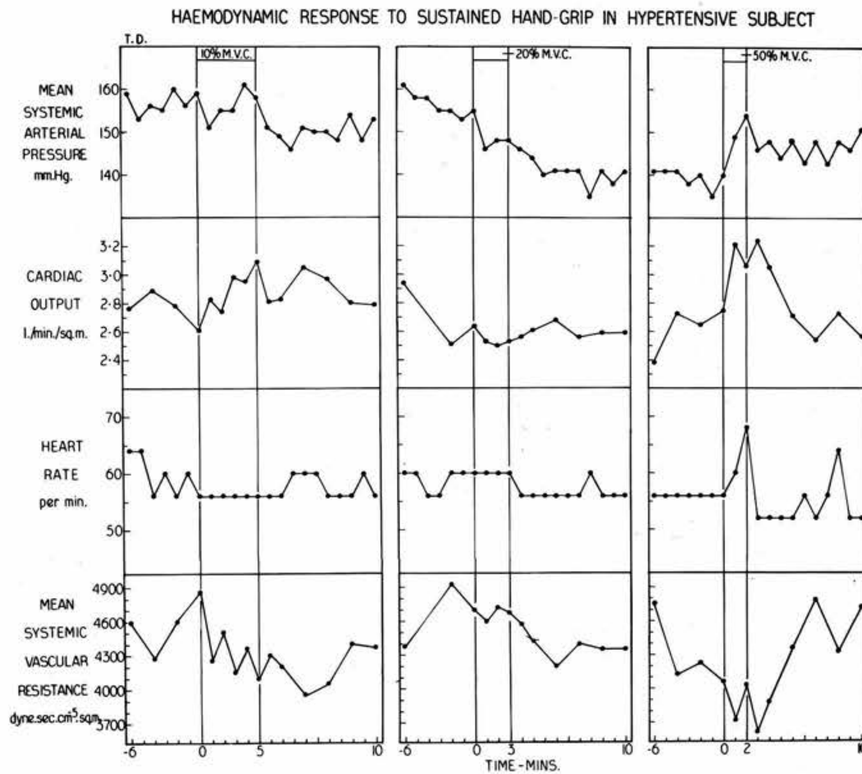

Figure 31. The effects of graded hand grip contractions on the systemic circulation in hypertensive subject.

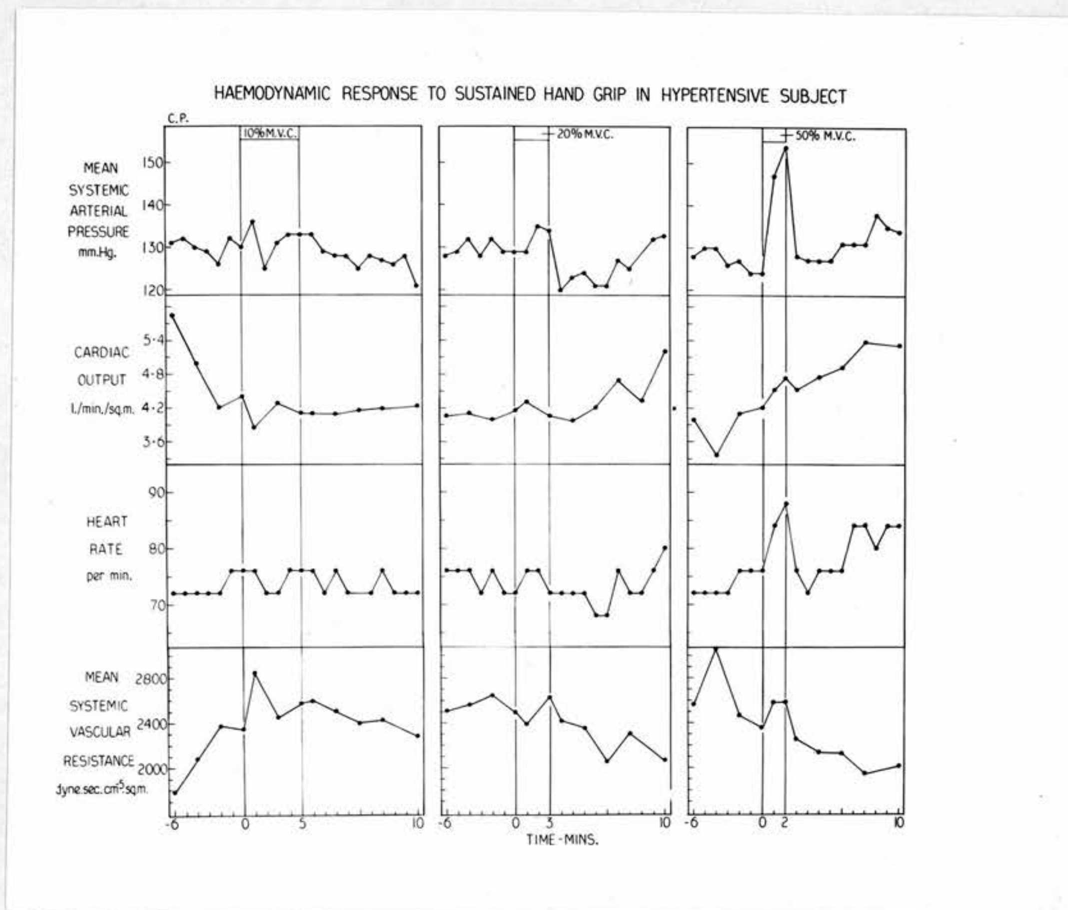

Figure 32. The effects of graded hand grip contractions on the systemic circulation in hypertensive subject.

brought about by a rise in systemic vascular resistance.

(ii) At 20 per cent M.V.C. there were definite increases in blood pressure and cardiac output in two of the four subjects.

(iii) At 50 per cent M.V.C. all subjects exhibited marked increases in systemic arterial pressure cardiac output, none experiencing any rise in systemic vascular resistance.

EFFECTS ON THE PULMONARY CIRCULATION (IN THREE SUBJECTS)

The results are illustrated in figs. 33 to 35.

(i) At 10 per cent M.V.C.: At this working level, during which changes within the systemic circulation were slight, no active changes were detected within the pulmonary circulation.

(ii) At 20 per cent M.V.C.: At a time when there were definite systemic arterial pressure and flow increases in two subjects (J.MacK. (i) and (ii)) the pressures within the pulmonary circulation remained unchanged, suggesting absence of activity in this circuit.

(iii) At 50 per cent M.V.C.: The response of the three subjects will be discussed separately.

T.D.: This subject exhibited a marked rise in cardiac output (0.5 l.sq.m./minute) and systemic arterial pressure (15 mm.Hg.). There was an increase in pulmonary arterial pressure of 4 mm.Hg., accompanied by a lesser increase in pulmonary-artery wedge pressure, thus increasing $\triangle$ P (fig. 35). He did not experience a fall in pulmonary vascular resistance, as did the other

subjects during such a flow increase. This would suggest either pulmonary vasoconstriction or a resistance of the pulmonary vessels to passive distension and to the opening up of fresh channels to accommodate the increased flow.

There was a slight rise in central blood volume.

J.MacK. (ii) who had a marked increase in systemic arterial pressure (23 mm.Hg.) and in cardiac output (0.5 l/sq.m./minute) experienced no change in pulmonary pressures (fig. 34). His pulmonary vascular resistance brought this about by maintaining an inverse relationship to flow.

There was a rise in central blood volume associated with the increase in cardiac output.

J.MacK. (i) also showed an increase in systemic arterial pressure and cardiac output (of a lesser order than at 20 per cent M.V.C.). This subject sustained a considerable increase in pulmonary arterial (6 mm.Hg.) and pulmonary-artery wedge (9 mm.Hg.) pressures (fig. 33), at the same time decreasing $\triangle$ P by a disproportionate rise in wedge pressure (from a mean resting level of 15 mm.Hg. to over 27 mm.Hg.). There was an associated fall in pulmonary vascular resistance. Vasoconstriction was therefore unlikely.

There was a moderate rise in central blood volume.

It is felt that the rise in pulmonary-artery wedge and pulmonary arterial pressure may here reflect a raised end-diastolic pressure in a left ventricle showing electrocardiographic signs of hypertrophy and strain, and which cannot cope adequately with increased pressure and flow work demands.

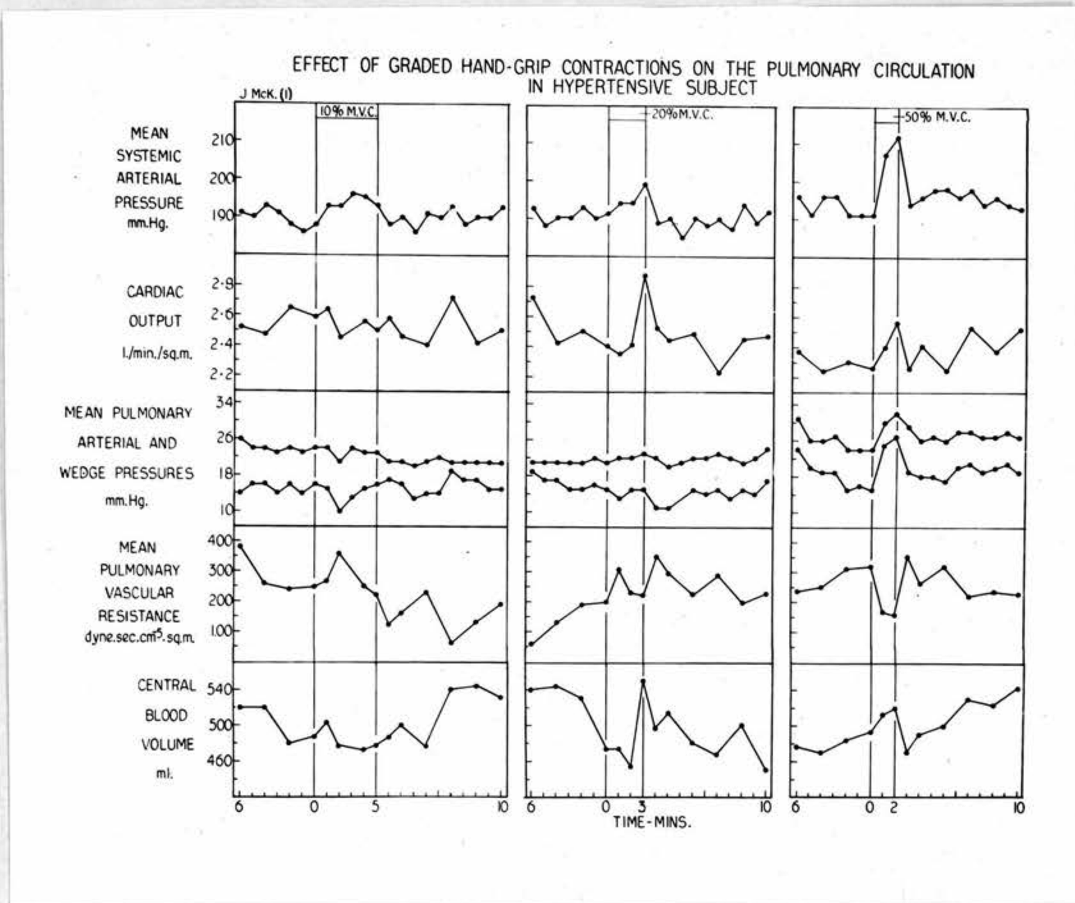

Figure 33. The effects of graded hand grip contractions on the pulmonary circulation in hypertensive subject.

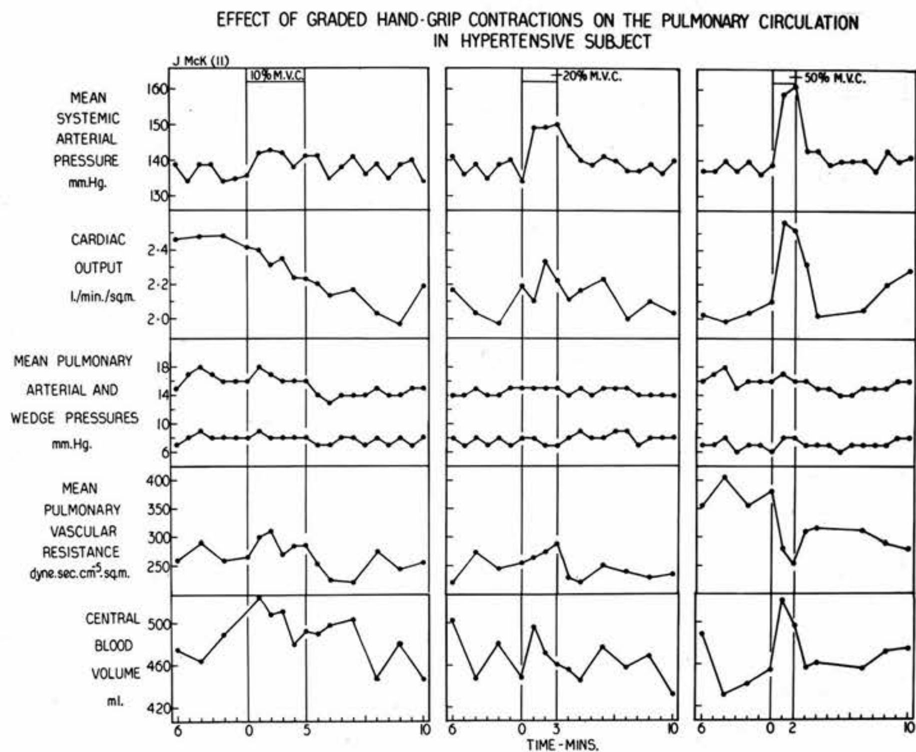

Figure 34. The effects of graded hand grip contractions on the pulmonary circulation in hypertensive subject.

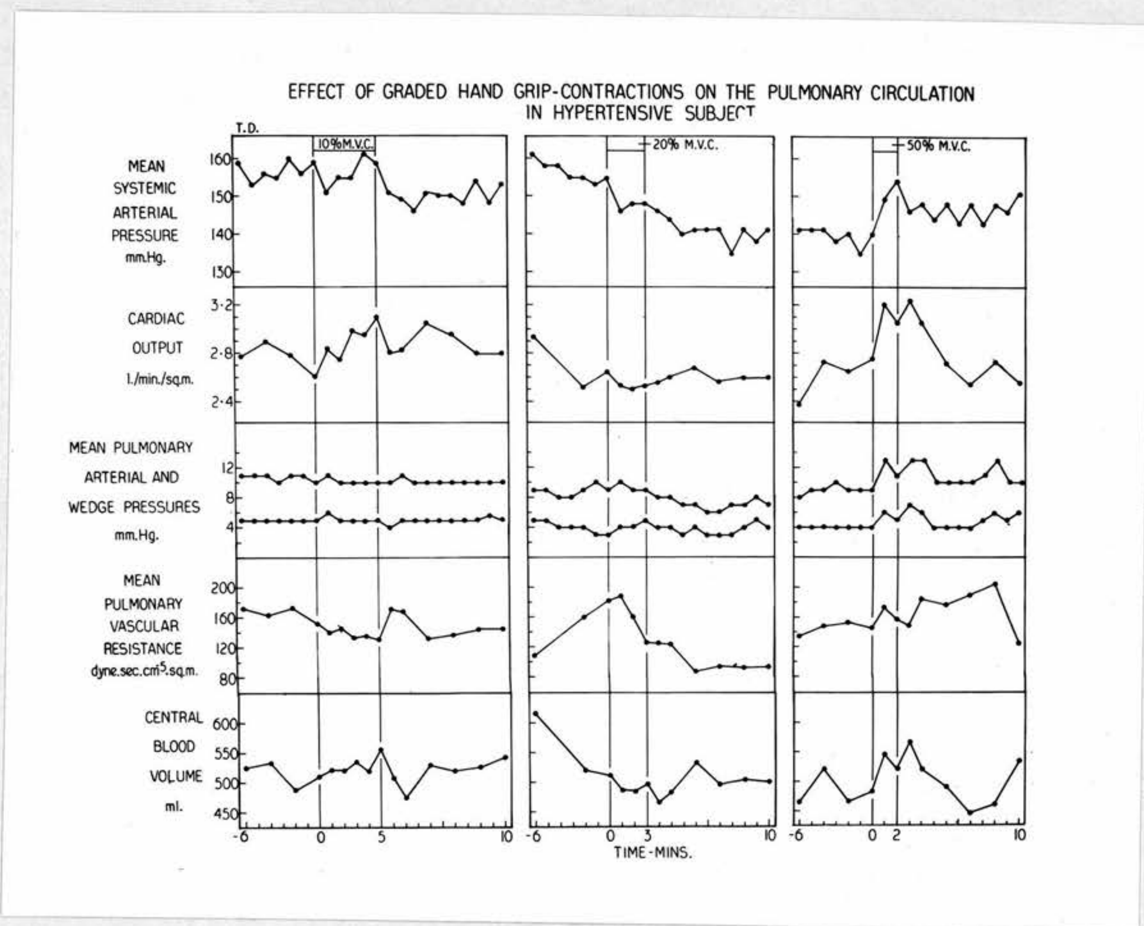

Figure 35. **The effects of graded hand grip contractions on the pulmonary circulation in hypertensive subject.**

DISCUSSION:

QUALITATIVE NATURE OF RESPONSE

It might have been suspected (see introduction to this section) that hypertensive subjects would have a greater tendency to bring about a pressor response by an increase in systemic vascular resistance. No evidence was forthcoming in support of this suspicion. If one considers eight normal subjects (the original four of Lind et al, plus the four dealt with in an earlier section of this presentation) in comparison to eight hypertensive subjects, it emerges that, at the higher levels of contraction, one subject in the normal group responded solely by an increase in systemic vascular resistance, two in each group responded by a combined increase in cardiac output and resistance, while all other subjects responded solely by a rise in cardiac output. Brod (1960), also, in a comparison of normal and hypertensive subjects, could not demonstrate qualitatively different responses to other pressor stimuli such as emotional stress and the cold pressor test.

Of a total of seven hypertensive subjects there was evidence in two cases (A.A. and T.D.), of pulmonary vasoconstriction. There was no radical difference in trend in the normal group, in which one subject out of four (R.B.) provided evidence of pulmonary vasoconstriction .

Two hypertensive subjects did, however, show abnormal rises in wedge pressure (J.MacK. (i) and C.C.). Both of these subjects had electrocardiographic evidence of left ventricular hypertrophy and strain, and it is felt that the rise in wedge pressure was an index of left ventricular embarrassment when faced with increased pressure and flow work demands.

QUANTITATIVE NATURE OF RESPONSE

The numbers studied and different experimental conditions do not easily allow of a quantitative comparison between all of the hypertensive subjects and normals. The figures do allow, however, of some tentative comparison. The groups of four hypertensives (tables 26 to 29) and four normals (tables 1 to 4), who performed hand grip at 30 per cent M.V.C., did so under exactly similar experimental conditions. The hypertensive group had a 17 per cent mean rise in blood pressure (absolute rise = 27 mm.Hg.), while the normal subjects had a 20 per cent rise (absolute rise = 21 mm.Hg.). There was here, therefore, no large disparity. Moreover the difference in age (average of normals = 36 years; average of hypertensives = 54 years) would favour a greater response in the hypertensive group. Pickering and Kissin (1936) for instance, showed the cold pressor response to increase with age. There was no evidence here, therefore, that hypertensive subjects had an abnormally high pressor response to hand grip. Heart rate changes did, however, appear to differ, in that the hypertensive group had a mean rise of 19 per cent (16 beats per minute), while the normals, even when one excluded the subject (R.B.) who did not have an increase, experienced a mean rise of 13 per cent (9 beats per minute). A similar difference had been noted by Alam and Smirk in their experiments in dynamic exercise. They considered that the baroreceptors responded to the increase in pressure by modifying the heart rate response. It is difficult to readily accept such a thesis since the actual mechanism of the pressor response is usually a tachycardia dependent increase in cardiac output. Pressure and heart rate changes usually parallel one another and these usually keep increasing. It is

therefore the inability of the baroreceptor to check the heart rate increase which allows a maintained pressor response. Alam and Smirk went on to infer that baroreceptor function is abnormal in hypertensives, hence their greater pulse rate response. Such an implication, it is here felt, is too far reaching and supported by evidence too tenuous and circumstantial.

It is difficult to discuss the quantitative aspects of the cardiac output response. One of the normal subjects (R.B.), who had no increase in heart rate, did not experience a rise in cardiac output. If one excludes him from consideration, it is found that the remaining normal subjects had a somewhat greater mean rise in flow (22 per cent or 0.793 l./sq.m./minute as against 15 per cent or 0.431 l./sq.m./minute). This information, is, however, weighted.

The early promise of widespread clinical application of the cold pressor test (Hines and Brown 1932; 1933-34) was never fulfilled. One has not examined enough subjects performing hand grip to make any definitive statistical comment on the magnitude of the response in hypertensives, nor were any pre-hypertensives studied. The available data does, however, suggest that if there is a difference in population between hypertensive and normal subjects, the overlap will be such as to make clinical application difficult. It also suggests that hypertensive subjects respond to the pressor stimulus from the statically contracted muscles of the forearm, by a qualitatively similar response to normal subjects.

THE EFFECT OF DRUG SYMPATHOLYSIS ON THE CIRCULATORY RESPONSE TO HAND GRIP

Anti-hypertensive therapy was about to be instituted in some of the hypertensive subjects studied (see preceding section) An opportunity was therefore afforded to note the effect of acute medical sympatholysis on the response to hand grip.

TECHNIQUES:

These are described in the preceding section .

PLAN OF INVESTIGATION:

Four subjects were studied.

Two subjects (J.MacK. (i) and J.MacK. (ii)) performed hand grip at 20 per cent M.V.C. for three minutes before and after the administration of guanethidine.

Two subjects (J.R. and C.C.) performed hand grip at 30 per cent M.V.C. for five minutes before and after guanethidine.

The initial dose of guanethidine was 10 mg., administered intravenously. Further doses of 5 mg. were given at approximately ten minute intervals until a significant lowering of the systemic arterial pressure or abolition of the response to the Valsalva manoeuvre was achieved. The following total doses were given:

J.MacK. (i)	15 mg.
J.MacK. (ii)	30 mg.
J.R.	30 mg.
C.C.	20 mg.

RESULTS:

Table 34 contains a brief analysis of the results (the complete data is contained in tables 28, 29, 30 and 31). The results are illustrated in figs. 36 to 39.

SYSTEMIC CIRCULATION

The rise in blood pressure was less after the administration of guanethidine than during the control study in three of the four subjects (J.MacK. (i); J.MacK.(ii) and J.R.). In the fourth subject (C.C.) the absolute rises were equal, though the percentage increase was greater following guanethidine.

The cardiac output changes followed a dissimilar pattern. The post-drug exercise period was characterized by a both greater absolute and percentage increase in flow in three of the four subjects (see table 34).

There was a mild fall in systemic vascular resistance in two subjects during hand grip after guanethidine. This had never been observed under other circumstances.

PULMONARY CIRCULATION

The pulmonary circulation behaved passively both before and after sympatholysis in all but one subject (C.C.). The exceptional subject had shown evidence of left ventricular decompensation in the control run (see page 74). After guanethidine, however, his pulmonary-artery wedge pressure did not become elevated in the course of the work performance. Pulmonary vascular resistance did increase in this subject, possibly indicating pulmonary vasoconstriction, despite the exhibition of guanethidine.

TABLE 34

The Effect of Guanethidine on the blood pressure and cardiac output response to hand grip

Subject	Increase in Mean Systemic Arterial Pressure mm.Hg		Increase in Cardiac Output l./min./sq.m.	
	Before	After	Before	After
J. MacK. (i)	8(4%)	3 (2%)	.356(14%)	.035(1.5%)
J. MacK. (ii)	12(9%)	-1(1%)	.126(6%)	.351(14%)
J.R.	31(17%)	17(10%)	.369(10%)	.483(16%)
C.C.	39(26%)	38(32%)	.371(8%)	.498(15%)

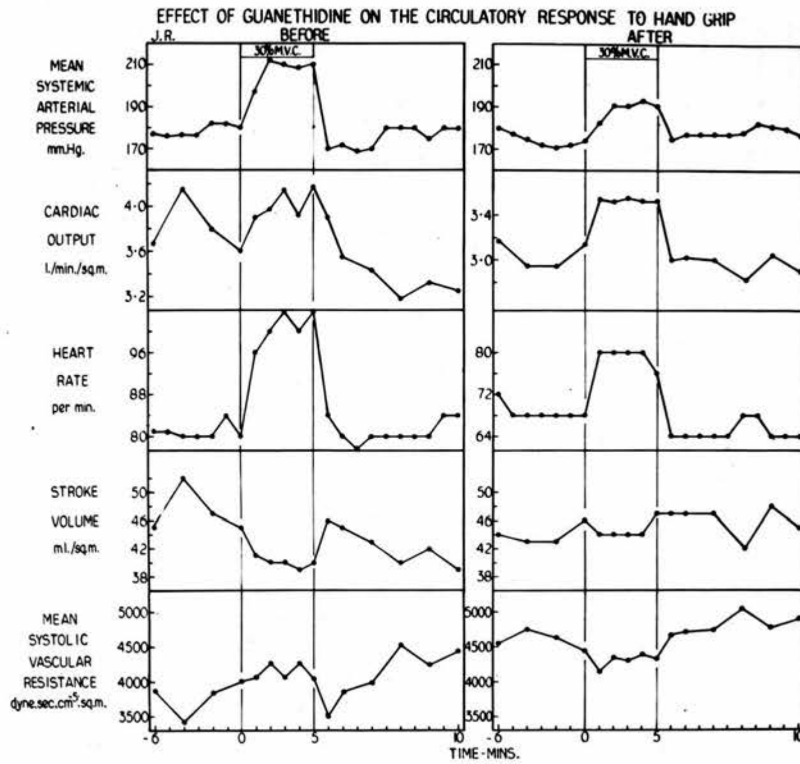

Figure 36. The effect of guanethidine on the circulatory response to hand grip in hypertensive subject.

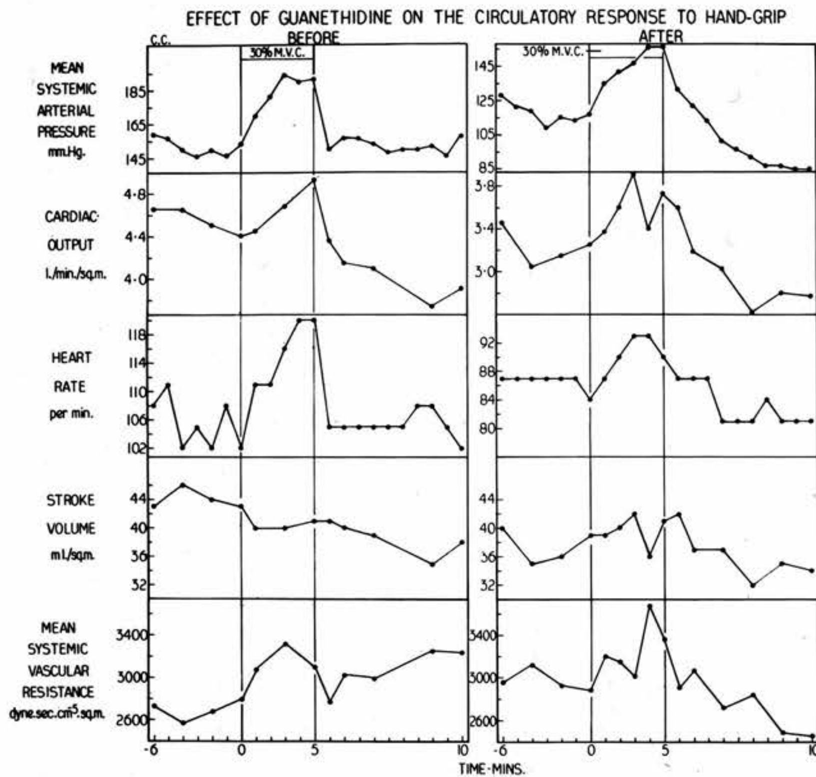

Figure 37. The effect of guanethidine on the circulatory response to hand grip in hypertensive subject.

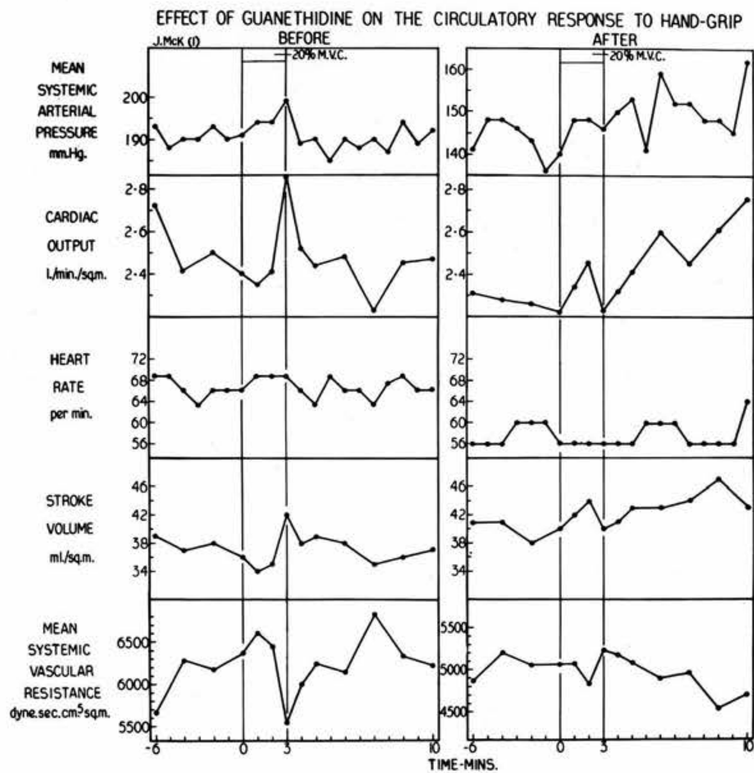

Figure 38. The effect of guanethidine on the circulatory response to hand grip in hypertensive subject.

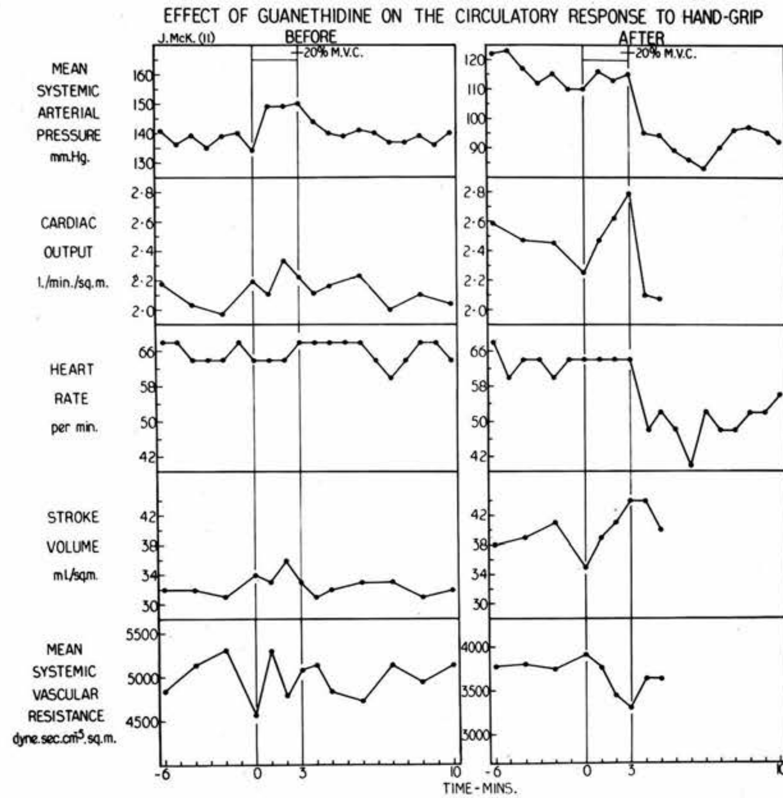

Figure 39. The effect of guanethidine on the circulatory response to hand grip in hypertensive subject.

DISCUSSION:

It has been shown that guanethidine will not decrease the cardiac output response to supine dynamic leg exercise (Taylor, S.H., Sutherland, G.R., Hutchinson, D.C., Langford Kidd, B.S., Robertson, P.C., Kennelly, B.M., and Donald, K.W., 1962). There are good grounds for suspicion that in three of our four subjects, the drug has not only failed to block the cardiac output response, but has actually facilitated it by decreasing vascular resistance and therefore pressure work. The result might, however, be different in subjects who exhibited a purely vasocontrictive response.

Why two subjects should exhibit a fall in systemic vascular resistance during hand grip following guanethidine, is not clear. A possible explanation is that the vasodilatation is due to circulating adrenaline released from the adrenal medulla. The adrenal medulla is unaffected by guanethidine.

Since most subjects respond to hand grip by an increase in cardiac output, usually through the mediation of, as least in part, a heart rate increase, and since the positive inotropic and chronotropic sympathetic effects on the myocardium are beta in type (Ahlquist, 1948), most blocking success might be expected from a beta blocker such as, for instance, nethalide (Dornhorst and Robinson, 1962). There is little evidence so far, however, that these substances block the circulatory response to exercise. Harrison, Braunwald, Glick, Mason, Chidsey and Ross (1964) have found that it attenuated the exercise response. Before drawing definite conclusions about attentuation in response, however, it would be necessary to establish the consistency of the response in quantitative terms. This Harrison et al did not do. The fact that these workers have also shown that beta adrenergic blockade will block the response to the administration of isoprenaline

by no means establishes that a beta blocker will compete as successfully against nor-adrenaline released from sympathetic nerve endings in close proximity to its receptors (as in the myocardium). Another reason for caution in drawing conclusions from such circumstantial data is the functional overlap between alpha and beta receptors. Dibenamine, the well known alpha blocker has, for instance, definite anti-inotropic effects on a myocardium reputed to have only beta receptors. For these reasons, the results of hand grip after the administration of a beta blocker might be difficult to analyse. It would, however, be a rewarding study.

HAND GRIP DURING TREADMILL EXERCISE

Characteristic circulatory changes occur during the dynamic exercise of walking. These include alterations in blood pressure. The systolic pressure rises, the diastolic pressure almost invariably falls, while mean pressure may rise or fall somewhat, or may not change significantly. The lack of any marked rise in mean pressure is almost certainly due to vasodilatation in the working lower limbs. This is brought about by local axon reflexes and by the direct effect of matabolites on the arteriolar muscle. Such changes would appear to be physiologically suitable for the performance of work by the large muscle groups of the lower limbs.

The volume of muscle working during the performance of hand grip is, on the other hand, small. Would, therefore, the influence of such a small muscle group dominate the almost mandatory vasodilatation in the large volume of lower limb muscles if hand grip were performed while walking ? If so, it would be a remarkable illustration of the potency of the stimulus from statically contracted muscle. It was decided to have the subjects perform hand grip, firstly, after a steady state had been reached, during a moderate, non-fatiguing level of treadmill exercise. The manoeuvre would be then performed at a fatiguing level of treadmill exercise. During fatiguing treadmill exercise the mean blood pressure has been noted to sometimes rise (studies on upright exercise performed in this laboratory). It was thought possible that, because of this, the pressor effect of hand grip might be different to that during non-fatiguing exercise.

TECHNIQUES:

A 55 cm. nylon catheter was percutaneously introduced into the brachial artery of the non-working arm. Continuous phasic and electronically integrated mean pressures were recorded through this catheter.

PLAN OF INVESTIGATION:

Observations were made on five healthy males whose ages ranged from twenty-six to thirty-eight years. All subjects were fully trained beforehand in the experimental protocol. The maximal hand grip was determined prior to the start of exercise. Measurements were made for six minutes while the subject stood still on the treadmill. The treadmill was then started, at 2.5 miles per hour. Following completion of a ten minute period of walking, the subject, while continuing to walk at the same rate, performed hand grip at 35 per cent M.V.C. for five minutes. Following cessation of hand grip, he continued to walk at the same speed for a further ten minutes. The treadmill was then elevated to an angle of 10° and the entire procedure was repeated at this more severe exercise level. Previous work on other subjects in this laboratory has shown that walking at 2.5 miles per hour on the flat entails, after reaching a steady state, a total body oxygen uptake of about 400-500 ml./sq.m/minute. Walking on an incline of 10° at this speed entails an oxygen uptake of the order of 1200 ml./sq.m/minute.

RESULTS:

Measurements were made of heart rate and systemic arterial pressure. The results are presented in tables 35 to 39 and figs. 40 and 41.

EFFECT ON SYSTEMIC ARTERIAL PRESSURE

Two of the five subjects studied (S.T. and J.M.) showed definite rises in systemic arterial pressure (9 and 12 mm.Hg., respectively) during the performance of hand grip while walking on the flat. These were the two oldest subjects. The other three subjects showed slight overall increases in pressure, though there were individual control observations as high as the mean levels reached during the performance of hand grip. The blood pressure settled at a lower level than during the control period, after cessation of hand grip, in three subjects (J.S., H.S. and S.T.).

Hand grip, while walking on an incline, resulted in two different patterns of response, which accounts for the illustrative separation of the subjects into groups of three and two. Three of the five subjects (S.T., J.M. and R.S.) experienced a marked increase in mean systemic arterial pressure (20, 16 and 8 mm.Hg., respectively). The oldest two subjects again were included in this group. As is evident from fig. 40, the pressor response was considerably greater for the same level of hand grip while walking uphill. It is significant, however, that the greater rise during the fatiguing exercise occurred from a lower baseline, and in only one instance (R.S.) was the final absolute level during hand grip greater during the heavier rate of treadmill work (see fig. 40). In fig. 41 a different response pattern is evident. Neither of these two subjects showed a rise in blood pressure while performing hand grip. One of the subjects (J.S.) showed a fall, with a further fall on cessation of hand grip, thereby setting his mean blood pressure on an entirely new baseline (approximately 20 mm.Hg. lower) while still walking at the same pace. This post-grip fall in mean pressure also occurred to a lesser extent during exercise on the flat. The other of the

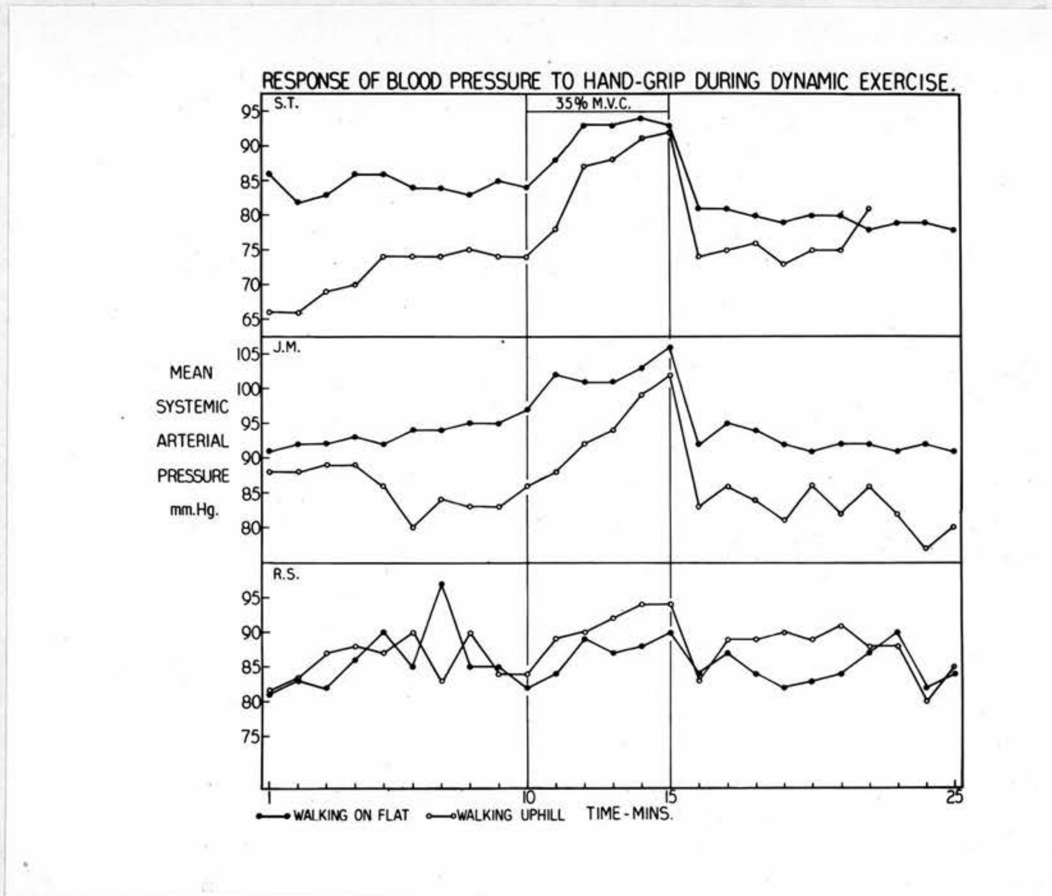

Figure 40. The effect of hand grip on the blood pressure during treadmill exercise in 3 normal subjects.

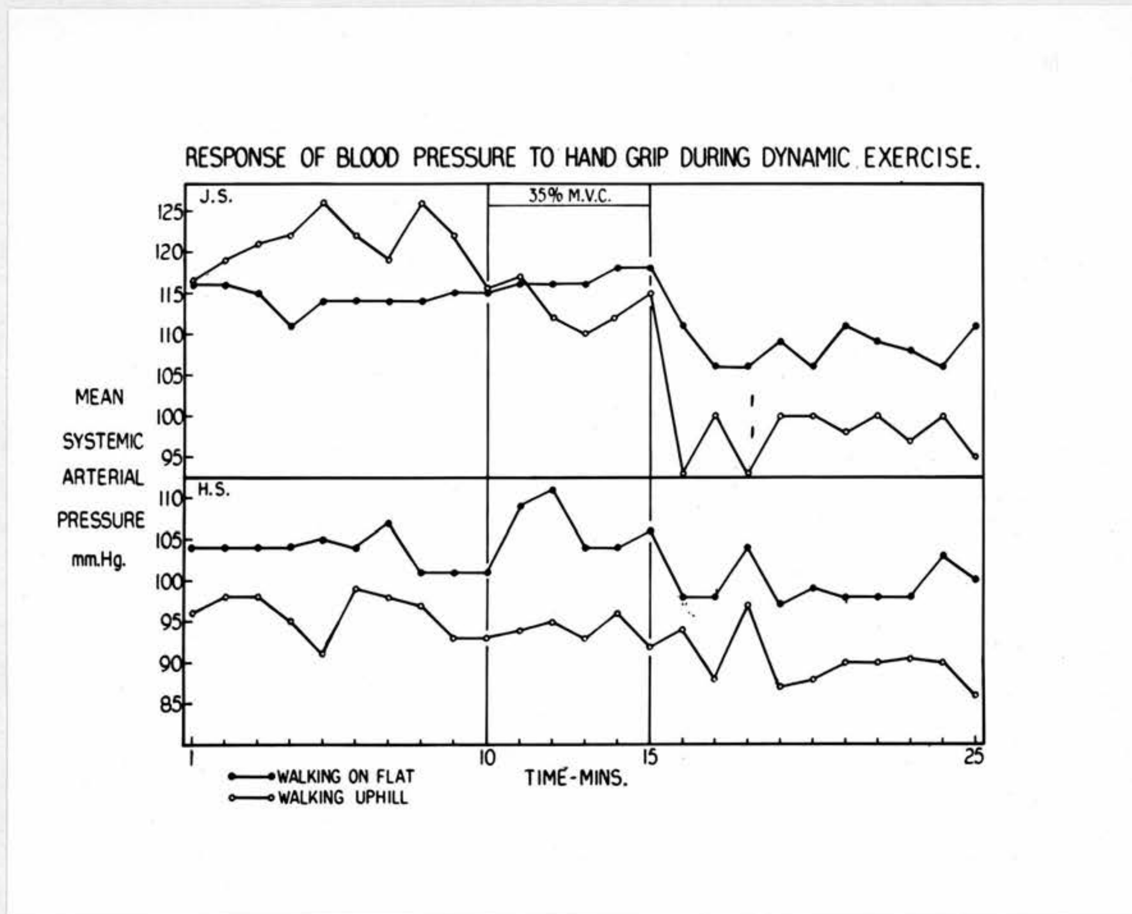

Figure 41. The effect of hand grip on the blood pressure during treadmill exercise in 2 normal subjects.

two subjects illustrated in fig. 41 (H.S.) did, while exhibiting no definite fall in mean systemic arterial pressure during hand grip, nevertheless, settle, after the static work, on a somewhat lower baseline while continuing to walk on the incline.

EFFECT ON HEART RATE

It was not possible to relate changes in heart rate to those in systemic arterial pressure.

During the performance of hand grip while walking on the flat, two subjects only (H.S. and J.M.) experienced a rise in heart rate while gripping (tables 35 and 37). The new level was maintained on relaxation. Neither of these two subjects experienced a definite rise in blood pressure. One of the five subjects (S.T.), who exhibited a marked pressor response, had no associated heart rate increase. A rise did occur, however, after the cessation of hand grip.

While walking on the incline, all subjects were in an unsteady state and had a constantly rising heart rate. Hand grip simply resulted in a continuation of the general rising trend, which persisted when the static work ceased.

DISCUSSION:

It is clear that the pressor response to hand grip is not so consistent during treadmill exercise. It is also clear, however, that it does occur. The influence of hand grip in this set of circumstances is rather emphasized by the fact that the final levels achieved on both the flat and the incline in those subjects experiencing the pressor response did not differ by more than 5 mm.Hg.

The post-grip fall in pressure in J.S. is difficult to explain. This type of phenomenon has occasionally been observed with oxygen uptake. It may, be that the subject was not entirely 'basal' for that level of dynamic exercise prior to gripping. Such a hypothesis would then explain why his blood pressure did not rise during hand grip (since it was already elevated) and would suggest the lowered blood pressure following hand grip to be the true 'basal' pressure. The meaning of what constitutes a true basal state under a given set of conditions is not always clear however. This fall in blood pressure must be here considered to be unexplained.

It is not clear why three subjects should show large responses and the other two subjects not do so. The only feature which differentiates these two groups is age (older subjects J.M. and S.T. were 39 and 38 years respectively; other subjects J.S., R.S. and H.S. were 33, 27 and 26 years respectively).

THE EFFECT ON THE CIRCULATION OF ISCHAEMIC DYNAMIC WORK OF THE LOWER LIMBS

Dynamic work of the upper limb, when performed during vascular occlusion, is associated with rises in systolic and diastolic blood pressure (Alam and Smirk, 1937). It was claimed by Assmussen, Christensen and Nielsen (1943) that, on blocking the circulation through both lower limbs during dynamic exercise, there occurred a sudden increase in the 'arterial blood pressure', which was then followed by a return to values slightly higher than normal while exercise continued. Details are not, however, provided, nor is the method of measuring blood pressure described. In a more recent publication (Assmussen and Nielsen, 1964), a constant rise in systolic blood pressure is reported by these workers to occur during bicycle ergometry with the circulation to both lower limbs occluded. Since there has not been, to the author's knowledge, a continuous record of systolic, diastolic and mean systemic arterial pressure during dynamic work of the lower limbs under conditions of vascular occlusion, it was felt that extremely useful information could be derived from such a study. Two experiments were therefore designed. They were (i) the study of the circulatory effects of total vascular occlusion to both lower limbs during treadmill exercise by normal subjects, and (ii) the study of circulatory events during treadmill exercise in subjects with intermittent claudication. Intermittent claudication is a condition where there exists a limited arterial inflow to the muscles of one or both lower limbs, which limitation becomes apparent on exercise. It has been shown (Shepherd, 1950) that some subjects with intermittent claudication slowly increase the blood flow through the claudicating limb after the cessation of exercise, while

others exhibited simply a prolongation of the time required to return to resting levels. Normal subjects, on the other hand, exhibit an extremely rapid decline in blood flow after the cessation of exercise. It has also been established (Pentecost, 1964) that the oxygen debt incurred during exercise is abnormally high in subjects with intermittent claudication and total payment is afterwards delayed. The latter worker has suggested, at the same time, from data on arterio-venous oxygen differences, that changes in blood flow are not related in a simple fashion to oxygen uptake, for the flow remains high after payment of the debt. Shepherd (1963) points out that there is a greater flow some minutes after exercise than immediately after, but remains in doubt as to the explanation. Intermittent claudication does however present a situation where there exists an undoubted muscular ischaemia. The mechanism invoked to explain the resulting pain has been that of stimulation of pain receptors by some factor whose accumulation occurs during ischaemic muscular work (Lewis, Pickering and Rothschild, 1931). Such an accumulation must of necessity be due to a greater rate of production that clearance of this substance. If a pressor reflex were caused by the same or a similar factor, the systemic arterial pressure should rise in such subjects during exercise of a degree sufficient to induce pain. The additional factor of venous occlusion in normal subjects (vide supra (i)) might be expected to result in more striking circulatory changes because of hold-up in the limbs of the relevant factor. If the blood pressure rises before the onset of pain, the stressful aspect of the latter cannot be invoked as the cause. There may be no difference, in any case, between the peripheral mechanisms of painfully induced pressor reflexes and the reflex pressor response to ischaemic

work. Indeed, it is conceivable that sub-liminal painful stimuli may be able to effect pressor responses. We have already suggested (page 53) that pressor reflexes during static work travel via c-fibres and Lissauer's tract. These pathways also, of course, subserve pain. The relationship is therefore close.

THE CIRCULATORY EFFECTS OF TOTAL VASCULAR OCCLUSION TO BOTH LOWER LIMBS DURING TREADMILL EXERCISE IN TWO NORMAL SUBJECTS

TECHNIQUES

W.B.: In this subject a triple lumen venous catheter was introduced through the median basilic vein, passed centrally through the right side of the heart, and fixed in the pulmonary-artery wedge position. Pulmonary-artery wedge pressure was taken through the lumen at the catheter tip, pulmonary artery pressure through a second lumen 15 cm. proximal to the tip, and dye injections were made through the third lumen 20 cm. proximal to the catheter tip. A 55 cms. nylon catheter was introduced into the brachial artery of both right and left arms. These were passed centrally into the aortic root. Continuous phasic and mean arterial pressures were recorded through one of these catheters. Blood was withdrawn through the other catheter during the cardiac output determinations.

B.L.: In this subject one 55 cm. nylon catheter was introduced into the left brachial artery.

PLAN OF INVESTIGATION

W.B.: Measurements were initially made during a six-minute period

of standing. The subject then walked on the unelevated treadmill at 2.5 m.p.h. for ten minutes. This was followed by a five-minute period during which the subject continued to walk with, however, the circulation to both limbs occluded by the inflation of cuffs over both upper thighs to 300 mm.Hg. A further ten minutes of exercise at the same level with free lower limb circulation followed. This exercise procedure was then repeated with treadmill at 10° incline. At this level of exercise, however, the circulation was occluded for only two minutes and the periods of exercise before and after occlusion were each of six minutes duration. Measurements were then made during a final six-minute standing period. Cardiac output and mixed venous saturation determinations were made minute by minute during vascular occlusion and at two-minute intervals at other times. Pressures were minitored continuously.

B.L.: Systemic arterial pressure and heart rate only were measured in this subject. The exercise protocol was similar except in a few details. These were:-

(i) He could manage to continue exercise during vascular occlusion for only three minutes on the flat and for one minute on the incline.

(ii) The period of occlusion on the incline was flanked by two ten-minute periods of exercise with free circulation (see fig. 42).

RESULTS

The results are presented in tables 40 and 41, and illustrated in figs. 42 and 43.

EFFECT ON MEAN SYSTEMIC ARTERIAL PRESSURE AND HEART RATE

In both subjects there is a steady baseline of mean systemic arterial pressure after about the fourth minute of exercise. Inflation of the cuffs results in a continuous rise. It was noted from the pressure trace that, immediately on inflation, there is a rise which is again almost immediately followed by a return to normal. This fall is then succeeded by a continuous rise which is noted in the first measurement in fig. 42, at the end of one minute. The fall is presumably due to a sudden decrease in circulating blood volume because of sudden filling of a preferentially dilated area. In both subjects the final rise in mean pressure has been about 40 mm.Hg. (at the end of five minutes) and 30 mm.Hg. (at the end of three minutes), respectively. At the higher level of exercise it can again be seen that there is a steady baseline of mean systemic arterial pressure created before the onset of vascular occlusion. It is clear that the occlusion results here in an even more rapid rise in blood pressure. The final rises in mean pressure were 41 mm.Hg. (at the end of two minutes) and 26 mm.Hg. (at the end of one minute). The pressure again rapidly reverted to pre-occlusion levels on deflating the cuffs.

Heart rate changes were of interest. One subject (B.L.) showed a slight increase during the period of occlusion while exercising on the flat, while the other subject (W.B.) showed a definite decrease. Both subjects were on a rising baseline (in terms of heart rate) during the uphill exercise. The superimposition of vascular occlusion brought about a fall in heart rate in each case, with a continuation of the upward trend afterwards. One further consistent feature was the very marked increase in heart rate in the first

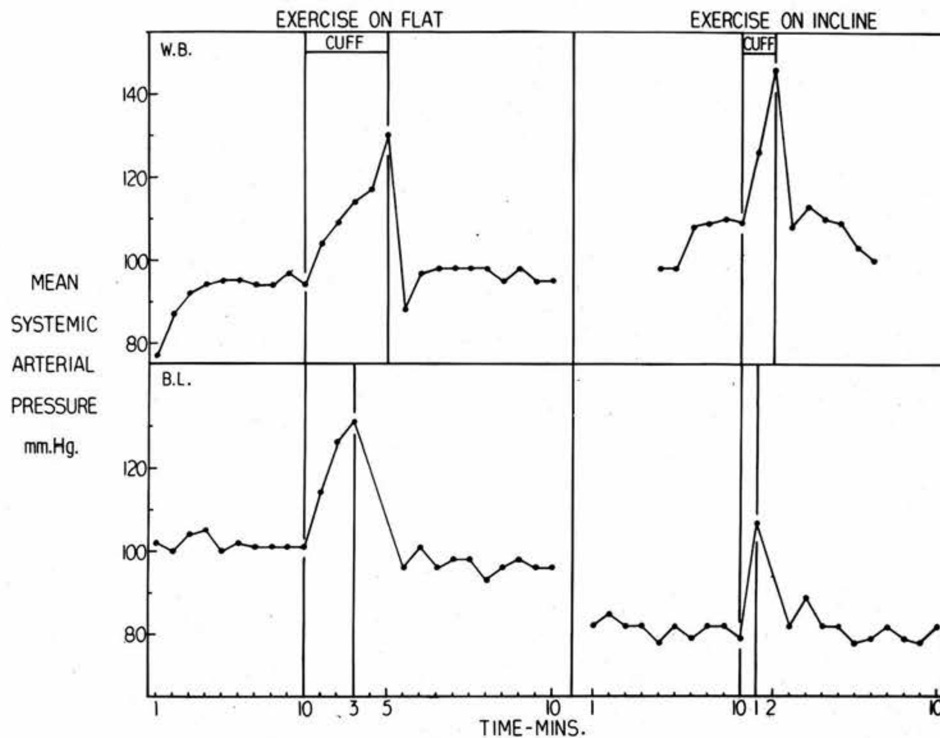

Figure 42. The pressor effect of total vascular occlusion to both legs during treadmill exercise in 2 normal subjects.

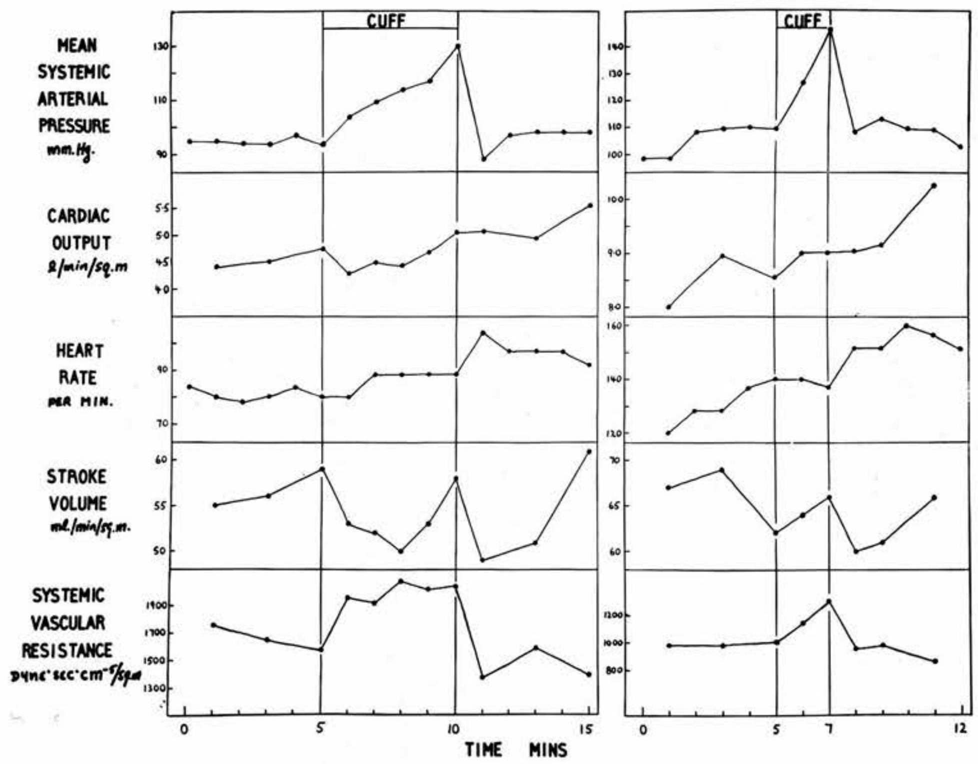

Figure 43. The haemodynamic effects of total vascular occlusion to both legs during treadmill exercise in a normal subject.

minute after deflation of the cuff. In the four instances these increases were 16, 24, 16, 28 beats per minute. In three of these instances the heart rate was lower in the second minute following deflation than in the first minute, so that this increase represents a sudden and limited event.

OTHER HAEMODYNAMIC CHANGES IN W.G. (fig. 43)

Cuffing during exercise on the flat resulted in a rapid fall in cardiac output. This was due to a decrease in stroke volume. It was accompanied by an increase in systemic vascular resistance, much of which may have been a mechanical event. There is, however, then, a continuing increase in systemic vascular resistance, while cardiac output gradually rises to, finally, pre-occlusion levels. This was caused mainly by a return to original exercise levels of the stroke volume. Deflation of the cuffs resulted in a sudden, very large drop in systemic vascular resistance, accompanied by a fall in mean systemic arterial pressure. A large increase in heart rate resulted in a maintenance of the cardiac output. This occurred despite a fall in stroke volume, gradually bringing about a further increase in cardiac output.

The circulation behaved similarly at the higher exercise level except in one or two details. The heart rate was, for instance, continually increasing, so that there is no evidence of a fall in the second minute after deflation. The stroke volume does not show a decrease in the first minute of inflation, though it does so immediately after deflation. Cardiac output is maintained throughout the period of occlusion at pre-occlusion levels. There is a continuous rise in systemic vascular resistance during the period

of occlusion. These changes will be discussed at the end of this section.

THE CIRCULATORY EFFECTS OF TREADMILL EXERCISE IN TWO SUBJECTS WITH INTERMITTENT CLAUDICATION

TECHNIQUES

These were exactly as for subject W.B. in the preceding series.

PLAN OF INVESTIGATION

Observations were made on two subjects (J.B. and S.M.), one male and one female, whose ages were 48 and 60 years respectively. J.B. had a stenosis of his left superior gluteal artery (demonstrated by angiography), with claudicating pain in the left thigh, while S.M. had typical claudication of both calves. J.B. was otherwise normal, while S.M. suffered from mild hypertension (diastolic pressure varied between 100 and 115 mm.Hg.). She was not on anti-hypertensive therapy.

One subject was studied sitting for a six-minute period, standing for a similar period, walking on the flat at 2.5 m.p.h. for ten minutes, standing again for six minutes and, finally, sitting for six minutes. The other subject (S.M.) felt dizzy on approaching the treadmill. Only one set of determinations was therefore made before starting the exercise. These were made while the patient was standing. For the same reason, the study was terminated following one further set of determinations after the end of exercise.

RESULTS

The results are presented in tables 42 - 43, and illustrated in fig. 44.

The subjects are discussed separately.

SUBJECT S.M.:

Effects on the Systemic Circulation: It is clear from table 42 and fig. 44 that this hypertensive subject, who felt dizzy at the start of the procedure, was somewhat hypotensive before exercising. Consequently, the extremely large increase in mean systemic arterial pressure which occurred on exercise must be interpreted with caution. Her mean pressure had, however, risen by 60 mm.Hg. to a level of 159 mm.Hg. by the fourth minute of exercise. While not increasing further it nevertheless remained at high levels throughout the exercise period. Heart rate increased but little and the cardiac output response is therefore almost solely due to an increase in stroke volume. It should be noted that the cardiac output figures achieved were extremely low in absolute terms. They did, nevertheless, represent an increase of more than 2 litres/sq.m./minute over the low resting figure (1.778 l/sq.m./minute). It is clear that while the increase in cardiac output should bring about a return to near normal levels of mean systemic arterial pressure, the further elevation was due to an extremely marked increase in systemic vascular resistance. A rise of over 6,000 dyne.sec.cm. -5 can only represent intense vasoconstriction. There was an immediate fall in resistance at the end of exercise.

Effects on the Oxygen Uptake: For the level of exercise performed (2.5 m.p.h.), the total body oxygen uptake levels, calculated from cardiac output and arterio-venous oxygen differences, are normal. As there is only one set of determinations after the cessation of exercise, comment cannot be made on the oxygen debt incurred.

Effects on the Pulmonary Circulation: As the exercise progressed, pulmonary-arterial pressure rose slightly. Pulmonary-artery wedge pressure appeared to rise by a greater amount. Pulmonary vascular resistance fell as the exercise progressed. Central pulmonary blood volume underwent an increase. It was considered that there occurred no active changes within the pulmonary circulation. The only finding considered abnormal was an abnormally elevated pulmonary-artery wedge pressure (25 mm.Hg.).

SUBJECT J.B.

Effects on the Systemic Circulation: This subject also experienced a quite marked rise in mean systemic arterial pressure (28 mm.Hg.) during exercise, which rapidly returned to normal on its cessation. Such a rise does not normally occur in normal subjects on such exercise. The increase was due to a large rise in cardiac output (3 l/min./sq.m.). This was in turn due to an increase in both heart rate and stroke volume. While there was a moderate fall in systemic vascular resistance, it was not enough to offset the pressor effect of the output response. Systemic vascular resistance afterwards returned to a value somewhat below pre-exercise levels.

Effect on Oxygen Uptake: Total body oxygen uptake behaved normally both during and after exercise. The highest figure achieved during exercise was 580 m./sq.m./minute. A large oxygen debt was not incurred (see table 43).

Effects on the Pulmonary Circulation: There were normal mild elevations in pulmonary arterial and pulmonary-artery wedge pressures, with a slight decrease in Δ P. There was a marked decrease in pulmonary vascular resistance. This was considered to be due to passive distension and

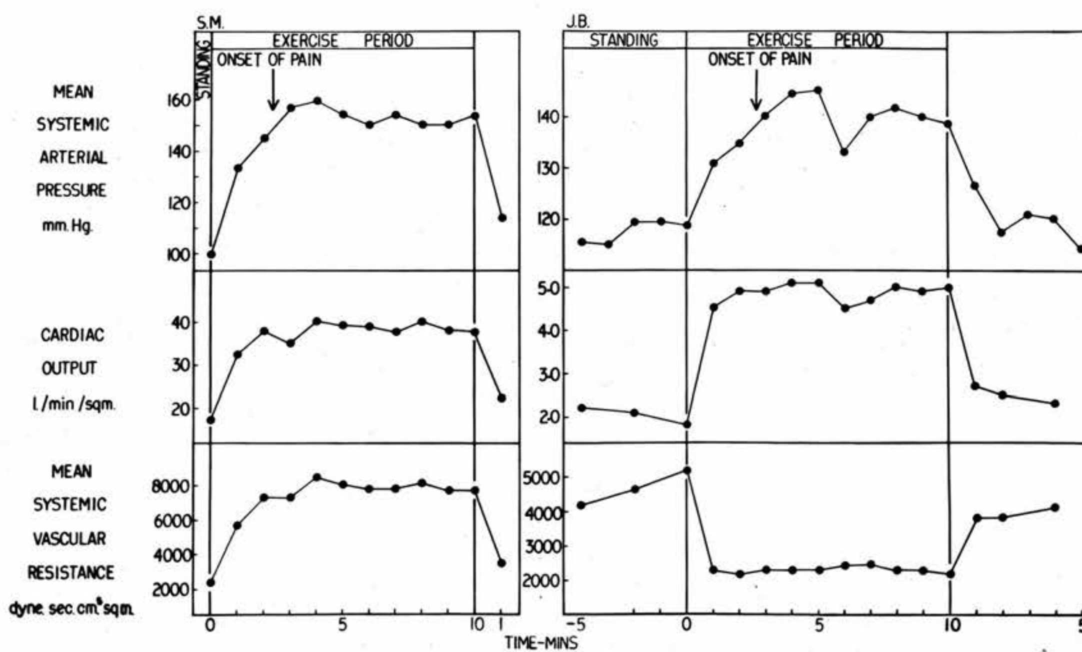

Figure 44. Circulatory responses to treadmill exercise in two subjects with intermittent claudication.

the opening up of fresh channels. There was also, as is normal with an increased flow, a small rise in central pulmonary blood volume.

DISCUSSION

The studied on two normal subjects during treadmill exercise with occluded circulation were in part an amplification of the upper limb experiments with vascular occlusion. They also served to show that it was not the particular mechanical character of the muscular effort which mattered so much as the lack of circulatory integrity which accompanied it. The continuous rise in pressure which occurs cannot be ascribed to the mechanical shutting off of a preferentially dilated area. Firstly, on looking at the actual pressure trace, one notes an original small sharp rise. This is followed by a return to normal, which is then succeeded by a secondary, continuous rise. The initial rise is clearly due to the sudden shutting off of the leg circulation. The immediately subsequent fall is probably due to a sudden large drop in venous return and filling pressure. The secondary rise in systemic blood pressure was shown in subject W.B. to be due to a continuous increase in systemic vascular resistance. This further rise in resistance must then represent active vasoconstriction for the inflated cuffs have ceased to be variables.

The maintenance of cardiac output at exercise levels clearly establishes that the response of the heart to exercise is not due to a humoral factor from the limbs, but is neurogenically dependant. This may be from an irradiation from the motor cortex, as suggested by Krogh and Lindhard (1913), from impulses arising in the legs, as suggested by Assmussen and Nielsen (1949, 1964) or through sympathetic stimulation of the adrenal

glands. It may be that the irradiation from the cortex suggested by Krogh and Lindhard occurs at the beginning of exercise and leads to the non-specific circulatory response described by Rushmer (alluded to on page 37). Brod (1960) also provides support for the contention that mental activity produces a cardio vascular state simulating that created by exercise. It would be more likely, however, that the continued circulatory response is more influenced by the degree of exercise . The afferent source of information on the degree of exercise is the lower limbs. Assmussen and Nielsen (1949) claimed that the cardiac output response to exercise was due to impulses which arose in the working limbs through mechanical stimulation, by the muscle, of nerve endings. These authors (1964) claim now that such nerve endings are chemically stimulated. Some support for the latter proposal has already been offered in this presentation where it was shown that a pressor response could be maintained (cardiac output was not measured) under conditions of vascular occlusion. There is also support for a stimulatory influence, from the adrenal glands. The stimulation to catecholamine release is neurogenically (via the sympathetic) mediated. This may very well, therefore, be an important factor. A situation whereby vasodilatation cannot occur in the lower limbs, which arises in the cuffing experiments and to a lesser extent in the experiments on subjects with claudication, is an unusual one in which to have a high level of circulating catecholamines. Such a high level is known to occur (Braunwald, E., Chidsey, C.A., Harrison, D.E., Gaffney, T.E., and Kahler, R.L., 1963). These substances will increase cardiac contractility, bring about vasoconstriction in the large majority of the regional vascular territories not directly involved in the exercise, and yet not balance this change by dropping vascular resistance in the working muscle. In this

complicated set of circumstances it is difficult to know exactly what role is played by impulses from the ischaemic muscles, and how much of this role is effected, on the efferent side, via the sympathico-adrenal axis.

The responses to exercise on the part of the two subjects with intermittent claudication are dissimilar. Neither are they similar to the responses of normal individuals or subjects comparable in other respects. Hypertensives, into whose age group falls subject S.M., usually respond to exercise on the flat at 2.5 m.p.h. by an increase in mean arterial pressure of about 20 mm.Hg. (unpublished work performed in this laboratory). They do not, however, at this level of exercise, exhibit a rise in systemic vascular resistance, and an increase of over 6,000 dyne.sec.cm.-5 sq.m. is highly abnormal. This increase in resistance which was associated with a limited rise in cardiac output, brought about a large increase in perfusion pressure. Lack of dilatation in the claudicating limbs will not account for the positive rise in vascular resistance. Intense vasoconstriction must have occurred. Whether this vasoconstriction occurred only in other regional territories is open to question. It has been suggested that active vasoconstriction occurs in the lower limbs in these subjects. This observation was prompted by the known increase in lower limb blood flow that tends to occur after exercise in this state (Shepherd, 1963). Wherever the vasoconstriction occurred (and it probably did so in many areas) the stimulus causing the effect was clearly a powerful one. Since the abnormal circulation to the legs is the point of difference between this subject and other hypertensives, such a stimulus may well have come from the lower limbs.

The other claudicant (J.B.), suffered from a very localized and specific type of claudicating pain. This may have accounted for the fact that his systemic vascular resistance did not increase on exercise. He responded differently to normal subjects in that he exhibited a rise of over 25 mm.Hg. in mean systemic arterial pressure at a generally non-fatiguing level of exercise. Such a rise could be due to either an abnormally large cardiac output response or an insufficient degree of vasodilatation in the lower limbs. A drop of 2314 dyne.sec.cm.-5 in systemic vascular resistance would suggest that there was an appreciable degree of lower limb vasodilatations. There was, on the other hand, a large rise in cardiac output (2.963 l/min./sq.m.). The author is, however, not aware of any sufficiently comprehensive published data on the cardiac output response to different levels of upright exercise to allow a decision on whether this increase may be considered abnormally high.

Having discussed their possible mechanism of response, all that can be said about these subjects with intermittent claudication is that their circulations behaved somewhat differently to those of normal subjects when undergoing treadmill exercise. The study of more subjects is clearly required to establish that the abnormal rise in blood pressure consistently occurs.

SUMMARY AND CONCLUSIONS

Previous studies on the circulatory effects of static muscular work have been reviewed. Such effects included a rise in systolic and diastolic blood pressure. This increase, in the limited number of subjects fully studied, was brought about by a heart rate dependant increase in cardiac output. Particular attention has been paid to previous observations that static muscular exercise is ischaemic due to the resistance offered to local blood flow by the statically contracted muscles. It has also been previously shown that ischaemic dynamic exercise results in rises in both systolic and diastolic blood pressure.

In the initial part of this work studies on the circulatory effects of static forearm muscular exercise (isometric hand grip contractions) have been extended. Marked rises in blood pressure have been confirmed. The mechanism of such changes has been found to be usually a heart rate dependant increase in cardiac output. Rarely an element of vasoconstriction contributes to the pressor response. The normal subjects studied were, however, all young adults and it may be that older subjects respond differently. No active changes were noted in the pulmonary circulation. Changes in ventilation and oxygen uptake were slight and the oxygen uptake/cardiac output increase ratio was considerably less than for dynamic exercise.

The relationship between ischaemia of the exercising muscle and the generalized circulatory responses was studied. Total vascular occlusion of the exercising limb was shown to markedly potentiate the pressor response. The degree of potentiation was inversely proportional to the degree of contraction.

In other words, the additional effect of such artificially induced ischaemia is rather more during a weak contraction in which circulatory obstruction under natural conditions will be minimal. By the same token, the added effect is rather less during a strong contraction which is already similarly compromising local circulatory integrity. This suggested that the stimulus leading to the pressor response is initiated at the periphery, that is, in the working limb, and is closely related to ischaemia. Further experiments showed that the pressor response to static muscular exercise could be maintained after the cessation of contraction if total vascular occlusion to the working arm were effected before, and maintained after, relaxation. In such circumstances the only possible remaining pathway connection between the limb and the rest of the body is nervous and the response must therefore be considered to be reflexly determined. A consideration of the literature suggests the pathway to be subserved by c-fibres in the periphery and Lissauer's tract in the cord. The characteristic cardio vascular responses would suggest that the sympathetic nervous system constitutes the efferent limb. It was also shown that the maintenance of total vascular occlusion to a resting limb for twenty minutes did not result in any significant change in blood pressure. It was concluded from the foregoing that some substance is produced during ischaemic muscular exercise which stimulates a local afferent receptor, thus triggering a blood pressure raising reflex. Consideration of possible substances to fill this role led to a study of the concentration changes of certain constituents of effluent blood from statically contracting muscle. A marked fall occurred in oxygen saturation, with an associated rise in hydrogen ion and lactate concentration. Similarly a rise occurred in potassium concentration. The degree of concentration change was, with all

of these substances, proportional to the degree of contraction. The changes in oxygen saturation and in potassium concentration were completely in phase with the blood pressure changes, while hydrogen ion and lactate concentration changes were not. In the latter instances the largest rises occurred after the cessation of exercise and therefore after the return to normal of the blood pressure. This was taken to indicate that these substances were not the direct receptor stimulants.

It is difficult to conceive of a low pO_2 as a receptor depolarizer except through some concrete medium, as by an increase in lactate, etc. Potassium is a known depolarizing agent. The rise in its concentration has been sufficiently high in some of our experiments to lead to a calculated drop of 12 - 15% in the resting membrane potassium potential (application of the Nernst equation). This drop can be theoretically large enough to give rise to a propogated action potential. Such treatment of the Nernst equation is not, however, strictly valid in these circumstances where potassium is not the only ionic variable. This question remains unsettled. The problem may be resolved by observation of the effects of locally administered potassium under strictly controlled conditions.

Hypertensive subjects respond to hand grip in a qualitatively similar fashion to normal subjects. There is not enough available data to definitively state whether or not the quantitative response is also similar, but the evidence to hand suggests that it is so. Guanethidine did not block the cardiac output response to hand grip in hypertensive subjects. The flow response was, in fact, on the whole greater after the administration

of guanethidine. The pressor response was however attenuated because of mild falls in systemic vascular resistance. We already know that guanethidine does not decrease the cardiac output response to supine dynamic leg exercise.

The blood pressure response to hand grip during dynamic exercise involving large muscle groups (i.e. treadmill exercise) was studied. Significant rises did occur in blood pressure in some subjects, though not in heart rate. Responses were found to be not consistent.

The belief that ischaemia of exercizing muscle and not the static quality per se of hand grip contractions led to the characteristic circulatory changes, stimulated an enquiry into the effects of ischaemic dynamic work of the lower limbs. Total vascular occlusion of both lower limbs during treadmill exercise was found to result in a continuous rise in blood pressure during the period of occlusion. In one subject, more fully studied in such an experiment, the continuous rise in blood pressure was shown to be due to a rise in systemic vascular resistance. Cardiac output was, however, maintained at pre-occlusion levels.

In a further extension of the foregoing, the circulatory response to treadmill exercise was studied in two subjects with intermittent claudication. The results suggested that such subjects may have an abnormally large rise in blood pressure during such exercise. More data is required to confirm this finding and to establish the qualitative nature of the response.

SUGGESTED DEVELOPMENT OF THIS WORK

Considerable profit should result from utilization of the classical physiological method of exploring this reflex. This involves studying each component of the reflex arc separately, while controlling the other components. Let us consider the different points in the arc.

Afferent Receptor Site: It is of great interest to discover what substance actually depolarizes the receptor. A logical progression of this work is to study the effects of administration of potassium into an isolated arm. The most scientifically satisfactory method of achieving this end is by intra-arterial infusion as one has always the question of pain with intra-muscular injection.

A more complete biochemical study requires to be made of the effluent blood from the working muscle. With inadequate functioning of the Kreb cycle and build-up of lactate, an increase will occur in other substances, both substrate and enzyme. Any one of these factors could conceivably be the offending agent. No one point in the glycogenolytic chain is definitely known to be rate-limiting, however, so that one cannot concentrate on a particular point. A further difficulty is the problem of analysis of these substances, many of which are normally so low in concentration as not to be estimable by present methods.

Afferent Fibres: The ideal method of investigation of this aspect is by the study of subjects who are de-afferentiated in a selective fashion, though still retaining the power of muscular contraction. This may be seen in patients with syringomyelia.

Spinal Cord: Studies on subjects with lesions of the spinothalamic tracts in the spinal cord would be probably inconclusive. They would also be complicated by the almost invariably associated other lesions.

Efferent Pathway: This is clearly sympathetic. As the cardiac inotropic and chronotropic effects of the sympathetic are beta in type it would be interesting to note the effect of Beta blockade on the heart rate and cardiac output response to hand grip.

Finally, one feels it would be of exceptional interest to study the relationship between fatigue and static work in which it so readily occurs. It may be that some light will be thrown on that curious state.

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ACKNOWLEDGEMENTS

My gratitude is due to all members of the staff of the Department of Medicine (Royal Infirmary), University of Edinburgh, both medical and technical, for co-operation and helpful criticism at all stages of this study.