BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 18 1959

EXERCISE AND HEART DISEASE*

A STUDY IN REGIONAL CIRCULATION

BY

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Although there are many fascinating problems and observations concerning the intravascular pressures, the pulmonary ventilation and muscle metabolism in heart disease during exercise, I would like to devote this lecture more particularly to the subject of the blood flow to the body and its various regions during exercise in heart disease. In 1628 William Harvey wrote as follows: "The heart is the only organ which is so situated and constituted that it can distribute blood in due proportion to the several parts of the body, the quantity sent to each being according to the dimensions of the artery which supplies it, the heart serving as a magazine or fountain ready to meet its demands." Yet over 300 years later we have only a very limited knowledge of the distribution of the cardiac output under various circumstances and almost none of the mechanisms whereby this distribution is controlled and integrated. In heart disease the miraculous fountain of which Harvey wrote may not flow so freely, and I wish to describe some of the remarkable adaptations in regional circulation that occur under these conditions.

The cardiac output is reduced in many clinical states; in the majority of patients with heart failure, in patients with abnormal shunts, in myxoedema, and so on. However, the patients who are particularly suitable for this type of study, which involves exercise and the measurement of the cardiac output, are those with mitral stenosis. In these patients with severe intracardiac obstruction the cardiac output may be considerably reduced both at rest and on exercise for many years, while the patient is still able to live a restricted but relatively normal life with the support of periods of rest, digitalis, and perhaps diuretics. Most of these patients also suffer from atrial fibrillation, which, of itself, causes a considerable reduction of the cardiac output (Smith *et al.*, 1930). Further, in our unit, all patients in whom mitral valvotomy is being considered undergo routine cardiac catheterization, and this added information was obtained without further risk or inconvenience. All the findings reported here are therefore in patients with mitral stenosis, none of whom was in heart failure at the time of the investigation.

This work has been carried out in the Department of Medicine of Birmingham University at the Queen Elizabeth Hospital. It would not have been possible without the constant support of Professor Melville Arnott. Drs. Wade and Bishop have worked closely with me during most of these studies. I would also like to mention others who have been with the team for varying periods and who have all contributed: Dr. Taylor, Dr. Wormald, Dr. Muth, Dr. Cumming, and Dr. Wong. Mr. Pincock and Mr. Mills have helped throughout with expert technical assistance.

*The Bradshaw Lecture delivered before the Royal College of Physicians of London on November 6, 1958.

Space does not allow detailed description of our techniques (Donald *et al.*, 1954), but I would like to mention some of the salient features. The patients were very mildly sedated and lay supine with one or two pillows. The cardiac catheter was introduced into a superficial arm vein and the tip passed well into the pulmonary artery under radioscopic supervision. It is our experience that right atrial blood sampling is highly unreliable owing to the streaming of caval blood and the movement of the catheter. The position of the tip of the catheter was also constantly checked by pressure recordings. Arterial blood samples were obtained from an indwelling needle in the brachial artery. All studies were carried out while breathing room air, the expired gas being collected in a Tissot spirometer. Exercise was performed on a bicycle ergometer attached to the screening table. This allowed a very steady and predetermined rate of work to be maintained. We are well aware that this is not a natural exercising position, and it is possible that some of our findings were influenced by it, in particular the blood flow to the exercising legs.

CARDIAC OUTPUT AT REST AND ON EXERCISE

Let us first consider the measurement of the cardiac output by the technique of cardiac catheterization. Here is the Fick principle as applied to this measurement:

$$\text{Oxygen uptake (ml./min.)} = \text{Flow (l./min.)} \times \text{Increased oxygen content per unit volume blood (ml. per l.)}$$

$$\text{Cardiac output (flow l./min.)} = \frac{\text{Oxygen uptake (ml./min.)}}{\text{Arterio-mixed-venous blood oxygen content difference (ml. per l.)}}$$

The great pioneer of cardiac catheterization, Dr. André Cournand, who trained me in this field, has rightly emphasized that the accurate determination of the cardiac output by the Fick principle demands a steady cardio-respiratory state and simultaneous measurement of all the parameters concerned. As an absolute steady state of all cardio-respiratory parameters is very

difficult to obtain under experimental conditions, a number of workers became discouraged and others suggested that observations of the cardiac output by this technique were quite inaccurate and unreliable. In an early study (Donald *et al.*, 1953) we were able to show that, under carefully controlled conditions, the repeatability of the measurement of the cardiac output was highly satisfactory. In 36 repeated observations in supine subjects with a wide range of resting cardiac output (11.86–2.54 l./min.) the coefficient of correlation between the first and second measurement was r=0.95 and the standard error of a single observation was 8.0%. Repeatability is not absolute proof of accuracy, but it is strong supporting evidence, and the steadiness of the oxygen uptake and arteriovenous oxygen content difference (A–V difference) further increased our confidence.

Normal Subjects

Let us first consider the cardiac output at rest and on exercise in the normal subject, as the findings in disease would have little meaning without this information. The resting cardiac output is difficult to determine in the normal subject, firstly, because cardiac catheterization of healthy people is not lightly undertaken, and, secondly, because of the extreme lability of cardiac output under the stress of the procedure. However, there is now fairly general agreement that the cardiac output in the supine position in normal subjects showing no objective evidence of stress or excitement varies between 2.5 and 4.6 l./min./sq. m.—that is, between 4.5 and 8.25 l./min. in an average-sized man (basal surface area of 1.8 sq. m.). There is still some debate about the upper normal limit but not the lower limit, which is the more important in this context.

At the beginning of our investigation we decided that there were quite inadequate data concerning the response to exercise in normal subjects studied under the same conditions as patients with heart disease. We therefore carried out a series of studies on ourselves and other obliging colleagues under the conditions already described (Donald *et al.*, 1955a). One unsolved problem in studying the exercising cardiac output by the "Fick and catheter" technique, both in normal subjects and in those with heart disease, was the period of exercise necessary to attain a relatively steady state, particularly of the parameters (O_2 uptake, A–V difference) used to estimate the cardiac output. We therefore measured the oxygen uptake during each minute of exercise and followed the changes of mixed venous and arterial blood saturation by frequent sampling. The analysis of the many small blood samples thus collected was made possible by Gatman's spectrophotometric technique, which we modified for this purpose (Wade *et al.*, 1953).

Four groups, each consisting of three males and one female, were exercised at different levels with oxygen uptakes corresponding approximately to those found while walking on the flat at 1½, 2, 3, and 5 m.p.h. We found that an almost steady level of oxygen uptake was reached within one minute in all instances. Further, the mixed venous blood saturation also achieved a steady level within one minute. We were thus able to demonstrate that the cardiac output rose very rapidly and remained almost constant during five minutes' exercise under these conditions (Fig. 1). With regard to the order of change of cardiac output during exercise, Fig. 2 shows the cardiac output related to the oxygen uptake. These findings accorded well with the sparse data then available (Hickam and Cargill, 1948; Riley *et al.*, 1948; Dexter *et al.*, 1951), and subsequent studies by other workers, I am pleased to say, have also shown remarkable agreement (Freedman *et al.*, 1955). A further finding of considerable importance, which I shall mention later, was the return of the cardiac output to a steady resting value within about one minute.

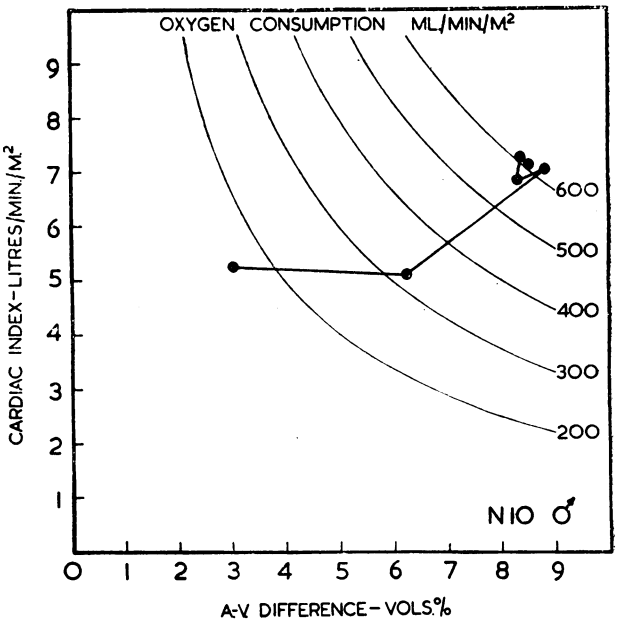

FIG. 1.—Illustrating the relationship of A–V difference, oxygen uptake (N.T.P.), and cardiac output (C.O.) at rest and during five minutes' steady exercise in a normal subject.

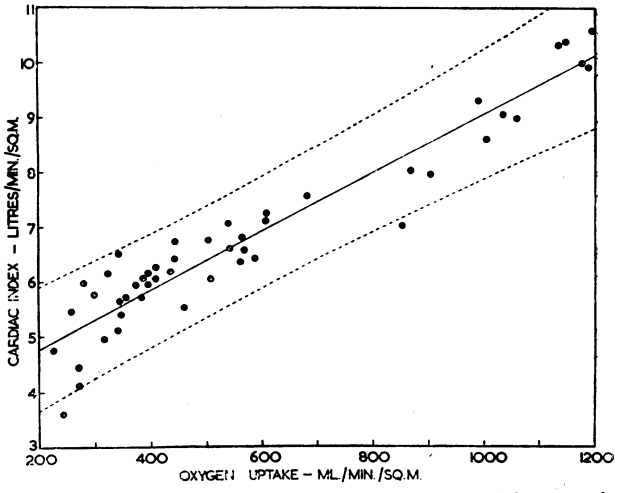

FIG. 2.—Cardiac output and oxygen uptake (N.T.P.) in normal subjects during various degrees of exercise. Regression line and 95% confidence limits shown.

Heart Disease

It has been shown by many workers that the resting cardiac output is usually reduced in patients who are disabled by mitral stenosis, and I will not burden you with our own detailed figures. Although the mean resting cardiac output is always much lower in any group of disabled patients with mitral stenosis than in a group of normal subjects, a number of these patients have resting cardiac outputs within the accepted normal range, even sometimes, when in frank heart failure (Hamilton *et al.*, 1932). Yet such patients may have

reduced skin blood flow and peripheral cyanosis. These disabled patients perform considerably increased respiratory work even at rest owing to the increased ventilatory volumes and reduced lung compliance (Christie and Meakins, 1934; Mead *et al.*, 1953; Marshall *et al.*, 1954). This may well be the reason for the circulatory adjustments while the cardiac output is apparently normal.

In many patients with mitral stenosis the resting oxygen uptake is greatly increased, and this increase correlates with the level of the resting ventilation (Fig. 3). Measurements of the oxygen cost of

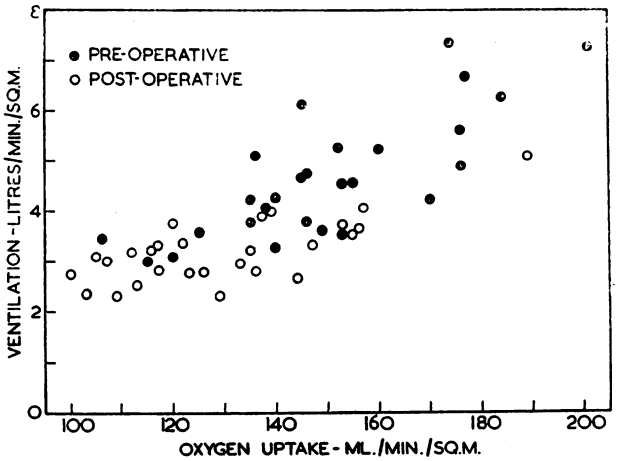

FIG. 3.—Resting ventilation and oxygen uptake in same patients with mitral stenosis before and after valvotomy. Gas. vol. N.T.P.; normal O_2 uptake, 139 ml./min./sq.m., S.D. 22; normal ventilation, 3.02 l./min./sq.m., S.D. 0.38.

breathing in such patients during voluntary hyperventilation would suggest that this increased oxygen uptake is entirely due to increased respiratory work. The added oxygen demands are therefore higher in the more disabled patients. Both the resting ventilation and oxygen uptake fall dramatically after successful mitral valvotomy. The increased ventilation and oxygen uptake also correlate with the level of the resting cardiac output (Fig. 4), and when the ventilation, respiratory work, and oxygen uptake fall after mitral

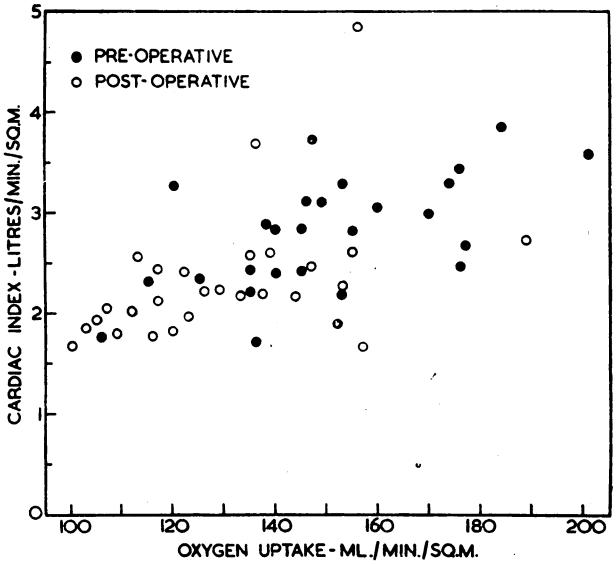

FIG. 4.—Resting cardiac output and oxygen uptake (N.T.P.) in same patients with mitral stenosis before and after valvotomy.

valvotomy the resting cardiac output is almost always less than before the operation (Donald *et al.*, 1957a). It is therefore somewhat naive to expect a simple relationship between the degree of disability and the level of cardiac output, as not only have these patients increasingly impaired cardiac action, but they also have an increasing load of respiratory work and oxygen demands. They are, as it were, in a constant state of respiratory exertion proportional to their disability, and in these circumstances the term "resting cardiac output" is somewhat misleading.

To return to the subject of exercise, minute-to-minute studies, as described in the normal subjects, were carried out on patients with mitral stenosis during supine leg exercise (Donald *et al.*, 1954). These patients were exercised to a previously determined level, which they could tolerate without excessive breathlessness or discomfort. They were, on the whole, exercised to a far higher level than had been previously reported in cardiac patients. A number of important differences emerged. Firstly, the mixed venous blood saturation fell to a much lower level than in normal subjects performing a similar degree of exercise. Further, in many instances there was a greater delay in the achievement of a steady level of mixed venous blood saturation and of a maximum oxygen uptake. However, it was shown that cardiac outputs determined in the fifth minute of exercise were not greatly in error owing to the slightly changing state even in severely disabled patients.

Fig. 5 shows the cardiac output, A–V difference, and oxygen uptake at rest and during each minute of five minutes' exercise. The comparable data of a normal subject at about the same level of work are also shown for the purpose of comparison. It will be seen that many of these patients are incapable of raising the cardiac output to any important degree and how the increased body oxygen uptake is achieved almost exclusively by greatly increased extraction of oxygen from the limited blood flow even, in some cases, when

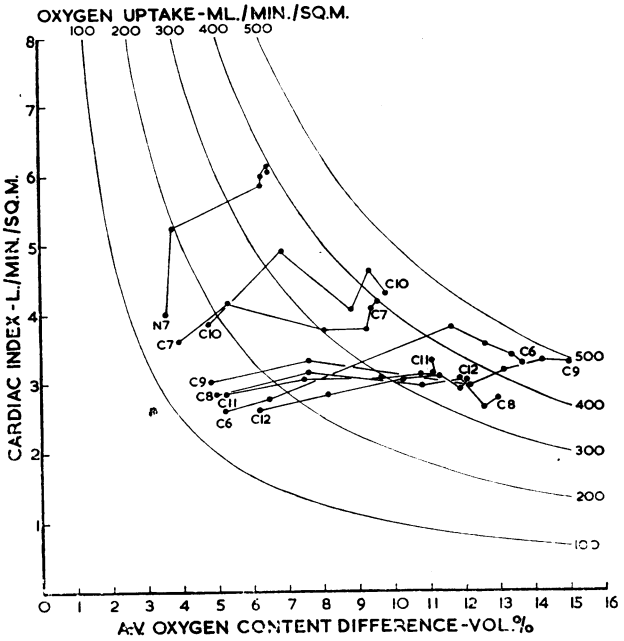

FIG. 5.—Cardiac output, A–V difference, and oxygen uptake, N.T.P. (Cartesian co-ordinates), in patients with mitral stenosis at rest and during five minutes' steady exercise. N, normal subject.

the initial cardiac output is well within the normal range. Further, in many instances the A–V difference and oxygen uptake are still increasing in the fifth minute of exercise. It is to be emphasized, however, that young patients with classical signs of mitral stenosis in sinus rhythm often have a normal rise of the cardiac output on exercise and that many patients have intermediate responses.

During these studies we were impressed by the very low level of mixed venous blood saturation encountered during exercise (as low as 6%); and crude calculations, assuming complete extraction of oxygen from the blood passing up the inferior vena cava, strongly suggested that such levels of mixed venous blood saturation could be achieved only by a considerable reduction of blood flow to the parts of the body not involved in the exercise.

REGIONAL BLOOD FLOW

We therefore decided to study in some detail the A-V differences in different regions of the body in these patients with mitral stenosis during leg exercise, hoping it would afford further information concerning the distribution of the reduced cardiac output under these conditions.

First we measured the cardiac output during the fifth minute of exercise in the usual manner. As we thought it probable that regional circulatory behaviour was most influenced by the degree of cardiac output increase on

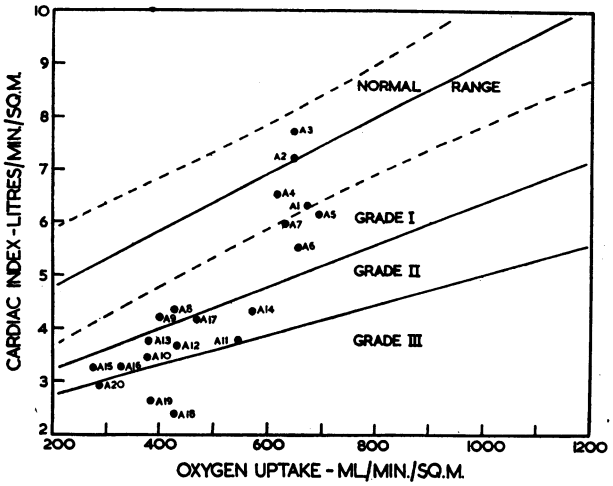

FIG. 6.—Cardiac output during exercise in mitral stenosis plotted against oxygen uptake (N.T.P.). Normal regression line and 95% confidence limits shown. Three arbitrary grades of impairment of exercising C.O. are delineated.

exercise, we graded the cardiac output response into normal and three degrees of impairment (Fig. 6). Those with a grade III response had practically no increase in cardiac output on exercise. This grading is, of course, quite arbitrary, but has been exceedingly useful.

After a period of rest of at least 20 minutes, we moved the catheter so that its tip lay well in the major vein draining the limb or organ under consideration. Several samples of venous blood were taken at rest, and the exercise was repeated at exactly the same level, frequent small venous blood samples being drawn off during exercise and recovery. Less frequent arterial blood samples were also taken. We were thus able to follow closely any changes in regional A–V difference under these conditions, appropriate allowance being made for the changes in blood oxygen capacity during exercise.

Before describing our findings let us consider the Fick principle again:

$$\text{Regional } O_2 \text{ uptake} = \text{Regional blood flow (R.B.F.)} \times \text{Regional A–V difference}$$

If we assume that the oxygen uptake of the region under consideration is not appreciably altered during the short period of exercise then the multiple of blood flow and oxygen A–V difference will remain constant. Thus changes in regional blood flow will be inversely related to the changes in regional A–V difference. That is, if the regional A–V difference is doubled, then the regional blood flow has been halved. As there were rarely any marked changes of arterial blood saturation, a fall in regional venous saturation indicates an increase in A–V difference and a reduction in regional blood flow. I would like to emphasize at this stage that as the arterial blood saturation in most of these patients was of the order of 93%, a fall of regional venous saturation from, say, 83 to 73% implies a doubling of A–V difference and a halving of regional blood flow. A fall of regional venous saturation from 53 to 43%, however, implies only a 25% increase of A–V difference and a reduction of regional blood flow of only a quarter of resting flow.

One does not like to make this assumption concerning the constancy of the regional oxygen uptake in the arm, the brain, the liver, and kidney during supine leg exercise, even though it is a very reasonable one. In this instance we have been fortunate in so far as no other workers, using a wide variety of techniques, have been able to show any important change in the oxygen uptake of the regions not physically involved in muscular activity (Kleinerman and Sokoloff, 1953; Scheinberg *et al.*, 1953; Wade *et al.*, 1956). Further, in no important instance have the findings concerning the regional blood flow on exercise, using other techniques, differed from those based on this important assumption.

Again the Fick principle can also be used to compare the regional blood flow with that in normal subjects, thus:

$$\text{Regional } O_2 \text{ uptake} = \text{R.B.F.} \times \text{R.A–V difference}$$

If we assume, or have evidence, that the regional oxygen uptake in the cardiac patient is the same as in normal subjects, then:

$$\text{Regional } O_2 \text{ uptake} = \text{R.B.F.} \times \text{R.A–V diff.} = \text{Normal R.B.F.} \times \text{Normal R.A–V diff.}$$

$$\therefore \text{Regional blood flow} = \frac{\text{Normal R.A–V diff.}}{\text{Regional A–V diff.}} \times \text{Normal R.B.F.}$$

Owing to differences of body size, shape, and experimental conditions, it is, of course, wise to make such comparisons only in groups of patients and normal subjects.

Arm

We first studied the A–V differences in the arm, the tip of the catheter lying in the axillary vein (Donald *et al.*, 1955b). The resting A–V difference was greatly increased in many of these patients (normal, 2.1 to 5.0, mean, 3.3 vol.%), and this increase was inversely related to the level of the resting cardiac output. Many patients with cardiac outputs in the normal range had abnormal A–V arm differences. Those with definitely subnormal cardiac outputs (below 2.5 l./min./sq. m.) had a mean A–V difference of 9.3 vol.%, suggesting an almost threefold reduction of arm circulation. The arm appears to be a region in which the circulation is reduced quite severely and at a relatively early stage.

We then studied the axillary A–V difference during leg exercise. Those patients with little or no increase

of cardiac output on exercise showed a considerable depression of axillary venous saturation and increase in A–V difference which usually persisted to the end of the exercise (Fig. 7). This indicated a very considerable and sustained decrease of total arm blood flow. There

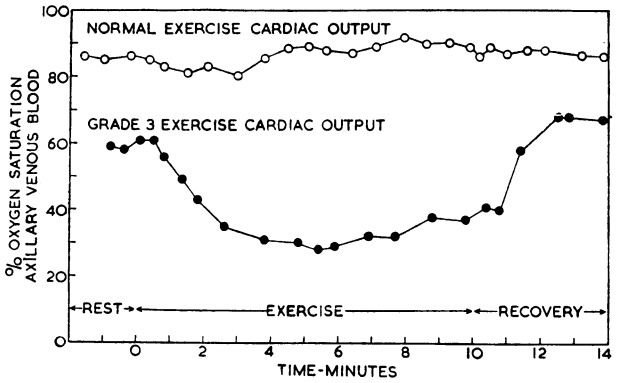

FIG. 7.—Axillary venous blood percentage saturation at rest and during exercise and subsequent recovery in two patients with mitral stenosis. Grade III impairment exercising C.O.; O_2 uptake, 425 ml./min./sq.m. Normal exercising C.O.; O_2 uptake, 649 ml./min./sq.m. The behaviour in the latter patient is similar to that in normal subjects. Arterial saturation, of the order of 93%, showed no important change and is not shown in these or subsequent figures. Note greater significance of changes of venous saturation at higher levels as regards changes in blood flow (see text).

was, however, great variation of behaviour of the arm A–V difference. The patients with normal or near normal exercising cardiac outputs also showed an increase of A–V difference in the first few minutes of exercise, but it often returned to the resting figure or became even less (Fig. 7).

At this stage we felt it was necessary to study the same phenomenon in normal subjects at similar levels of exercise (Bishop *et al.*, 1957). These, too, showed a definite but usually transient increase of arm A–V difference, which, as in the less disabled cardiac patients, then decreased very considerably. At higher levels of exertion the increase of arm A–V difference was usually more marked and more sustained.

We considered that these changes in A–V difference were mainly related to changes in hand and arm skin blood flow and could be explained as follows. The normal subject or the patient with a normal exercising cardiac output has a normal skin flow which becomes transiently reduced at the commencement of exercise. However, this soon passes off and the skin flow then increases considerably in order to allow increased heat loss. The severely disabled cardiac patient who already has a reduced skin flow, as frequently evidenced by the cold blue hand, reduces this even further and appears able, for reasons of circulatory economy, to inhibit the skin vasodilatation which normally occurs after exercise has proceeded for a few minutes.

However, the arm has two major circulations, that of skin and that of muscle, and these may behave very differently under certain conditions (Grant and Pearson, 1938). Attempts were therefore made to study these two arm circulations separately during leg exercise. The skin circulation was studied by hand calorimetry (Greenfield and Scarborough, 1949); this measures the heat loss, which is closely related to immediate skin blood flow. These experiments mainly confirmed our impressions and showed in normal subjects (Bishop *et al.*, 1957) a transient reduction of heat loss followed by a very great increase. A number of very disabled patients with mitral stenosis had a smaller heat loss and skin blood flow at rest and showed a definite and sustained reduction of heat loss during exercise (Muth *et al.*, 1958). There was a moderate but definite increase of heat loss after exercise. However, in a number of other disabled patients a definite increase in heat loss occurred after a few minutes' exercise, although they maintained a wide arm A–V difference and, presumably, a reduction in total arm blood flow.

We therefore turned our attention to the muscle circulation in the arm during leg exercise. This caused us great difficulties. Forearm water plethysmography measures both skin and muscle circulation. In any case, experiments soon showed it to be impracticable under exercising conditions. Strain gauge plethysmography was equally unsuccessful. The rate of clearance of radioactive sodium injected into forearm muscle (Kety, 1949) was not significantly changed by leg exercise in either normal subjects (Bishop *et al.*, 1957) or in patients with heart disease (Muth *et al.*, 1958). However, this technique of measuring changes in blood flow is now considered to be somewhat insensitive even by its originator. We then employed the technique of retrograde venous catheterization. Dr. Mottram (1955) developed this ingenious method, and we are most grateful to him for his personal advice and assistance in the early stages. A thin nylon catheter is passed through a needle in a retrograde direction from a vein in the antecubital fossa. Radiographs are taken in two planes to confirm that the catheter is deep in the forearm musculature. A cuff at the wrist is inflated above arterial pressure, before sampling, to reduce the possibility of contamination by skin blood. There is little doubt that there are a number of communications between the superficial and deep forearm veins and that the proportion of deep venous blood deriving from skin circulation may vary from person to person and under different conditions. However, with these reservations, it is justifiable to assume that deep venous blood is mainly composed of blood derived from the forearm muscles.

The arm "muscle" A–V difference was then studied by this technique in normal subjects and in patients with

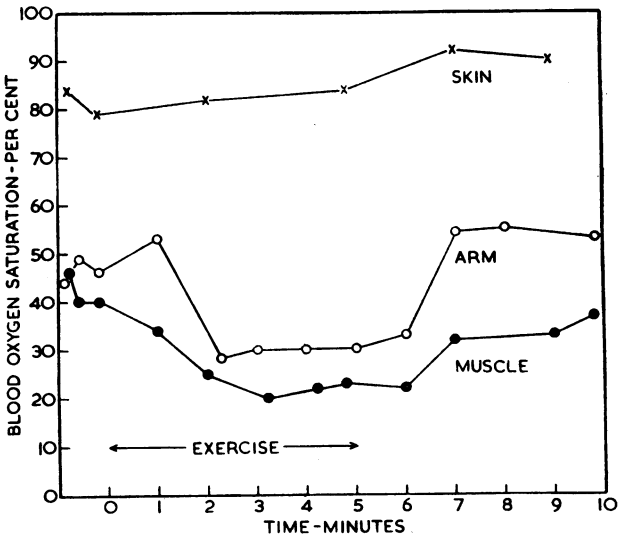

FIG. 8.—Percentage oxygen saturation of blood during rest, recovery, and exercise from deep forearm vein (●), axillary vein (O), and superficial forearm vein (X) in patient with mitral stenosis and grade III impairment of exercising C.O.

heart disease during leg exercise (Muth *et al.*, 1958). In normal subjects the arm muscle A–V difference was unaltered during leg exercise, apart from a transient decrease that Roddie and Shepherd (1956) have already reported, when the legs were raised on to the ergometer. The disabled cardiac patients showed a markedly different behaviour. Although the resting muscle A–V difference was normal, leg exercise caused an increase of arm muscle A–V difference, which was maintained until the end of leg exercise and recovered a few minutes afterwards. The findings in one case are illustrated in Fig. 8. It will be seen that although the skin blood saturation increased (skin A–V difference decreased) as exercise proceeded, the muscle and arm blood saturation decreased (A–V difference increased) and remained so until the end of the exercise. These findings suggest that there is a very considerable reduction of arm muscle blood flow during leg exercise in these disabled patients which does not occur in normal subjects under the same conditions.

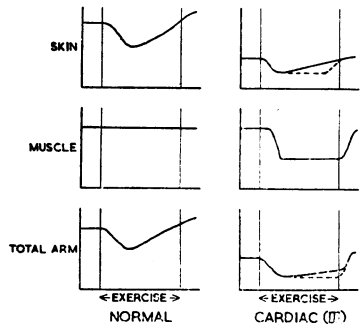

FIG. 9.—Roughly quantitative diagram summarizing inferred changes in skin, muscle, and total blood flow in resting arm during leg exercise in normal subjects and cardiac patients with impaired exercising C.O.

We may conclude that during leg exercise in normal subjects there is at first a reduction of blood flow to the skin of the hand and arm followed by a pronounced increase (Fig. 9). There is little or no change in forearm muscle blood flow. In patients with heart disease and restricted cardiac output response to exercise, the blood flow to skin is markedly reduced at rest, while the forearm muscle blood flow is relatively normal. Leg exercise results in the reduction of both skin and muscle blood flow. As exercise continues the muscle blood flow remains low, but the skin blood flow increases, although this increase is later and smaller than in normal subjects, and does not occur in some patients, chiefly those with the most restricted cardiac output response to exercise.

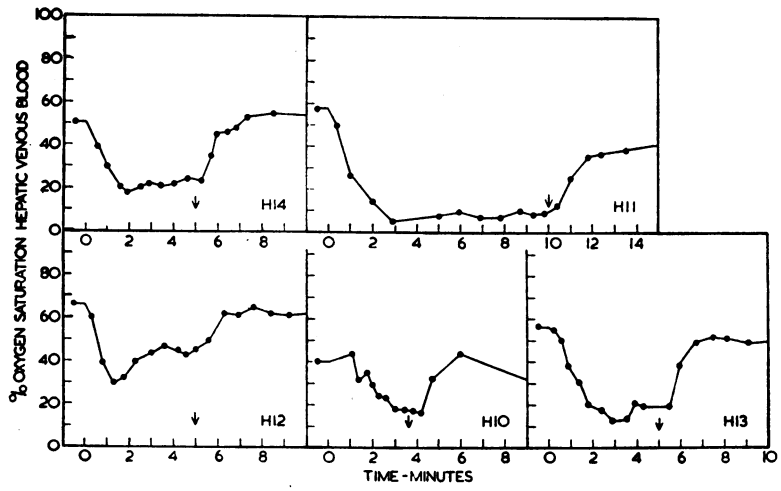

FIG. 10.—Hepatic venous oxygen saturation at rest, during exercise, and recovery (commencing at O, ends at signal) in patients with mitral stenosis and grade III impairment of exercising C.O. Mean oxygen uptake 450 ml./min./sq.m.

Splanchnic Circulation

We next turned our attention to the splanchnic circulation. The tip of the catheter was passed well into the right lobe of the liver and the stability of this position during deep inspiration was assured. The resting hepatic A–V difference again appeared to be inversely related to the level of cardiac output (Bishop *et al.*, 1955). The hepatic A–V difference was only abnormally increased in patients with cardiac outputs less than 2.5 l./min./sq. m. It would appear that marked reduction of resting splanchnic blood flow occurs at lower levels of general blood flow than is the case with the arm circulation. Although, at this time, it was generally accepted that there was a reduction in splanchnic circulation on exercise in normal subjects, the evidence was very scanty and inconclusive (Barcroft *et al.*, 1925; Barcroft and Florey, 1929; Bradley, 1948). Again we assumed that the splanchnic oxygen uptake was not appreciably altered during a short period of leg exercise. Work since carried out on normal subjects during moderate leg exercise, using the bromsulphthalein extraction technique in combination with A–V difference studies, has supported this assumption (Wade *et al.*, 1956).

We first studied normal subjects (Bishop *et al.*, 1957) and found that the hepatic A–V difference did not increase until a fairly high level of exercise was carried out (1,070 ml./min./sq.m.—that is, walking at 5 m.p.h.). However, in the normal subjects exercising at lower levels, in whom the hepatic A–V difference did not increase during exercise, there was a definite and sustained increase of hepatic A–V difference after the exercise had ceased. Interpreting these findings into changes of splanchnic blood flow, we considered that splanchnic vasoconstriction was not invoked in normal subjects by leg exercise until a fairly high level of exertion was reached. The apparent post-exercise decrease in flow, even after very moderate exercise, was of great interest. You will recall that we had demonstrated that in normal subjects in these ranges of exercise the cardiac output returns to the resting value within about a minute. It is equally certain that the blood flow to the skin and to the recently exercised muscles continues to be raised for some time after exercise. There must therefore be a reduction of blood flow to some regions in the body at this time, and it would appear that the splanchnic circulation takes a large part in this reduction. Our grandmothers may have been intuitively aware of the possible reciprocity of splanchnic and skin circulation when they emphasized the hazards of a hot bath after a large meal.

Turning to the patients with heart disease, we found very marked increases of hepatic A–V difference on moderate leg exercise (450 ml./min./sq. m.; 3 m.p.h. on flat) in the more disabled patients (Fig. 10). Hepatic venous saturations of below 10% were recorded in some instances (Bishop *et al.*, 1955). It has been shown that the splanchnic oxygen uptake is not significantly altered from normal even in congestive cardiac failure (Myers and Hickam, 1948). We can therefore reasonably use the A–V

differences to relate the resting and exercising splanchnic flow to that in resting normal subjects (Myers *et al.*, 1950). Such calculations showed that in a group of disabled patients with little or no increase of cardiac output on exercise the mean splanchnic blood flow, which was one-half of the normal resting value at rest, was reduced to one-quarter of this value on moderate leg exercise (O_2 uptake, 457 ml./min./sq. m.). Some of the more disabled patients showed a depressed hepatic venous saturation 10 and even 20 minutes after exercise. The prolonged widening of the A–V difference and reduction of splanchnic blood flow after this brief exercise almost certainly allow the limited skin vasodilatation and increased heat loss which are found after exercise in even very disabled patients.

Our main conclusions were that a reduction of splanchnic blood flow is invoked by a far smaller degree of exertion in these patients with heart disease than in normal subjects. Further, in many cases the splanchnic blood flow is decreased for some time after even very moderate exertion. It would thus appear that a patient with a fixed cardiac output who is up and about will suffer from repeated, marked, and prolonged reduction of splanchnic blood flow. The hepatic cells are therefore exposed to considerably lowered oxygen tensions over long periods, and it is possible that this may play a part in the causation of the disturbances of liver function and structure which are found in a number of these patients and which are at present solely attributed to increased venous pressure.

Kidney

The next regional A–V difference to be studied was that of the kidney (Bishop *et al.*, 1958). The oxygen uptake of the kidneys has been shown to remain constant during extreme renal metabolic activity (Bucht *et al.*, 1949; Clark and Barker, 1949), and there is little doubt that changes in A–V difference are a direct reflection of changes in blood flow. The tip of the catheter was passed well into the right renal vein and its position checked again by radioscopy after exercise. Again the resting renal A–V difference was found to be inversely correlated with the cardiac output. All patients with cardiac outputs below 2.5 l./min./sq. m. had abnormal renal A–V differences (normal, 1.1 to 1.9 vol. %, mean 1.4; Cargill and Hickam, 1949) and presumably decreased renal blood flow. However, a number of patients with relatively normal cardiac outputs had abnormally increased renal A–V differences.

The high kidney blood flow in relation to the oxygen demands results in a very high renal venous saturation. For the reasons already given, if the venous saturation is relatively normal, a change of renal blood flow of over 200 ml./min. would cause a change of only 2% of renal venous saturation, and this technique is therefore somewhat insensitive. However, a slight but definite increase of renal A–V difference occurred almost immediately on leg exercise in disabled patients with mitral stenosis returning rapidly to the resting level afterwards. Assuming that these patients had renal oxygen uptakes similar to normal subjects, it can be calculated, using Homer Smith's (1951) figures for normal renal blood flow (1,100 ml./min./1.73 sq. m.), that in nine patients with mitral stenosis (five grade I, one grade II, and three grade III, impairment exercising cardiac output), the mean renal blood flow was 760 ml./min. at rest and that it fell to 470 ml./min. on leg exercise (mean O_2 uptake, 530 ml./min./sq. m.). The more severely disabled patients in this group, with little or no increase of cardiac output on exercise (grade III response), had a more marked increase of renal A–V difference during exercise. The mean calculated renal blood flow during moderate exercise was 20% of the normal resting value. These figures are in remarkable agreement with renal blood flow measurements during exercise in patients with heart disease by other workers using renal clearance techniques (Aas and Blegan, 1949; Freeman *et al.*, 1955; Judson *et al.*, 1955; Werkö *et al.*, 1954). The only important advantage of our technique is that it allows immediate changes of flow to be studied in a manner not possible with the renal clearance methods.

The reduction of renal blood flow during moderate exercise in the patients with little or no rise of cardiac output is very striking, although the exercising renal venous saturations are still far higher than is the case of the splanchnic circulation under these conditions. Recently, considerable attention has been given to the long-known occurrence of protein (Collier, 1907), increased casts, and red blood cells (Barach, 1910) in the urine of athletes after exercise. It has been suggested (Alyea and Parish, 1958) that this may be due to marked reduction of renal blood flow and resultant hypoxia during violent exertion. These patients, who have low exercising outputs and are still ambulant, would appear to be in even greater danger of permanent renal damage than any marathon runner. Nitrogen retention is unusual in cardiac patients who have not had excessive mercurial therapy, but the disturbances of renal function causing water and sodium retention which are usually attributed to decreased renal blood flow and increased venous pressures may also be related to the repeated hypoxic insult to the kidney during the activities of everyday life.

We have not studied normal subjects by this technique, but other workers (Barclay *et al.*, 1947; Chapman *et al.*, 1948; White and Rolf, 1948), using renal clearance methods, have shown that a reduction of renal blood flow occurs on exercise in normal persons, but that it is to a lesser degree for a given exertion than in patients with severe heart disease (Freeman *et al.*, 1955) and presumably restricted cardiac outputs.

Brain

The next regional circulation to be studied during leg exercise was that of the brain (Bishop *et al.*, 1958). The catheter was passed up the jugular vein well above the angle of the mandible, and thus blood was drawn from within or close to the jugular bulb and above the facial vein, the highest external tributary of the internal jugular vein. In the seven patients studied the mean A–V difference was a little greater than the mean value reported (Kety and Schmidt, 1948) in normal subjects (normal, 6.2; cardiacs, 8.0 vol. %), and this would suggest that mean cerebral blood flow was slightly decreased in these patients. Only two patients, however, had resting A–V differences outside the normal range (3 to 8.7 vol. %). On leg exercise, although there were slight changes in jugular A–V difference, there were no important trends, some increasing and some decreasing slightly. Assuming that the mean resting cerebral oxygen uptake in the patients was the same as the mean normal value, and that it did not change during exercise, then the mean cerebral blood flow at rest was 82%, and on exercise 85% of the mean normal

resting cerebral blood flow. We have no similar studies in normal subjects, but a number of workers, using Kety's nitrous oxide technique, have shown no important change of cerebral blood flow or of cerebral oxygen uptake on exercise (Kleinerman and Sokoloff, 1953; Scheinberg *et al.*, 1953). We conclude that the cerebral blood flow in these patients with heart disease was slightly reduced at rest, but, as in normal subjects, there was no important change during exercise.

If the regional A–V difference is studied with the catheter tip low in the jugular vein in patients with restricted cardiac outputs during leg exercise, there is a considerable widening of the A–V difference. This is undoubtedly due to venous blood deriving from skin and perhaps muscle in the head and neck, where vasoconstriction occurs on exercise. The well-known fact that such patients show an increase in cyanosis in the face and ears on exercise is, in retrospect, obvious evidence of considerable skin vasoconstriction.

Exercising Legs

Finally we studied the A–V difference changes in the legs (Donald *et al.*, 1957b). A catheter was passed into the femoral vein via the inferior vena cava. In some instances a small nylon catheter was placed direct into the femoral vein.

A feature of considerable interest was that, in contrast to the arm, the resting femoral A–V difference was not unduly increased in many very disabled patients. This may be due to the fact that, at rest at least, the heat loss from the foot and necessary skin blood flow variation is not of the order of that from the exposed hands and face. It is also further indirect evidence that the resting muscle blood flow is normal in these patients.

At a given level of leg exercise the femoral A–V difference was much greater and, presumably, the leg blood flow smaller in patients with restricted cardiac outputs than in normal subjects.

Frequent determinations of the femoral venous saturation changes during leg exercise and recovery in normal subjects showed a dramatic fall of saturation in the first minute of exercise and an almost equally rapid recovery after exercise. These normal subjects showed a rise of femoral venous saturation as exercise proceeded. As there were no marked changes in arterial blood saturation and the oxygen uptake was at a steady level, this suggests that there was an increase of leg blood flow at this time. It is probable that this was due to skin vasodilatation in the leg to allow increased heat loss.

The patients with mitral stenosis and impaired exercising cardiac outputs showed not only lower levels of femoral venous saturation but also a steady or even slightly decreasing femoral venous saturation as exercise proceeded (Fig. 11). Those with normal cardiac output responses showed a rise of saturation during exercise as in normal subjects. It is likely that, as in the arm, the more disabled patients were able largely to inhibit skin vasodilatation for reasons of circulatory economy.

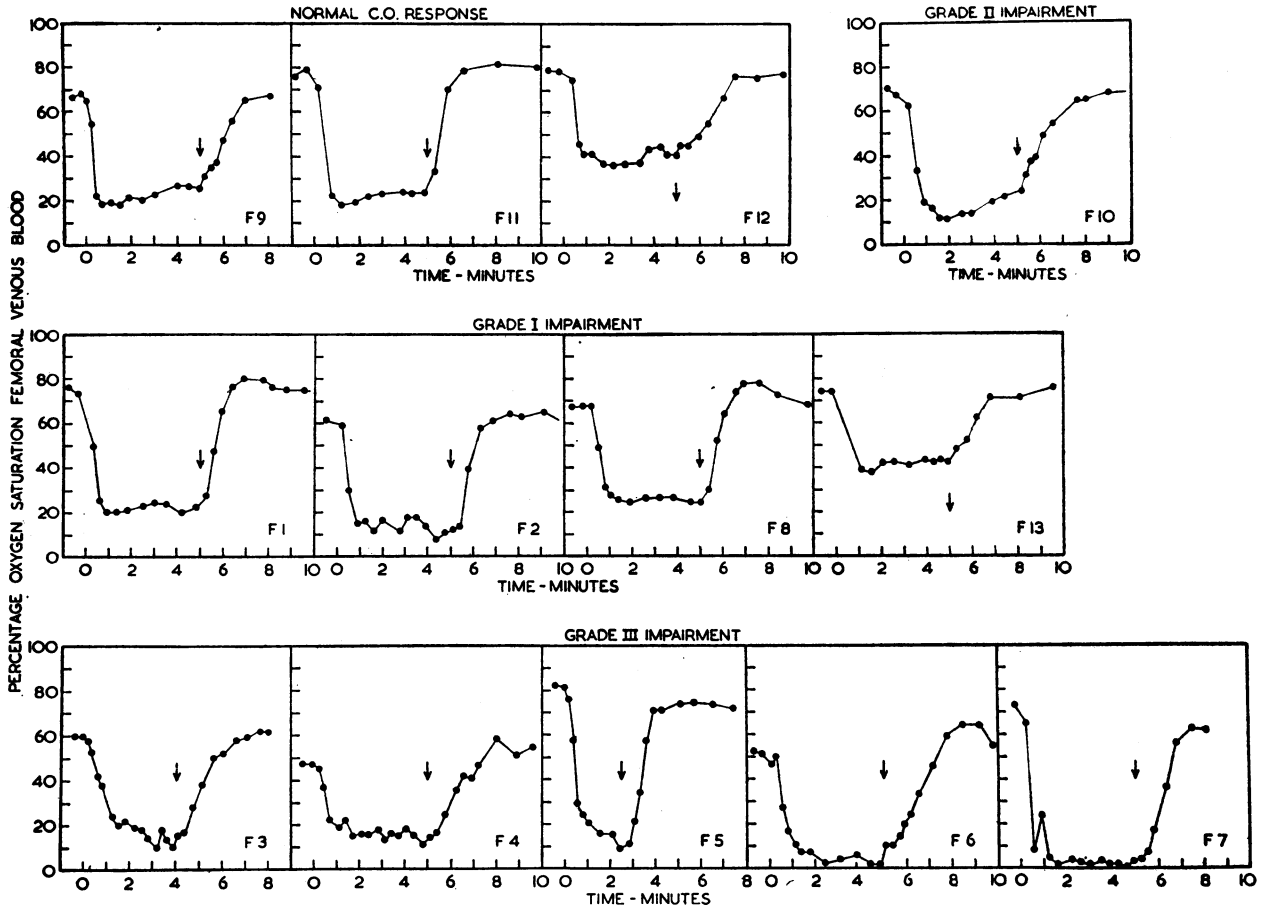

FIG. 11.—Femoral venous blood oxygen saturations at rest and during leg exercise and recovery in patients with mitral stenosis. Exercise between zero times. Oxygen uptakes between 450 and 650 ml./min./sq.m. except F2 (820) and F3 (320). C.O. response shown. Note rise of femoral venous saturation during exercise in patients with normal exercising C.O. as in normal subjects.

A further remarkable finding was that in some of the most disabled patients femoral venous blood was obtained in a number of instances in which no oxygen could be demonstrated. These patients did not complain of any undue weakness or discomfort in the legs. This astonishing ability of naturally exercising muscle to strip oxygen completely out of the circulating blood has not been previously demonstrated. A further point is that these very low saturations are strong supporting evidence of extreme reduction of skin blood flow in the exercising legs.

We next attempted to estimate from these data the actual blood flow to the exercising legs. We assumed that all the increased oxygen uptake during exercise was in the exercising legs, and that the femoral A–V difference was representative of the A–V difference of all leg regions involved in the exercise. If this were the case then:

$$\text{Blood flow to exercising legs} = \frac{\text{Resting leg } O_2 \text{ uptake} + \text{increase in } O_2 \text{ uptake}}{\text{Exercising femoral A–V difference}}$$

Even if some muscles outside the legs were involved in the exercise, provided their A–V difference was of the order of that in the femoral vein, then this equation would measure the blood flow to the exercising muscles no matter where they were situated. The resting oxygen uptake of the leg was estimated from the measured resting A–V difference and previous plethysmographic measurements of resting leg flow. Errors in this estimation would have but little effect on the total flow calculations during exercise. Fig. 12 shows the figures

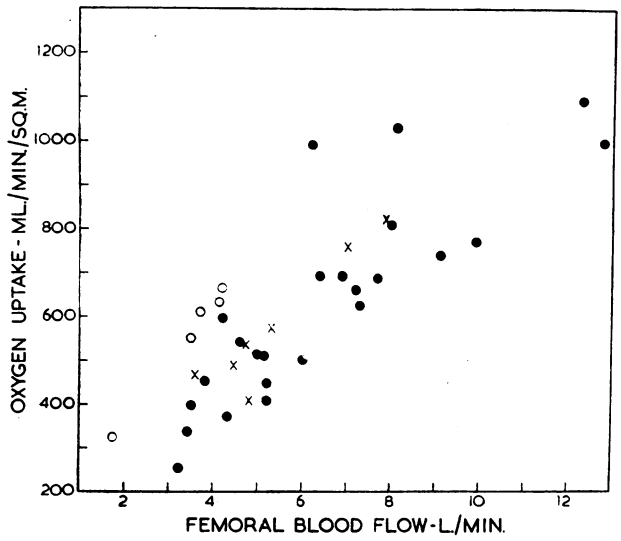

FIG. 12.—Calculated leg blood flow related to oxygen uptake (N.T.P.) during leg exercise. Normal heart and exercise C.O. (●); mitral stenosis and grade I impairment of exercising C.O. (X); mitral stenosis and grade III impairment of exercising C.O. (O).

of leg blood flow, obtained in this way, in the fifth minute of leg exercise related to the degree of exercise, as measured by the oxygen uptake, in normal subjects and in those with heart disease. It will be seen that the patients with heart disease have a lower leg blood flow at a given level of exercise.

We felt, as I have already mentioned, that some of the differences of leg blood flow were due to the differences in behaviour of skin circulation. It will be remembered that, in the arm, skin vasoconstriction was most marked in the normal subjects in the second and third minute of exercise. After this, skin vasodilatation usually occurred. In the cardiac patient skin vasoconstriction was more prolonged. We therefore estimated leg blood flow in both the second and the fifth minute of exercise. In the five normal subjects at a given level of exercise, the mean leg blood flow was 5.0 l./min. in the second minute and increased to 6.6 l./min. in the fifth minute. In five patients with heart disease, and almost fixed cardiac outputs during exercise of the same order, the mean leg blood flow was 4.1 l./min. in the second minute and 3.9 l./min. in the fifth minute. The figures in the second minute almost certainly represent far more closely the comparative muscle flow.

CONCLUSIONS

We thus see that even in these grossly disabled patients the circulatory adjustments have been so efficient that the blood flow to the exercising muscles was of the order of 80% of that in normal subjects with a normal cardiac output response to exercise. As the cardiac output is low and fixed, this can be achieved only by a very considerable reduction of blood flow to the whole skin, to muscles not involved in the exercise, to the splanchnic area, and to the kidneys. Only the cerebral blood flow is exempt and continues at the resting level. The advantages of an adequate cerebral circulation during exercise are obvious, but it is nevertheless remarkable to see it maintained so efficiently under these conditions of extreme circulatory stress.

There is little doubt that the coronary blood flow, which is about 5% of the cardiac output and proportionately increased on exercise, is also maintained at normal levels in these patients, as in no single instance did a patient complain of ischaemic heart pain. The left ventricular work is usually much less than normal on exercise owing to the low cardiac output, but the right ventricular work is often very considerably increased, especially in the presence of a high pulmonary vascular resistance.

The respiratory work carried out by these patients during exercise (White *et al.*, 1958) is of a very high order owing to the increased volumes ventilated and the reduced lung compliance, and this is a further, as yet unmeasured, demand on the limited circulation. The increased blood flow to the respiratory muscles is, at present, included in our estimate of exercising muscle blood flow.

The heat balance of the disabled cardiac patient in the presence of restricted skin blood flow is a problem of considerable interest, particularly as many have raised basal oxygen uptakes owing to increased respiratory work. There is certainly an increased loss of heat from the lungs due to hyperventilation, but further work on this subject is needed. The relatively short periods of exertion tolerated by these patients may render the problem of heat loss during exercise less important. Further, it is possible that the increase in anaerobic muscle metabolism due to decreased blood flow and muscle oxygen tensions may reduce the immediate heat production during muscle contraction.

The normal A–V difference found in the muscles of resting patients with low cardiac outputs suggests that, in contrast to the skin, their blood flow is maintained at normal levels. This would explain why these patients have normal arterial blood lactic acid concentrations even when in frank congestive failure (Donald *et al.*, unpublished). However, the reasons why resting muscle should be so privileged in the presence of such low

general body blood flow are not yet apparent. We have only indirectly demonstrated vasoconstriction in the resting muscle in the arm of disabled cardiac patients during leg exercise. It is highly probable that this occurs in all resting muscle during exercise in such patients, but again further work is needed on this aspect. The vasodilatation in exercising muscle appears to be an irresistible local phenomenon completely dominating any other humoral or neural influences. The maintenance of a normal arterial blood pressure on exercise in these patients with a low and fixed cardiac output, despite the extreme dilatation of the vascular bed in exercising muscle, is essential for the adequate perfusion of brain and heart. It is tolerably certain that vasoconstriction in all resting muscles contributes to this remarkable preservation of the blood pressure during exercise.

The possible dangers of repeated hepatic and renal ischaemia in these patients during exertion have already been discussed. At present we have little knowledge of the oxygen tension levels which will interfere with tissue enzyme and cellular function in these organs. Meanwhile it would appear reasonable to warn such patients not to exercise repeatedly to their maximum tolerance.

Finally, we have not specifically studied the actual mechanisms which are responsible for this highly integrated circulatory economy, and this will be the next stage of the investigation. Such evidence as we have suggests that both humoral and neural mechanisms are involved. It is probable that almost all these changes in regional blood flow in the exercising cardiac patient are also invoked in healthy subjects at higher levels of exertion. Further study of these phenomena in such patients will therefore not only increase our knowledge of heart disease but also strengthen our understanding of the functions of the normal circulation.

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VACCINATION AGAINST WHOOPING-COUGH

THE FINAL REPORT TO THE WHOOPING-COUGH IMMUNIZATION COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND TO THE MEDICAL OFFICERS OF HEALTH FOR BATTERSEA AND WANDSWORTH, BRADFORD, LIVERPOOL, AND NEWCASTLE*

In the previous investigations, reported to the Whooping-Cough Immunization Committee of the Medical Research Council (Medical Research Council, 1951, 1956), there were two main objectives. The first was to obtain, from the results of strictly controlled trials, an assessment of the prophylactic value of pertussis vaccines in children, and the second to determine whether the prophylactic value of vaccines could be assessed by a laboratory test. Field trials were made with a large number of vaccines, and the results showed considerable differences in protective activity, some vaccines giving substantial protection and others hardly any. Laboratory tests also showed that the vaccines differed widely in their ability to protect mice against intracerebral pertussis infection and in their ability to produce specific agglutinin in mice and in children. A comparison between the field and laboratory results showed a substantial degree of correlation between the activity of vaccines in protecting children and their potency in protecting mice. There was also evidence of a correlation between protection in children and the production of agglutinin in both mice and children.

While this work was in progress, Pillemer, Blum, and Lepow (1954) reported the preparation of an antigenic fraction from *Bordetella pertussis*. The preparation involved the sonic disintegration of *B. pertussis* and the treatment of the extract with autoclaved human red cell stromata with the formation of a stromata-antigen complex which contained only a small fraction of the