J. Physiol. (1979), **288**, *pp.* 529–547
With 8 *text-figures*
Printed in Great Britain

THE CONTROL OF BLOOD FLOW THROUGH HUMAN FOREARM MUSCLES FOLLOWING BRIEF ISOMETRIC CONTRACTIONS

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(*Received 29 March 1978*)

SUMMARY

1. The blood flow through the forearm was measured 2 sec after single, brief isometric hand-grip contractions. The tension and duration of those contractions varied from 10 to 100% of the maximal voluntary contraction (m.v.c.) and from 2 to 12 sec, respectively.

2. The blood flow increased linearly with tension up to about 60% m.v.c. but further increases in tension, up to 100% m.v.c., did not elicit higher blood flows than were found at 60% m.v.c. The same relationship between tension and the resultant blood flow held for all durations of contractions, from 2 to 12 sec. The blood flow immediately after (2 sec) contractions at a given tension increased linearly with the duration of the contraction, from 2 to 12 sec. Maximal exercise blood flow was approached only in response to the longest contractions (12 sec) at tensions of 60% m.v.c. or higher.

3. Brief alterations (2–5 sec) of transmural pressure across blood vessels did not result in a significant change of blood flow, either in the resting forearm or when the vessels were dilated by brief, isometric contractions. When the tension was applied or released either rapidly or gradually ('ramp' contractions) there was no correlation between the rate of change of stretch on arterial vessels and the resultant blood flow. However, there was a direct relationship between a force–time integral (duration of contraction × peak tension) and blood flow. All these results make it clear that changes in blood flow in the forearm elicited by brief isometric contractions are not the result of a myogenic reflex but are metabolically induced.

4. Successive contractions exerted at 60% m.v.c. for 4 sec induced a blood flow of $21{\cdot}2 \pm 1{\cdot}6$ ml.min^{-1}.100 ml.$^{-1}$ when a rest interval of 8 sec was allowed between the contractions. Blood flows remained constant at this submaximal level, even when muscular fatigue was induced, and when there was an accompanying large increase in blood pressure.

5. Isometric muscular activity by the contralateral arm which resulted in fatigue, associated with a large increase in mean blood pressure, did not alter the level of vasodilatation that was induced by brief, isometric contractions in the 'test' arm.

6. It is suggested that the vasodilatation in response to intermittent isometric contractions is the result of metabolic vasodilatation of distal segments and continued sympathetic vasoconstriction of the proximal segments of the forearm vascular bed.

INTRODUCTION

There is no doubt that the circulation through skeletal muscle during exercise is increased by locally released metabolites or hormones (e.g. Gaskell, 1877; Kjellmer, 1965*a*; Skinner & Powell, 1967; Mellander, Johnson, Gray, Lund & Hjuing, 1967; Haddy & Scott, 1968; Forrester & Lind, 1969; Barcroft, Foley & McSwiney, 1971; Bockman, Berne & Rubio, 1975; Hilton, 1977) but it is still unclear precisely what influence is exerted by central or local neural mechanisms (Barcroft & Swan, 1953; Hilton, 1953; Donald, Rowlands & Ferguson, 1970) or by the myogenic reflex (Bayliss, 1902; Folkow, 1949; Sparks, 1964). Relatively prolonged changes in transmural pressure have produced variable alterations in blood flow (Patterson & Shepherd, 1954; Patterson, 1956; Holling & Verel, 1957; Blair, Glover & Roddie, 1959; Lind & McNicol, 1967) with the result that no definitive role has been assigned to the myogenic response of blood vessels in the human forearm. And recently, it has been suggested that a local neural reflex initiates the dilatation in response to muscular activity while metabolites, because of diffusion limitations, act to sustain the increased blood flow (Honig & Frierson, 1976).

The measurement of exercise hyperaemia is complicated by conflicting hemodynamic events during muscular contraction. For example, during fatiguing isometric contractions at tensions of 20–50% m.v.c., the local blood flow is thought to be augmented by a rise in mean arterial pressure (Humphreys & Lind, 1963; Lind & McNicol, 1967) or during heavy rhythmic exercise, by an increase of 'effective perfusion pressure' (Folkow, Gaskell & Waaler, 1970; Folkow, Hagland, Jodal & Lundgren, 1971). However, this hyperaemia is opposed by a compression of local vessels by the contracting skeletal muscles (Gaskell, 1877; Barcroft & Dornhorst, 1949; Humphreys & Lind, 1963).

In the present investigation, the forearm blood flow was measured shortly after the release of brief isometric contractions to try to avoid these difficulties. Three benefits accrued from using this procedure. First, there was no compression of the blood vessels by the skeletal muscles when blood flows were measured. Secondly, because the blood flow was measured 2 sec after release of the isometric tension, it was reasonable to assume that the changes in blood flow reflected the dilatation of the local vessels in response to the contraction (Corcondilas, Koroxenidis and Shepherd, 1964). And thirdly, because of the brevity of the isometric contractions it seemed unlikely that there would be much, if any, increase in arterial blood pressure. The changes in blood flow were measured in response to isometric contractions rather than to rhythmic exercise because the tension exerted can be accurately assessed as a proportion of the maximal voluntary contraction (m.v.c.). The changes in forearm blood flow to very brief isometric contractions, of 0·3 sec duration, at tensions which we estimate to be up to about 50% m.v.c. (see Discussion), were reported by Corcondilas *et al.* (1964) who found a direct relationship between tension and the resultant blood flow. In the present investigation we varied the duration of the contractions from 2 to 12 sec at tensions from 10 to 100% m.v.c.

Those experiments were intended to test the hypothesis that the vasodilatation induced by brief isometric contractions could be accounted for by the influence of locally released metabolites or hormones. If metabolites were the sole determinant of

exercise hyperaemia, then for any given duration of contraction there ought to be a direct relationship between the tension exerted and the resultant dilatation. Also, for any given tension exerted, an increase in the duration of the contraction ought to produce a direct increase in the blood flow, at least until the vessels become fully dilated. The results of our initial experiments supported this hypothesis only in part and therefore further experiments were designed to examine the influence of the myogenic properties of vascular smooth muscle in response to brief isometric exercise and to assess the potential effects of neural, sympathetic control.

Some aspects of these experiments have been reported briefly (Lind & Williams, 1977).

METHODS

Subjects. A total of eleven subjects (nine male and two female) took part in these experiments. Of these, seven were well trained to perform isometric hand-grip contractions, while four were not trained and participated in only the first experiment. The methods and procedures to be used were explained in detail to all the subjects and each one signed a statement of informed consent before taking part in the experiment.

Training. The seven subjects who were trained in forearm isometric exercise performed, each day, three brief (< 3 sec) maximal voluntary contractions at 3-min intervals on a hand-grip dynamometer (Clarke, Hellon & Lind, 1958). These were followed by five consecutive, sustained contractions at 40 % m.v.c. with a 3-min rest interval between each. The training procedure was followed daily for the first week and, in succeeding weeks, every other day until the endurance times on three successive training days were within $\pm 5\%$. The training period took between 3 and 6 weeks for different subjects.

Measurements. The blood flow through the forearm was measured by strain-gauge plethysmography (Whitney, 1953) with the venous collection cuff inflated automatically for 6 sec every 12 sec to a pressure of 50–55 mmHg (five measurements of blood flow.min^{-1}). During some of these experiments a wrist-cuff was inflated to arrest the circulation to the hand. In other experiments, no wrist-cuff was used. Arrest of the circulation to the hand usually reduced the blood flow through the resting forearm, as others have found (e.g. Kerslake, 1949), but did not affect the blood flow through the forearm following either single or repeated brief, isometric contractions (C. A. Williams & A. R. Lind, unpublished results). The resting forearm blood flow was measured for 2 min and thereafter as the experiment required.

In all the experiments reported here, the forearm blood flow was measured 2 sec after the isometric tension was released, whether it was a single brief contraction or one of a series of contractions. In pilot experiments, the blood flow was measured at intervals varying from 0·1 to 6 sec after the release of the tension; it was found that the pattern of vasodilatation following contractions at varying tensions was not affected by these intervals between the release of the contraction and the inflation of the venous collection cuff. An interval of 2 sec was chosen because shorter periods sometimes resulted in unreadable inflow curves due to movement artifacts. Therefore, the blood flows reported here refer only to the *first* flow in the post-contraction period. However, it is our contention that because the interval from the end of the contraction to the measurement of the blood flow is so short, the measurement represents the vasodilator effect of the muscular contraction without the complicating factors of compression or shearing forces on arterial vessels or of an increase in perfusion pressure. As can be seen in the Results section this contention is not always true because in some experiments the mean arterial pressure increased. But we have no reason to suppose that the other features of our assumption were affected in any of the experiments. The results of the various experiments are commonly expressed as the average blood flow and average mean blood pressure $\pm$ S.D. where that is appropriate. When calculation of the standard deviation was inappropriate, the range from the mean is given.

Procedures. The subjects were seated and the arm was either exposed to the ambient environment (22–24 °C) or immersed in water at 18 °C for 20 min before the experiment began, in order to minimize the skin blood flow (Barcroft & Edholm, 1945). In the latter circumstances, the deep muscle temperature is about 28 °C (Barcroft & Edholm, 1945; Lind, 1959).

At the start of each experiment, the subject exerted three consecutive maximum efforts (each < 3 sec) with a 3-min interval between them; the highest tension recorded was regarded as the m.v.c. The maximum efforts did not vary by more than ± 1 % for the trained subjects, but there was a greater variability (± 3 %) for the untrained subjects.

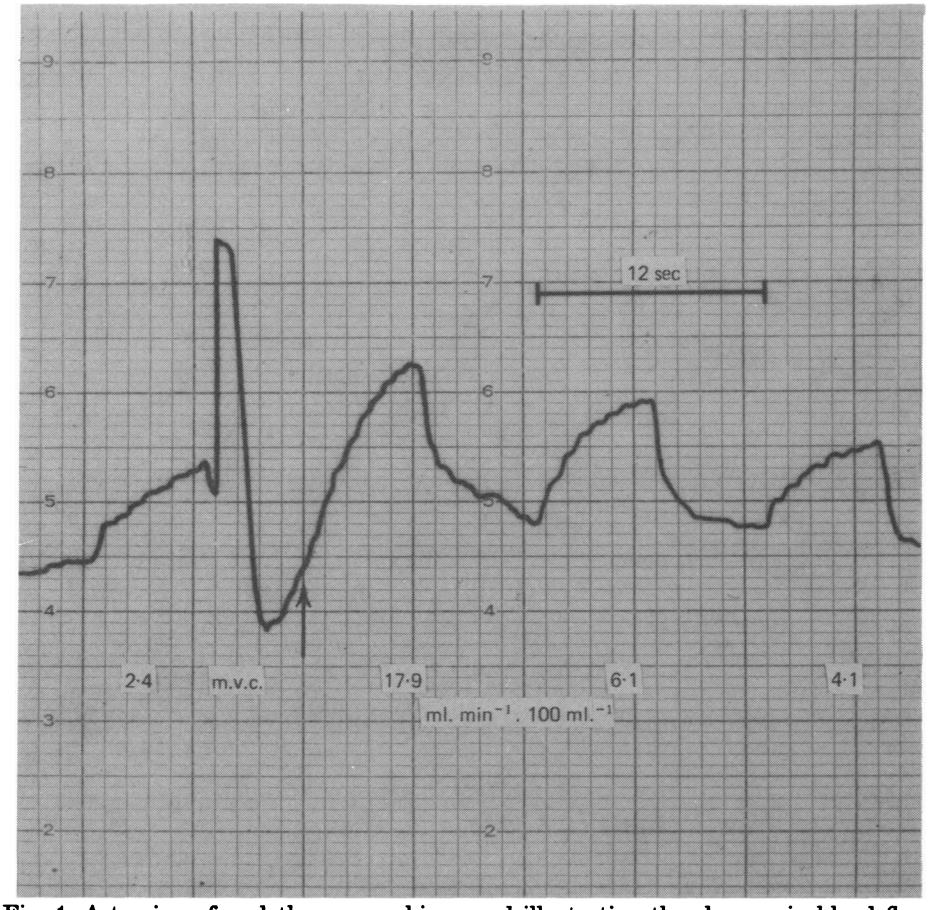

Fig. 1. A tracing of a plethysmographic record illustrating the changes in blood flow following one isometric contraction exerted at 100 % m.v.c. for 2 sec. The room temperature was 22 °C. Blood flow, in ml. min^{-1}. 100 $ml.^{-1}$, was measured 2 sec after the release of tension (at ↑); values are indicated below each inflow curve.

Experimental

Series 1. To test our working hypothesis, the forearm blood flow was measured in seven trained and four untrained subjects before and immediately (2 sec) after they exerted single, brief isometric contractions at tensions varying from 10 to 100 % m.v.c. An example of this kind of experiment is shown in Fig. 1. The last flow recorded from the resting period is shown on the left of the diagram followed by the movement artifact produced when the contraction was exerted. Thereafter, the record shows three blood flows measured after the contraction. The values for the blood flows in ml. min^{-1}. 100 $ml.^{-1}$ are associated with each inflow curve; only the first of these flows was taken as a reflexion of the vasodilatation induced by the exercise. It took no more than 0·3 sec to achieve the required tension for any of the contractions, which were held for 2, 4, 6 or 12 sec. In this and all other experiments, except where otherwise stated, the tension was developed and released as quickly as possible. At 100 % m.v.c., the tension can only be held briefly before falling rapidly; as a result, when the duration of the contraction was 4 sec or longer, the highest tension examined was 80 % m.v.c.

Series 2. The intention of the second series of experiments was also to test our working hypothesis. Here we measured blood flow immediately (2 sec) following each of a series of brief isometric contractions which were continued for periods up to 30 min or until muscular fatigue intervened. It was assumed that with successive contractions the blood flow following each contraction would progressively increase. Fig. 2 shows the blood flows recorded 2 sec after several of a series of contractions exerted at 60% m.v.c. for 2 sec. Four trained subjects were examined.

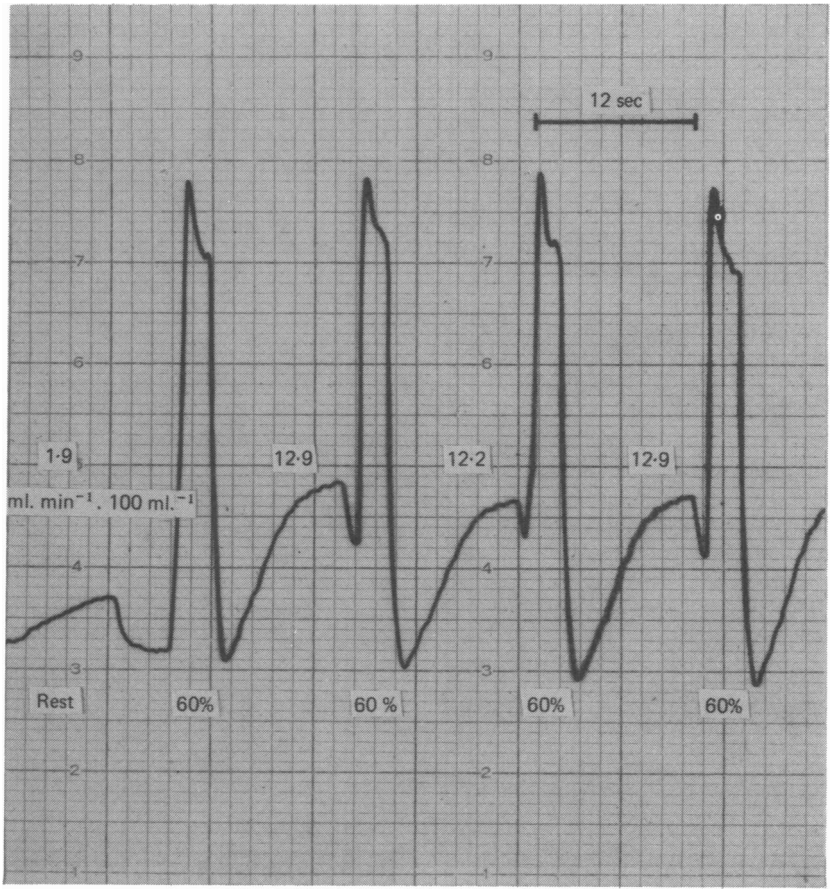

Fig. 2. A tracing of a plethysmographic record showing the blood flow in response to successive intermittent contractions exerted at 60% m.v.c. for 2 sec. The forearm was immersed in water at 18 °C for 20 min before the start of the experiment to minimize the blood flow to the skin, and remained in the water throughout the experiment. The values for blood flow in ml.min^{-1}.100 ml.$^{-1}$ are indicated above each inflow curve.

Blood pressure was measured by auscultation. Fatigue was defined as the time when the subject could no longer exert the tension required or, in the case of the longer (up to 12 sec) contractions, when the tension could be developed at first but could not be maintained for the required duration. The durations of the successive periods of contraction and relaxation were usually 2 : 10 or 4 : 8 sec, respectively, with variations in some experiments as described below (see Fig. 8).

The results of the experiments in series 1 and 2 could not be explained solely on the basis of a metabolically induced vasodilatation. Therefore, experiments were designed to examine other possible reasons for the patterns of vasodilatation following both single and repeated brief isometric contractions at different tensions. These are described, as follows.

Series 3. The term 'tachyphylaxis' originally denoted the loss of sensitivity of a tissue to a drug. Khayutin (1968) imaginatively applied the term to a change of sensitivity of vascular

smooth muscle in response to repeated stretching. To test the possibility that 'tachyphylaxis' might be responsible for the constancy of the vasodilation measured between repeated brief isometric contractions, experiments were performed on four trained subjects. Each subject exerted fifty consecutive contractions, the first and last ten of which were of 2 sec duration at 20% m.v.c. with 10 sec intervals between each while the intervening thirty contractions were of 4 sec duration at 60% m.v.c. with 8 sec intervals. The duration and tension of the intervening thirty contractions were chosen from the results of earlier experiments with the intention of maximizing the possible 'tachyphylaxis' suggested by Khayutin (1968) as an auto-regulatory process. The forearm blood flow was measured (as before) 2 sec after each of the fifty contractions.

Series 4. It was logical to consider the possibility that the myogenic properties of vascular smooth muscle may have been partly responsible for the patterns of vasodilatation that emerged from the results of the experiments in series 1 and series 2. The blood flow through the forearm of four trained subjects was measured 2 sec after changing the transmural pressure of the blood vessels. This was done by either (1) intermittent digital compression (for 2 sec every 12 sec) of the brachial artery to reduce the transmural pressure, or (2) by inflation (for 2–5 sec) of pneumatic cuffs placed on either side of the Whitney plethysmograph on the forearm, to increase the transmural pressure; the borders of the cuffs were 5–10 mm distant from the strain-gauge. In addition, to test the concept put forward by Sparks (1964) that the myogenic reflex depends, to a large extent, on the rate of stretch or distortion applied to the vascular wall, three trained subjects exerted isometric contractions when the peak target tension varied from 10 to 80% m.v.c. These tensions were developed in the following ways: (1) quickly applied and quickly released ('square wave'), (2) gradually and regularly increased to the target tension before being quickly released ('ramp-up'), or (3) rapidly developed and gradually and steadily released ('ramp-down'). The total duration of muscular activity in all these experiments was 4 sec.

Series 5. In the final series of experiments, conducted on two trained subjects, we examined the possible influence of a generalized sympathetic vasoconstriction of vessels serving active muscles. Two kinds of experiments were performed. First, the blood flow following each of the repeated isometric contractions held for 2 sec at 20% m.v.c. was measured in the 'test' forearm when the contralateral arm performed simultaneous 2 sec contractions at 80% m.v.c. to fatigue. Secondly, the blood flow was measured in the 'test' forearm following each of a series of brief contractions (20% m.v.c., 2 sec) when the contralateral arm developed and sustained to fatigue a tension of 60% m.v.c. Both procedures resulted in an associated increase in arterial blood pressure.

RESULTS

The levels of post-contraction blood flow in response to brief isometric contractions at different tensions

Series 1. As shown in Fig. 1, above, when a single contraction was exerted for only 2 sec, the forearm blood flow measured 2 sec after the end of the contraction increased above the resting level, and returned gradually to the resting level over a period of as long as 2 min, depending on the tension exerted.

The blood flow immediately (2 sec) following a single isometric contraction held for 2 sec when the tension varied from 5 to 100% m.v.c. is shown in Fig. 3. Each point represents the average flow (± S.D.) recorded 2 sec after the end of each contraction from a total of eleven subjects (seven trained and four untrained). There was a direct linear relationship between the degree of vasodilatation and the tension up to about 60% m.v.c. However, at tensions above 60% m.v.c., no further vasodilatation was found. When the duration of the contraction was extended from 2 sec to 4, 6, and 12 sec, the blood flows recorded immediately following the contractions showed the same pattern for four trained subjects, also reaching a peak at about 60% m.v.c. The results for one subject are shown in Fig. 4*A*; the responses from the other three subjects were similar, with variations only in the absolute values but not in the pattern. After a contraction at any given tension, the blood flow increased with the

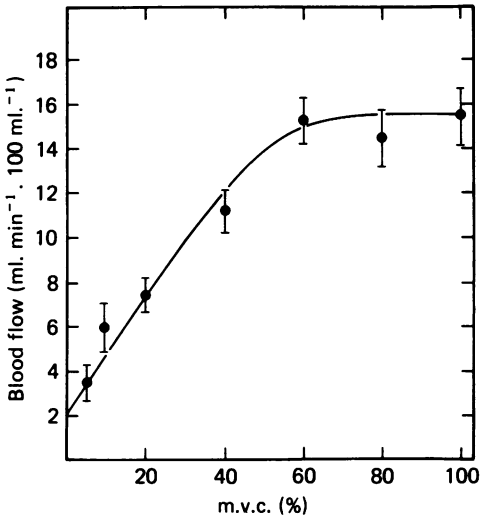

Fig. 3. The change in the blood flows measured in response to single contractions exerted for 2 sec. The ambient temperature was 23–25 °C. Each point represents the average flow in ml.min^{-1}. 100 ml.$^{-1}$ measured from eleven subjects (seven trained and four untrained). The bars represent the S.D. of the results.

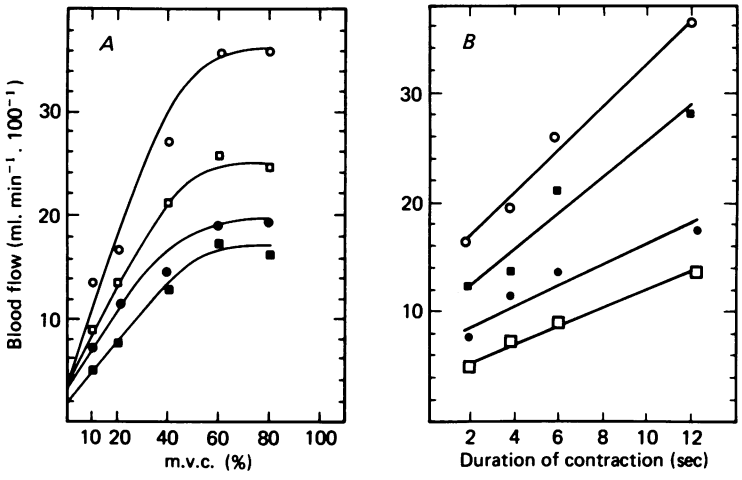

Fig. 4. *A*, the average blood flows recorded from one of the trained subjects in response to single contractions exerted for 2 (■), 4 (●), 6 (□), and 12 (○) sec. All flows were measured 2 sec following the release of tension. The results for three other subjects showed the same pattern of response. *B*, the change in blood flow in response to single isometric contractions of 10 (□), 20 (●), 40 (■), and 60% (○) m.v.c. exerted for various periods of time. Absolute levels of flow were taken from data represented in Fig. 4*A*.

duration of the contraction (Fig. 4*B*). Only the longest (12 sec) contractions at tensions of 60% m.v.c. and above induced a blood flow that approached maximal levels. A linear relationship was revealed between the duration of each contraction from 2 to 12 sec and the degree of vasodilatation at any one tension, as illustrated in Fig. 4*B*.

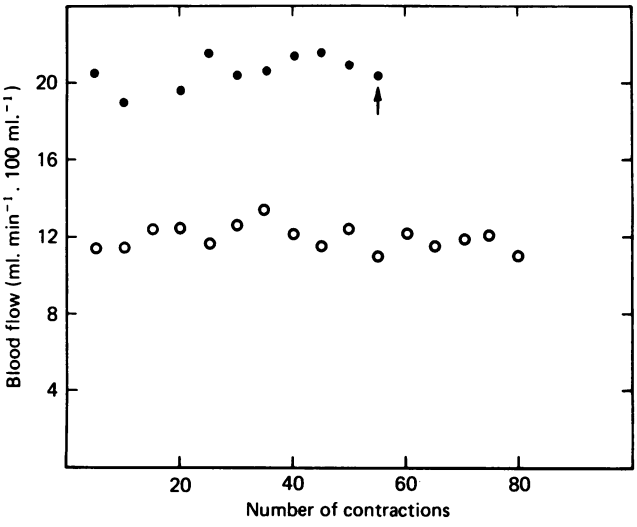

Fig. 5. The blood flow (ml.min^{-1}.100 ml.$^{-1}$) measured immediately (2 sec) following a series of contractions at 60% m.v.c. held for either 2 sec (○) or 4 sec (●). The blood flows are from one subject and are representative of the responses shown by all other subjects. Each point represents the average of five flows following the preceding five contractions. The total number of contractions exerted in a series is indicated on the abscissa. Contractions exerted for 2 sec were not fatiguing. Fatigue occurred after fifty-eight contractions were exerted at 60% m.v.c. for 4 sec (at ↑).

Series 2. Because there was an unexpected relationship between vasodilatation and the tension of single, brief contractions, blood flow was measured 2 sec after each of a series of brief contractions exerted for the same duration and at the same tension (see Fig. 2). For these experiments the arm was immersed in water at 18 °C to minimize the blood flow through the skin. The blood flow remained at an unchanged level immediately following each of the contractions and was dependent on the tension exerted and the duration of each contraction. A typical response from one of the subjects is shown in Fig. 5. The average of the post-contraction blood flows for four trained subjects was $11{\cdot}6 \pm 1{\cdot}5$ ml.min^{-1}.100 ml.$^{-1}$ following successive 2-sec contractions at 60% m.v.c. That level of vasodilatation remained steady for each subject throughout each experiment which, in some cases, lasted as long as 30 min. This exercise, where the duration of the contractions at 60% m.v.c. was 2 sec, with 10 sec intervals of rest, was not fatiguing for any subject, and no increase in blood pressure occurred. When the duration of each contraction at 60% m.v.c. was increased to 4 sec with intervening rest intervals of 8 sec, the average blood flow increased to $21{\cdot}2 \pm 1{\cdot}6$ ml.min^{-1}.100 ml.$^{-1}$ for the four subjects (Fig. 5), and again remained constant even though these intermittent contractions resulted in muscular fatigue for all the subjects. In these conditions, the blood pressure of all the subjects

increased markedly as is described below (see Fig. 8). It is worth emphasizing that in these experiments fatigue occurred without inducing maximal vasodilatation.

Evidence concerning 'tachyphylaxis' (series 3). Experiments were performed to establish whether 'tachyphylaxis' (Khayutin, 1968) of vascular smooth muscle contributed to the constant levels of blood flow found between serial intermittent contractions as shown in Figs. 2 and 5. Forearm blood flows following repeated contractions at a low tension, 20% m.v.c., were compared before and after performing successive contractions at a high tension, 60% m.v.c. Each of the contractions at 20% m.v.c. was held for 2 sec while those at 60% m.v.c. were held for 4 sec. This procedure was followed in an attempt to maximize the possible influence of 'tachyphylaxis'. In experiments reported here, the blood flow to the forearm muscles was found to be occluded during the contractions at tensions of 60% m.v.c. and above, similar to the earlier findings of Humphreys & Lind (1963). Therefore, during these contractions at 60% m.v.c. the vascular smooth muscle of resistance vessels was exposed to repeated brief periods of very high intramuscular pressures which must impose a large degree of stretch or distortion to the local blood vessels. The average forearm blood flow of four trained subjects in response to each of the first ten successive contractions, at 20% m.v.c., was $13{\cdot}4 \pm 2{\cdot}3$ ml.min^{-1}.100 ml^{-1}. The blood flow abruptly increased to an average of $22{\cdot}2 \pm 3{\cdot}1$ ml.min^{-1}.100 ml^{-1}. measured between each of the thirty contractions at 60% m.v.c. When the tension of the repeated contractions was returned to 20% m.v.c., the blood flow between the contractions declined rapidly, averaging $15{\cdot}0 \pm 0{\cdot}87$ ml.min^{-1}.100 ml.$^{-1}$ for the first minute of the successive contractions at the low tension and $14{\cdot}1 \pm 0{\cdot}87$ ml. min^{-1}.100 ml.$^{-1}$ for the last minute, values that were not different from those following the first ten contractions of the experiment ($P > 0{\cdot}05$).

Evidence concerning the influence of a myogenic response

The mechanical interference of tissue and blood pressures on blood flow (series 4). To examine the possibility that the changes in blood flow following brief isometric contractions, particularly at tensions of 60% m.v.c. or higher, were due to the myogenic properties of vascular smooth muscle, several experiments were carried out.

As mentioned above, the blood flow to the forearm muscles was found to be occluded at a tension of about 60% m.v.c.; thus local vessels must have experienced, in an intermittent fashion, a brief but marked decrease in transmural pressure. Therefore, digital compression of the brachial artery was applied repeatedly, each time for 2 sec, with 10-sec intervals between each compression. The blood flows through the resting forearm were recorded 2 sec after each compression of the artery. The average blood flow for four trained subjects was $3{\cdot}7 \pm 1{\cdot}7$ ml.min^{-1}.100 ml.$^{-1}$ before compression of the artery and was not significantly altered, averaging $4{\cdot}4 \pm 1{\cdot}7$ ml.min^{-1}.100 ml.$^{-1}$ ($P > 0{\cdot}3$) after the arterial compressions. To determine whether or not the post-contraction blood flow induced by intermittent isometric contractions at a low tension could be altered by deliberately superimposing changes in transmural pressure, the following experiment was conducted.

The blood flow was measured in four trained subjects after each of a series of

twenty 2-sec contractions at 20% m.v.c. There was no artificial interference of the artery for the first ten contractions and blood flow averaged $8{\cdot}9 \pm 1{\cdot}1$ ml.min^{-1}. 100 ml^{-1}. As the series of contractions continued, the brachial artery was digitally compressed for 2 sec, simultaneously with the contractions; the subsequent blood flows remained unchanged, averaging $9{\cdot}8 \pm 1{\cdot}2$ ml.min^{-1}.100 ml^{-1}.

Pneumatic cuffs were placed distally and proximally to the Whitney strain-gauge and were simultaneously inflated for 2–5 sec to various pressures in random order. Resting forearm flows from two trained subjects averaged $3{\cdot}7 \pm 0{\cdot}67$ ml.min^{-1}. 100 ml^{-1}. Two seconds following deflation of the pneumatic cuffs from pressures of 40, 70, 80, 110, 160 and 200 mmHg, the average flows were 3·6, 3·5, 4·6, 4·0 and 3·8 ml.min^{-1}.100 ml.$^{-1}$, respectively. A 2-min resting period was allowed between each of the inflations of the pneumatic cuffs; during this period there was no increase in blood flow above the flow measured 2 sec after the rapid deflation of the cuffs.

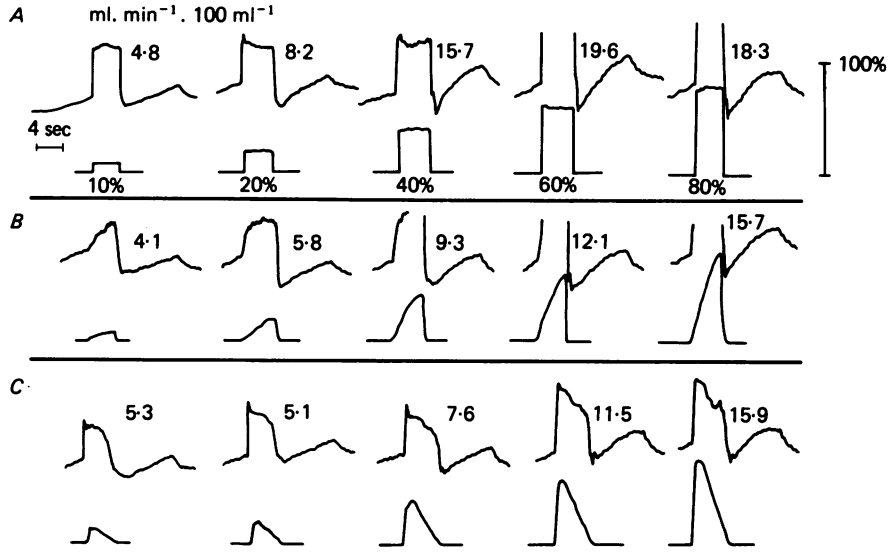

Fig. 6. A tracing is shown of records from one trained subject of blood flow and tension exerted in one experiment. The upper tracing in each panel shows the plethysmographic records with the artifacts due to the contractions, followed by the blood flows in response to isometric contractions (4 sec) applied in a 'square-wave' (panel *A*), 'ramp-up' (panel *B*), or 'ramp-down' (panel *C*) manner. The lower tracing in each panel illustrates the way in which tension was developed. The height of each signal represents the peak tension achieved, which ranged from 10 to 80% m.v.c. Vertical bar to the right indicates 100% m.v.c. The values for blood flow are given in ml.min^{-1}. 100 ml.$^{-1}$ above each inflow curve. The ambient temperature was 24 °C.

The change in blood flow induced by 'ramp' contractions. The blood flow was measured immediately after contractions where the tension was applied or released quickly or gradually (see Methods), to test the hypothesis (Sparks, 1964) that the myogenic response of vascular smooth muscle is due in large measure to the rapidity of stretch or distortion applied to the vessels concerned. Fig. 6 represents the results of such an experiment on one subject. In each panel of Fig. 6, the lower tracing shows the way in which tension was developed by the forearm muscles and the upper

tracing shows the blood flow measured 2 sec after release of the tension. The three types of contractions shown in Fig. 6 are examples of the target tension being achieved in a 'square-wave' (panel *A*), 'ramp-up' (panel *B*), and 'ramp-down' (panel *C*) manner. The peak tension in each of those experimental conditions ranged from 10 to 80% m.v.c. The values for forearm blood flow, in ml.min^{-1}.100 ml.$^{-1}$, following each of those contractions are associated with the tracings of the plethysmographic records. After each contraction, the forearm blood flow was allowed to return to resting, control levels before the next contraction occurred. In the experiment illustrated in Fig. 6, the resting forearm blood flow averaged 3·5 ml.min^{-1}.100 ml^{-1}.

Panel *A*, in Fig. 6 shows the blood flows immediately following 'square-wave' isometric contractions at varying tensions; these results yielded a pattern which has been well established from earlier experiments (Fig. 3), where the blood flow increased linearly with tension to about 60% m.v.c., with no further increase in the blood flow following contractions at higher tensions.

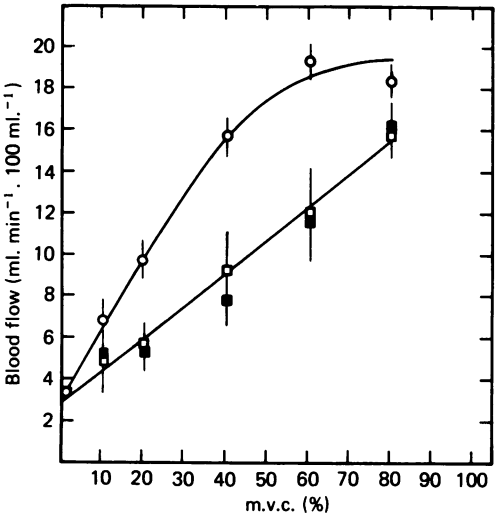

Fig. 7. The increase in blood flow given in ml.min^{-1}.100 ml.$^{-1}$, in response to 4 sec isometric contractions exerted in a 'square-wave' (○), 'ramp-up' (□), or 'ramp-down' (■) manner. The values in percentage m.v.c. on the abscissa refer to the peak tensions achieved. The data illustrated in this graph are the average results for two trained subjects performing the kind of experiment illustrated in Fig. 6. The range of values are indicated by the open vertical bars.

In panels *B* and *C* of Fig. 6, the blood flows following 'ramp-up' and 'ramp-down' contractions are illustrated. The blood flows following either kind of 'ramp' contraction were similar to each other in dimension and were always substantially lower than those found for 'square-wave' contractions when the peak tension was identical.

The results from the three trained subjects who performed this experiment are shown graphically in Fig. 7 where the ordinate represents the blood flow measured immediately following the contractions while the abscissa represents the peak tension developed in the different kinds of contraction. The blood flows following the 'square-wave' contractions are represented by the open circles and the vertical bars represent the range of the values. The pattern of response and the average values for

these blood flows were similar to those shown in Fig. 3. But the blood flows following each kind of 'ramp' contraction where the peak tension was the same as for the 'square-wave' contractions were much lower and showed a linear relationship with the peak tension exerted. Examination of the results in Fig. 7 shows that for any given peak tension the blood flows following the 'ramp' contractions were about the same as for 'square-wave' tensions of half that peak tension. For example, the average blood flow elicited by the 'ramp' contractions with a peak tension of 80% m.v.c. ranged from 14·8 to 16·8 ml.min^{-1}.100 ml.$^{-1}$ while the range of the values for a 'square-wave' tension at 40% m.v.c. was 15·0–16·5 ml.min^{-1}.100 ml^{-1}.

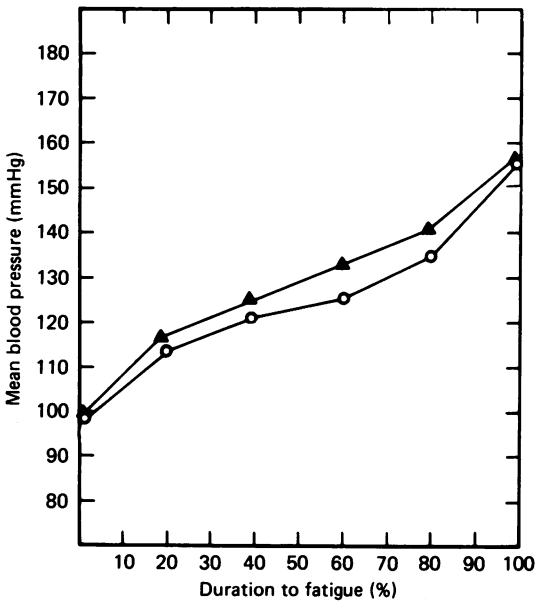

Fig. 8. The change in mean arterial blood pressure in response to successive intermittent contractions exerted at 40% m.v.c. (○) and 60% m.v.c. (▲). The duration of the successive periods of contraction and relaxation were 12 : 12 sec (○); and 4 : 8 sec (▲). Mean pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Each point represents the average of three experiments on two trained subjects. The total time taken to develop fatigue was normalized.

The change in forearm blood flow during simultaneous isometric contractions of different limbs

Series 5. There was no detectable change in the arterial blood pressure of the subjects while they performed intermittent isometric contractions that did not develop muscular fatigue. In contrast, there was a marked rise in the mean arterial pressure when the intermittent isometric contractions resulted in fatigue, irrespective of the tension exerted and the durations of the periods of contraction and relaxation. Fig. 8 shows the changes in mean blood pressure accompanying fatigue developed by intermittent contractions at 40 and 60% m.v.c. The mean blood pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Since there was a large variation among the four subjects in the number of contractions exerted

and therefore in the length of time taken to reach fatigue, the total time taken to develop fatigue was normalized. The mean blood pressure increased from $99 \pm 2{\cdot}8$ to $155 \pm 4{\cdot}5$ mmHg independently of both the tension exerted and the absolute time taken to reach fatigue. The mean blood pressure at the point of fatigue in these experiments corresponds closely to that found in response to sustained contractions as has been reported previously by Lind, Taylor, Humphreys, Kennelly & Donald (1964); Funderburk, Hipskind, Welton & Lind (1974) and Petrofsky and Lind (1975). Despite the increase in mean arterial pressure the blood flows measured following each of the intermittent isometric contractions remained constant (see Fig. 5 for example).

Because of this marked increase in blood pressure, it was important to determine what influence the sympathetic constrictor output may have had on the blood flow immediately (2 sec) following serial isometric contractions. Accordingly, blood flow was measured in three trained subjects between successive contractions, which were not fatiguing, exerted at 20% m.v.c. for 2 sec, while a sustained contraction at 60% m.v.c. was held to fatigue by the contralateral arm. Before the sustained contraction of the contralateral arm was exerted, forearm blood flows in the 'test' arm were measured between intermittent isometric contractions and averaged $8{\cdot}5 \pm 1{\cdot}0$ ml.min^{-1}.100 ml^{-1}. When those contractions were continued in the presence of a sustained contraction at 60% m.v.c. exerted by the contralateral arm, mean arterial blood pressure increased to 152 mmHg, while the blood flows averaged $8{\cdot}6 \pm 1{\cdot}7$ ml.min^{-1}.100 ml^{-1}. Furthermore, when intermittent contractions at 80% m.v.c. were exerted simultaneously for 2 sec by the contralateral arm, the blood flow in the 'test' forearm measured between the repeated contractions at 20% m.v.c. averaged $7{\cdot}8 \pm 1{\cdot}4$ ml.min^{-1}.100 ml.$^{-1}$, despite the increase of mean blood pressure to 154 mmHg.

DISCUSSION

One of the most striking findings from this investigation is the pattern of the blood flow immediately following single, brief contractions as the tension increased (Fig. 3), a pattern which held good for contractions where the duration varied from 2 to 12 sec. In all cases, for a given duration of contraction, the peak level of vasodilatation had already been achieved in response to a tension of 60% m.v.c. and did not increase further at higher tensions. Another striking feature of the results was the constant level of blood flow found between repeated, brief isometric contractions of the same duration and tension (see Fig. 2), even when those contractions ultimately led to fatigue with a concomitant large rise in mean blood pressure. Clearly in this type of exercise, muscular fatigue can occur without causing maximal dilatation. If it is accepted that the blood flow measured immediately (2 sec) following a contraction reflects the vasodilator effect of the preceding activity, then the bulk of the evidence of the present investigation leads us to believe that even following contractions of brief duration there is a balance of neural and metabolic mechanisms which control local blood flow while very little influence is exerted by myogenic reflexes.

Influence of the myogenic response. During an isometric hand-grip contraction at 60% m.v.c. or more we have confirmed earlier findings (Humphreys & Lind, 1963) that local arterial vessels are compressed or 'nipped', occluding the inflow to the

muscles of the forearm. Consequently, it was reasonable to investigate the possibility that the plateau phase of the results shown in Fig. 3 and the steady-state flow found between repeated brief contractions (see Fig. 5) may be the result of a myogenic reflex. Bayliss (1902) showed that when the circulation to the lower limb of an anaesthetized cat was restored after only 8 sec of occlusion of the abdominal aorta, there was a large increase in the volume of the limb, of several minutes duration and with the greatest increase in volume some 30 sec following restoration of the circulation. This response is not seen in the human forearm. Following digital compression of the brachial artery for 5–6 min in man, Blair *et al.* (1959) found no increase in forearm blood flow, while Holling & Verel (1957) and Lind & McNicol (1967) found a small, transient increase, complete in about 30 sec, which they attributed to reactive hyperaemia. It has also been shown that very high increases of transmural pressures are required before significant vasoconstriction in the human forearm is seen (e.g. Patterson & Shepherd, 1954; Patterson, 1956) and then it occurs only transiently.

In our experiments, there was no evidence of a myogenic reflex elicited by brief, intermittent changes in transmural pressure. There was never a delayed onset of dilatation following contractions at 60% m.v.c. nor was there any change in blood flow following artifically induced alterations in transmural pressure. Other studies also suggest that the myogenic response is not a predominant determinant of blood flow following brief occlusions. Kontos, Mauck & Patterson (1965) found that the reactive hyperaemia (attributed to a myogenic response) following a 5 sec occlusion of the femoral artery of dogs lasted for 10 sec and was abolished by venous congestion. Baez (1968) found an autoregulatory response in only about a third of isolated, artifically perfused, arteriolar preparations, and Lombard & Duling (1977) have also shown a transient myogenic response of arterioles lasting less than 10 sec in response to occlusions of 3–6 sec.

Sparks (1964) described the effect of a quick stretch on isolated human umbilical artery and found that the active tension developed was directly related to both the rate and the increment of stretch. During isometric contractions in the human forearm where the muscles shorten somewhat while the tendons are stretched, it is obvious that the arterial vessels to those muscles must be subjected to both transverse and shearing forces, providing a stretch to those vessels. Thereby, by Spark's hypothesis, very different flows would be expected in the forearm in response to 'square-wave', 'ramp-up' and 'ramp-down' contractions at a variety of tensions. For the same total duration of contraction (4 sec) the highest flows were always recorded following the 'square-wave' contractions, while the results from the 'ramp' contractions were substantially lower and indistinguishable from each other. All the evidence from the experiments discussed above make it clear that the blood flows following brief isometric contractions are little, if at all, affected by the myogenic reflex in man.

'Tachyphylaxis' (Khayutin, 1968) was another possible reason for the failure of blood flow to increase as a series of repeated contractions proceeded. But if the sensitivity of the arteriolar smooth muscle were to be altered either by mechanical (i.e. repeated stretching), or by metabolic or humoral influences in the course of repetitive contractions then the flow induced by contractions at 20% m.v.c. would have been greater following a series of contractions at 60% m.v.c. They were not.

Sympathetic vasoconstriction during intermittent isometric contractions. In our experiments a series of intermittent contractions which resulted in fatigue induced a marked increase in mean systemic arterial pressure. Intermittent contractions that were not fatiguing did not. Yet in both conditions the blood flow remained at a specific level which was dependent on the tension exerted and the duration of the contractions. In those experiments where fatigue occurred, and in the absence of any other influence, the blood flow ought to have increased in direct proportion to the rise in blood pressure. Similarly, the blood flow of the 'test' arm should have increased, but did not, between serial 2-sec contractions at 20% m.v.c. (which did not result in fatigue) while the contralateral arm held a sustained contraction at 60% m.v.c. to fatigue with an accompanying increase in mean arterial pressure. Clearly, there must have been a vasoconstriction of the vessels serving the active muscles of the 'test' arm. The only obvious candidates for the mechanism of control are the myogenic response or sympathetic vasoconstriction. While it is not possible from our evidence categorically to exclude the myogenic response as a contributor to that vasoconstriction, the results from all the previous experiments discussed above strongly suggest that this is unlikely. It seems more probable that the maintenance of the blood flow at steady levels in these experimental conditions is due to sympathetic constriction of the peripheral blood vessels.

Corcondilas *et al.* (1964) noted that the changes in blood flow following brief contractions of 0·3 sec duration were similar for both normal and sympathectomized subjects. But none of their experiments were continued to the point of fatigue, with associated increases in blood pressure, nor was the tension high enough to elicit evidence of the hyperbolic relationship between tension and the resultant vasodilatation that we have found. As intermittent isometric contractions proceed towards fatigue there may be an increasing influence on arteriolar vessels by the sympathetic nerves just as has been considered to occur during sustained isometric contractions (Lind *et al.* 1964). The concept that sympathetic constriction during exercise applies to both active and inactive muscles has been put forward by Barcroft (1968), while Donald *et al.* (1970) showed, in dogs, that the blood flow to rhythmically active hindlimb muscles is markedly reduced when the distal stumps of severed sympathetic nerves are stimulated. Previous studies have shown that distal segments of a vascular bed, including precapillary sphincters, rapidly adapt to constriction evoked by sympathetic stimulation due to the actions of locally released dilators (Folkow, Sonnenschein & Wright, 1968). More recently, it has been suggested that some vasodilator substances act by inhibiting adrenergic neurotransmisson in both veins and arteries during stimulation of the sympathetic nerves (Vanhoutte & Shepherd, 1973; Lorenz & Vanhoutte, 1975; McGrath & Shepherd, 1976; Verhaeghe, Vanhoutte & Shepherd, 1977). These considerations lead us to postulate from our results that during intermittent contractions which result in fatigue, the distal arterial segments (small arterioles and pre-capillary sphincters) of the vascular bed in the forearm are dilated the most by metabolites or humoral substances and by the time fatigue occurs, these vessels are wholly or almost wholly removed from any constrictor influence. But the more proximal vessels (i.e. larger arterioles and small arteries) in this bed may well remain under some constricter influence (Kjellmer, 1965*b*; Folkow *et al.* 1968; Donald *et al.* 1970), and are less likely to be affected to the same extent by local

dilator substances. Such evidence may help to explain why the blood flow did not reach maximal values despite the development of fatigue in response to intermittent isometric contractions. In addition, the failure to achieve maximal flow may be aided by the rapid removal of some dilators during the rest intervals. This would prevent an accumulation of these substances from one contraction to the next, the extent of their wash-out being dependent on both the amount and the time allowed for flow between contractions. This does not occur during a sustained contraction. There is an unremitting mechanical constriction of local vessels by the contracting muscle compelling the accumulation of flow-dependent metabolites which account for the maximal dilatation seen when the tension is released (e.g. Humphreys & Lind, 1963; Lind & McNicol, 1967).

Evidence concerning the metabolic control of blood vessels. The linear increase in blood flow (Fig. 3) following single brief contractions of the same duration as the tension increases to 60% m.v.c., can be explained on the basis that metabolites or local hormones released by the muscle induced the subsequent dilatation. Our results agree with those of Corcondilas *et al.* (1964) who also described a linear relationship between the increase in the immediate post-exercise flow and the strength of very brief isometric (0·3 sec in duration), forearm contractions; the tensions exerted by their subjects probably did not exceed 50% m.v.c., as judged by the m.v.c. of a large number of male subjects (Petrofsky & Lind, 1975). The results of our experiments involving 'ramp' contractions and 'square-wave' contractions provide strong evidence that a local metabolic or humoral mechanism (or both) is responsible for dilatation following single, brief contractions. The increase in the blood flow from the different types of 'ramp' contractions compared to those from the 'square-wave' contractions showed a direct relationship to the product of the tension and the duration of the contractions. For example, a 'ramp' contraction (4 sec) of either kind which achieved a maximum tension of 80% m.v.c. has the same product of duration and tension as has a 'square-wave' contraction at 40% m.v.c. If the flow depends on a metabolic or humoral mechanism, a 'ramp' contraction with a peak tension of 80% m.v.c. would be expected to produce much the same blood flow as that induced by a 'square-wave' contraction (4 sec) at 40% m.v.c. It did. A similar relationship existed at all other products of duration and tension. The implication is that in those circumstances the blood flow following such brief contractions is principally or entirely influenced by metabolites or local hormones released by the muscle. It is equally clear from the results (e.g. Fig. 3) that there is an upper limit to the direct influence of metabolic or humoral control, but our evidence does not indicate why that is so, or what other factors limit metabolic control; the matter is discussed briefly below with respect to the types of muscle fibre involved.

The evidence from all these experiments strongly supports the view that the myogenic response is not an important cause of the dilatation following brief isometric contractions. Instead, there is a clear relationship between metabolic events or the release of local hormones and the resultant blood flow. The results lead us to believe that the blood flow between successive, intermittent contractions is primarily influenced by local metabolic or humoral dilatation but that when the intermittent contractions result in fatigue, that dilatation is opposed by sympathetic vasoconstriction. We have no evidence to show whether or not the metabolites or hormones act

directly on the smooth muscle or on intrinsic neurons such as those described by Honig & Frierson (1976).

The relationship between the blood flow elicited by brief isometric contractions at different tensions remains intriguing but unexplained. In this context it is worth recalling that Folkow & Halicka (1968) demonstrated in the cat a similar pattern of response when the blood flow through the gastrocnemius muscle was measured during brief interruptions of a continued indirect stimulation at various frequencies. The gastrocnemius muscle has a mixed population of fibre types similar to that found in human forearm muscles. In contrast, in the cat's soleus muscle which is wholly comprised of slow-twitch fibres there was a linear relationship between tension (up to the maximal tetanic tension) and the related blood flow. It may be that the results we have described here reflect the different blood flow responses to motor units with slow and fast-twitch properties.

This work was supported by N.I.H. training grant HL07050-03, Air Force grant AFOSR-76-3084B and H.E.W. contract 210-77-0044.

We wish to express our gratitude to Professor H. Barcroft, Drs L. C. Senay and T. Forrester for their comments after reading this manuscript and to Dr J. Shepherd for his comments and suggestions.

REFERENCES

BAEZ, S. (1968). Bayliss response in the microcirculation. *Fedn Proc.* **27**, 1410–1415.

BARCROFT, H. (1968). Blood flow and metabolism in skeletal muscle. In *Circulation in Skeletal Muscle*, ed. HUDLICKA, O. Oxford: Pergamon.

BARCROFT, H. & DORNHORST, A. C. (1949). The blood flow through the human calf during rhythmic exercise. *J. Physiol.* **102**, 402–411.

BARCROFT, H. & EDHOLM, O. G. (1945). Temperature and blood flow in the human forearm. *J. Physiol.* **104**, 366–376.

BARCROFT, H., FOLEY, T. H. & MCSWINEY, R. R. (1971). Experiments on the liberation of phosphate from the muscles of the human forearm during vigorous exercise and on the action of sodium phosphate on forearm muscle blood vessels. *J. Physiol.* **213**, 411–420.

BARCROFT, H. & MILLEN, J. L. E. (1939). The blood flow through muscle during sustained contraction. *J. Physiol.* **97**, 17–31.

BARCROFT, H. & SWAN, H. J. C. (1953). *Sympathetic Control of Human Blood Vessels.* London: Edward Arnold & Co.

BAYLISS, W. M. (1902). On the local reactions of the arterial wall to changes of internal pressure. *J. Physiol.* **28**, 201–231.

BLAIR, D. A., GLOVER, W. E. & RODDIE, I. C. (1959). The abolition of reactive and post-exercise hyperaemia in the forearm by temporary restriction of arterial inflow. *J. Physiol.* **148**, 648–658.

BOCKMAN, E. L., BERNE, R. M. & RUBIO, R. (1975). Release of adenosine and lack of release of ATP from contracting skeletal muscle. *Pflügers Arch.* **355**, 229–241.

CLARKE, R. S. J., HELLON, R. F. & LIND, A. R. (1958). The duration of sustained contractions of the human forearm at different muscle temperatures. *J. Physiol.* **143**, 454–473.

CORCONDILAS, A., KOROXENIDIS, G. T. & SHEPHERD, J. T. (1964). Effect of a brief contraction of forearm muscles on forearm blood flow. *J. appl. Physiol.* **19**, 142–146.

DONALD, D. E., ROWLANDS, D. J. & FERGUSON, D. A. (1970). Similarity of blood flow in the normal and the sympathectomized dog hind limb during graded exercise. *Circulation Res.* **26**, 185–199.

FOLKOW, B. (1949). Intravascular pressure as a factor regulating the tone of the small blood vessels. *Acta. physiol. scand.* **17**, 289–310.

FOLKOW, B., GASKELL, P. & WAALER, B. A. (1970). Blood flow through limb muscles during heavy rhythmic exercise. *Acta. physiol. scand.* **80**, 61–72.

FOLKOW, B., HAGLAND, U., JODAL, M. & LUNDGREN, O. (1971). Blood flow in the calf muscle of man during heavy rhythmic exercise. *Acta. physiol. scand.* **81**, 157–163.

FOLKOW, B. & HALICKA, H. D. (1968). A comparison between 'red' and 'white' muscle with respect to blood supply, capillary surface area and oxygen uptake during rest and exercise. *Microvasc. Res.* **1**, 1–14.

FOLKOW, B., SONNENSCHEIN, R. R. & WRIGHT, D. L. (1968). Differential influences of nervous and local humoral factors on large and small precapillary vessels of skeletal muscle. In *Circulation in Skeletal Muscle*, ed. HUDLICKA, O. Oxford: Pergamon.

FORRESTER, T. & LIND, A. R. (1969). Identification of ATP in human plasma and the concentration in the venous effluent of forearm muscles before, during and after sustained contraction. *J. Physiol.* **204**, 347–364.

FUNDERBURK, C. F., HIPSKIND, S. G., WELTON, R. C. & LIND, A. R. (1974). Development of and recovery from fatigue induced by static effort at various tensions. *J. appl. Physiol.* **37**, 392–396.

GASKELL, W. H. (1877). Further researches on the vasomotor nerves of ordinary muscles. *J. Physiol.* **1**, 262–302.

HADDY, F. J. & SCOTT, J. B. (1968). Metabolically linked vasoactive chemicals in local regulation of blood flow. *Physiol. Rev.* **48**, 688–707.

HILTON, S. M. (1953). Experiments on the post-contraction hyperaemia of skeletal muscle. *J. Physiol.* **120**, 230–245.

HILTON, S. M. (1977). Evidence for phosphate as a mediator of functional hyperaemia in skeletal muscles. *Pflügers Arch.* **369**, 151–159.

HOLLING, H. E. & VEREL, D. (1957). Circulation in the elevated forearm. *Clin. Sci.* **16**, 197–213.

HONIG, C. R. & FRIERSON, J. L. (1976). Neurons intrinsic to arterioles initiate postcontraction vasodilatation. *Am. J. Physiol.* **230**, 493–507.

HUMPHREYS, P. W. & LIND, A. R. (1963). The blood flow through active and inactive muscles of the forearm during sustained hand-grip contractions. *J. Physiol.* **166**, 120–135.

KERSLAKE, D. (1949). The effect of the application of an arterial occlusion cuff to the wrist on the blood flow in the human forearm. *J. Physiol.* **108**, 451–457.

KHAYUTIN, V. M. (1968). Determinants of working hyperaemia in skeletal muscles. In *Circulation in Skeletal Muscle*, ed. HUDLICKA, O. Oxford: Pergamon.

KJELLMER, I. (1965*a*). Potassium ion as a vasodilator during muscular exercise. *Acta. physiol. scand.* **63**, 460–468.

KJELLMER, I. (1965*b*). On the competition between metabolic vasodilatation and neurogenic vasoconstriction in skeletal muscle. *Acta. physiol. scand.* **63**, 450–459.

KJELLMER, A. (1968). Determinants of working hyperaemia in skeletal muscle. In *Circulation in Skeletal Muscle*, ed. HUDLICKA, O. Oxford: Pergamon.

KONTOS, H. A., MAUCK, H. P., JR, & PATTERSON, J. L., JR (1965). Mechanism of reactive hyperemia in limbs of anesthetized dogs. *Am. J. Physiol.* **209**, 1106–1114.

LIND, A. R. (1959). Muscle fatigue and recovery from fatigue induced by sustained contractions. *J. Physiol.* **147**, 162–171.

LIND, A. R. & MCNICOL, G. W. (1967). Local and central circulatory reponses to sustained contractions and the effect of free or restricted arterial inflow on post-exercise hyperaemia. *J. Physiol.* **192**, 575–593.

LIND, A. R., TAYLOR, S. H., HUMPHREYS, P. W., KENNELLY, B. M. & DONALD, K. W. (1964). The circulatory effects of sustained voluntary muscle contraction. *Clin. Sci.* **27**, 220–244.

LIND, A. R. & WILLIAMS, C. A. (1977). Changes in the forearm blood flow following brief isometric, hand-grip contractions at different tensions. *J. Physiol.* **272**, 97–98*P*.

LOMBARD, J. H. & DULING, B. R. (1977). Relative contributions of passive and myogenic factors to diameter changes during single arteriole occlusion in the hamster cheek pouch. *Circulation Res.* **41**, 365–373.

LORENZ, R. R. & VANHOUTTE, P. M. (1975). Inhibition of adrenergic neurotransmission in isolated veins of the dog by potassium ions. *J. Physiol.* **246**, 479–500.

MCGRATH, M. A. & SHEPHERD, J. T. (1976). Inhibition of adrenergic neurotransmission in canine vascular smooth muscle by histamine; mediation by H_2-receptors. *Circulation Res.* **39**, 566–573.

MELLANDER, S., JOHANSSON, B., GRAY, S., JONSSON, O., LUNDVALL, J. & HJUING, B. (1967). The effects of hyperosmolarity on intact and isolated vascular smooth muscle. Possible role in exercise hyperemia. *Angiology* **4**, 310–322.

MOHRMAN, D. E. & SPARKS, H. V. (1974). Role of potassium ions in the vascular response to a brief tetanus. *Circulation Res.* **35**, 384–390.

PATTERSON, G. C. (1956). The role of intravascular pressure in the human forearm. *Clin. Sci.* **15**, 17–25.

PATTERSON, G. C. & SHEPHERD, J. T. (1954). The blood flow in the human forearm following venous congestion. *J. Physiol.* **125**, 501–507.

PETROFSKY, J. S. & LIND, A. R. (1975). Aging, isometric strength and endurance and cardiovascular responses to static effort. *J. appl. Physiol.* **38**, 91–95.

SKINNER, N. S. & POWELL, W. J. (1967). Action of oxygen and potassium on vascular resistance of dog skeletal muscle. *Am. J. Physiol.* **212**, 533–540.

SPARKS, H. V. (1964). Effect of quick stretch on isolated vascular smooth muscle. *Circulation Res.* **14**, suppl. I, I–254–260.

VANHOUTTE, P. M. & SHEPHERD, J. T. (1973). Venous relaxation caused by acetylcholine acting on the sympathetic nerves. *Circulation Res.* **32**, 259–267.

VERHAEGHE, R. H., VANHOUTTE, P. M. & SHEPHERD, J. T. (1977). Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. *Circulation Res.* **40**, 208–215.

WHITNEY, R. J. (1953). The measurement of volume changes in human limbs. *J. Physiol.* **121**, 1–27.