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EFFECT OF REGIONAL α- AND β-ADRENERGIC BLOCKADE ON BLOOD FLOW IN THE RESTING FOREARM DURING CONTRALATERAL ISOMETRIC HANDGRIP

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SUMMARY

1. In a previous study we have shown that an isometric handgrip is accompanied by a rapid decrease in vascular resistance in the resting (contralateral) forearm, lasting for about 1 min, which in all probability is neurogenic.

2. In the present study the distribution of the vasodilatation was investigated by analysing O_2 saturation in a deep vein, draining mainly muscle tissue. Some possible neurogenic mechanisms for the vasodilatation were tested by repeating the handgrip after local β- and α-adrenergic blockade of the resting forearm with propranolol and phentolamine, respectively.

3. Without blockades the forearm vascular resistance decreased and the deep vein O_2 saturation increase to similar degrees on contralateral handgrip. Propranolol markedly reduced both the decrease in resistance and the increase in deep vein O_2 saturation. Phentolamine did not alter the initial decrease in resistance, but with phentolamine resistance continued to decrease after 1 min.

4. It is concluded that the rapid decrease in vascular resistance in the resting forearm on contralateral handgrip takes place, to a great extent, in muscle. It is mediated by neurogenic β-adrenergic mechanisms and if the contraction is prolonged it gradually changes to a vasoconstriction mediated by α-adrenergic mechanisms.

INTRODUCTION

Muscle activity is accompanied by pronounced cardiovascular alterations including increases in heart rate, arterial pressure and cardiac output. That these changes are partly of neurogenic origin is apparent from studies showing that an isometric contraction of a limited muscle group produces an instantaneous and quite large increase in the variables mentioned (Tuttle

& Horvath, 1954; Lind, Taylor, Humphreys, Kennelly & Donald, 1964; Freyschuss, 1970; Eklund, Kaijser & Knutsson, 1974). The effect on local blood flow and vascular resistance of the altered vasomotor influence produced by muscle activation can be studied in a resting limb, not taking part in the exercise, where the response is not modified by local metabolic and mechanical factors. During an isometric contraction, performed as a dorsiflexion of the foot or a handgrip with the contralateral arm, Eklund *et al.* (1974) recently described a pronounced and rapid blood flow increase in the resting forearm, due to a decrease in regional vascular resistance. The flow increased rapidly at a time when blood pressure was only moderately increased and probably could not have been because of distension of resistance vessels. Furthermore, forearm blood flow had increased already within 30 sec of the contraction, i.e. before it was possible for catecholamines, released from the adredal medulla, to appear in the forearm (Koslowsky, Brzezinska, Nazar, Kowalski & Franczyk, 1973).

A neurogenically induced decrease in vascular resistance might be produced by a decrease in vasoconstrictor activity or an increase in vasodilator activity. However, since exercise is considered to be accompanied by an increase in sympathetic nerve activity (Delius, Hagbarth, Hongell & Wallin, 1972) the second possibility seems to be the more likely or at least the more important. Sympathetic cholinergic fibres are described e.g. in the cat, and in this species they are considered to be the main mediators of neurogenic vasodilatation (Folkow, Haeger & Uvnäs, 1948). In man, it has been proposed that they mediate vasodilatation in skeletal muscle during emotional stress (Blair, Glover, Greenfield & Roddie, 1959). However, cholinergic nerve terminals could not be demonstrated in muscle samples from monkey or man (Bolme & Fuxe, 1970; Bolme, Novotny, Uvnäs & Wright, 1970). The vasodilatation which we have described in connexion with muscle activation might thus be induced by sympathetic β-adrenergic effects. The possibility of such a mechanism is supported by the finding that under α-adrenergic blockade, sympathetic stimulation decreases vascular resistance in the dog (Viveros, Garlick & Renkin, 1968). However, at the present time, it is not possible to exclude the contention that also in man vasodilatation might be produced by sympathetic cholinergic mechanisms.

The aims of the present investigation were:

(1) to study to what extent neurogenic adrenergic mechanisms contribute to the blood flow changes in the resting arm during contralateral isometric handgrip, especially the possibility of a β-adrenergic mechanism mediating the initial vasodilatation. This question was elucidated by performing the contralateral handgrip with the resting arm under the influence of regional β- and α-adrenergic blockade, and

(2) to study the distribution of the blood flow increase between muscle and subcutaneous tissue by analysing the O_2 saturation of blood draining the musculature of the resting forearm during contralateral isometric handgrip.

METHODS

Subjects

The object was to study the mechanisms behind the blood flow increase by contralateral handgrip. Since in our previous study we found this increase to vary greatly between individuals we first made a preparatory test in a group of subjects to exclude those who had forearm blood flow increase of less than 50%. Thus out of sixteen healthy male subjects of average physical fitness, eleven were accepted for the study and their informed consent were obtained. Their ages ranged between 22 and 42 years.

Chemicals

For the infusion of drugs and for pressure recording a Teflon catheter (outer diameter 1·4 mm) was introduced percutaneously about 10 cm into the brachial artery of the resting arm. The same type of catheter was used for the catheterization of the deep venous system of the forearm. It was then introduced into a cubital vein in the distal direction and manipulated into a deep vein so that the tip could not be palpated. The distance it had been introduced, 4–8 cm, was measured and checked again when the catheter was withdrawn at the end of the experiment. With the catheter in this position it is possible to sample blood almost exclusively draining muscle tissue provided the circulation of the hand is occluded (Coles, Cooper, Mottram & Occleshaw, 1958; Idbohrn & Wahren, 1964).

Blood flow in the resting forearm was measured by venous occlusion plethysmography with an airfilled plethysmograph according to Dohn (1956) and Graf & Westersten (1959), the plethysmograph cuff being placed around the thickest part of the forearm. Venous occlusion pressure was 50 mmHg. During the recording of inflow curves the circulation of the hand was occluded by a wrist cuff inflated to 240 mmHg. Blood flow was calculated in ml. $\times$ min^{-1} $\times$ 100 ml. of tissue^{-1}.

Arterial pressure was measured with a capacitative transducer (EMT 34 or 35, Siemens-Elema) and recorded on a Mingograph 81 (Siemens-Elema). Mean pressure was determined by electrical damping, time constant 3 sec.

O_2 saturation of the deep venous blood ($sdvO_2$) was analysed with an Instrumentation laboratories CO-Oximeter (model 182).

The isometric contralateral contraction was performed as a handgrip utilizing a hand-dynamometer with immovable handles (Flygtekniska Försöksanstalten). The force developed was measured with a strain-gauge and displayed to the subject on an oscilloscope. Before the experiment the maximal voluntary contraction force (mvc) of the subject was determined. The subject was then instructed to hold a contraction at 1/3 mvc, which force was marked by a line on the oscilloscope, for 2 min. 1/3 mvc ranged between 150 and 200 N ($\sim$ 15–20 kp) in the different subjects. With the equipment used, contraction at 1/3 mvc leads to fatigue in 2·5–3 min.

The subjects were studied in the recumbent position with the resting arm at heart level. Arterial mean pressure and e.c.g. were recorded continuously before, during and for 2 min after the contralateral handgrip. Plethysmographic inflow curves were recorded with shortest possible intervals, 5–6/min. Deep venous blood was sampled at rest, at 30, 60, 90, and 120 sec of the contralateral handgrip and again 30 and 90 sec after the contraction.

Propranolol(Inderal®) was used as β-blocking agent, 0·5 mg of which was dissolved in 3 ml. isotonic NaCl and infused through the brachial artery catheter over 1 min, the infusion starting 4 min before the contralateral handgrip. With this procedure the flow increase induced by isoprenaline is reduced to less than 10 % for at least 10 min (Johnsson, 1967; Robinson & Wilson, 1968). In our control experiments the intraarterial infusion of 0·02 μg isoprenaline/min for 2 min without adrenergic blockade produced a forearm blood flow increase of four to five times the resting value. Intra-arterial injection of propranolol abolished this flow increase; even 30 min after propranolol no increase in total forearm blood flow was induced by 0·02 or 0·04 μg/min isoprenaline. However, a slight increase in $sdvO_2$ was produced by the higher dose, which could suggest an increase in muscle blood flow of about 20 %. At 60 min after propranolol the infusion of 0·02 μg isoprenaline produced a slight increase, which was less than 50 % in total forearm blood flow. Phentolamine (Regitine®) was used as an α-blocking agent. A solution of 200 μg/ml. was infused continuously at a rate of 0·9 ml./min from 4 min before to 2 min after the contraction (Taylor, Sutherland, MacKenzie, Staunton & Donald, 1965).

The experiments started with two contractions performed without regional autonomic blockade at an interval of 10 min and followed by 30 min rest. Propranolol was always administered before phentolamine since we were primarily interested in the early vasodilatation and since our own observations suggested that the α-adrenergic blockade could persist, to some degree, for more than 2 hr. The subject then performed two contractions with the resting arm under regional β-blockade. Following at least another 45 min rest, two contractions were performed with the resting arm under regional α-adrenergic blockade.

Forearm blood flow at rest before contralateral handgrip was for each subject calculated from at least six inflow curves. During contraction it was calculated as the mean for 15 sec intervals. The data from the pairs of contractions in each experimental situation (i.e. control, β-blockade, α-blockade) were averaged. Forearm vascular resistance was calculated as arterial mean pressure in mmHg divided by forearm blood flow in ml. $\times$ min^{-1} $\times$ 100 ml^{-1}.

RESULTS

Values in the text are given as mean $\pm$ S.D. unless otherwise stated. Differences between the experimental situations are calculated from paired data.

Heart rate and arterial mean pressure

As in previous study (Eklund *et al.* 1974) the handgrip increased heart rate at first rapidly and then more slowly, in the control situation without α- and β-blockade from 64 + 8 at rest to 87 $\pm$ 11 beats/min at the end of the contraction, and the arterial mean pressure almost linearly from 92 $\pm$ 10 at rest to 124 $\pm$ 8 mmHg at the end of contraction.

Regional β- and α-adrenergic blockade neither affected the heart rate and arterial pressure at rest nor modified the reaction of these variables during contralateral handgrip. Thus, there were no signs of systematic effects of the drugs (Fig. 1).

Blood flow in the resting forearm (Fig. 2)

Without regional blockade contralateral handgrip increased blood flow in the resting forearm from $3{\cdot}6 \pm 1{\cdot}4$ at rest to $6{\cdot}5 \pm 2{\cdot}7$ ml. $\times$ min^{-1} $\times$ 100 ml.$^{-1}$ at one min of contralateral handgrip, i.e. by almost 100 %. In five of the subjects blood flow increased slightly longer to reach its maximal value between 60 and 90 sec, but in most subjects blood flow tended to decrease again during the second min. Regional β-adrenergic blockade did

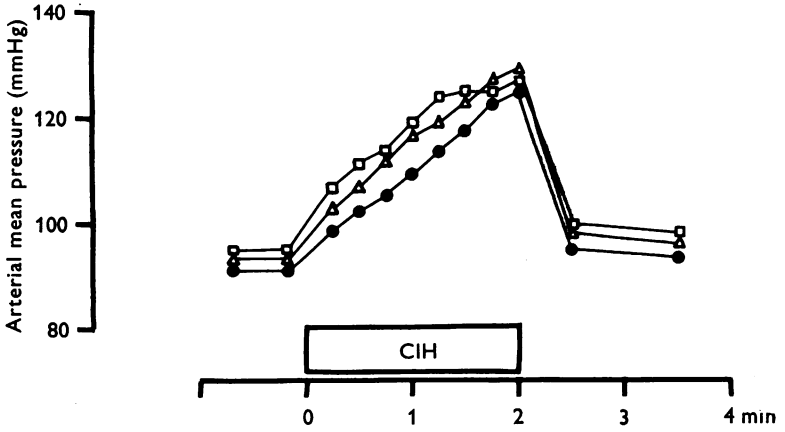

Fig. 1. Arterial mean pressure at rest and during contralateral isometric handgrip (CIH) in the control situation without blockade (filled circles), after close arterial infusion of propranolol (open triangles) and phentolamine (open squares), respectively.

not significantly lower the forearm blood flow before handgrip, being $3{\cdot}2 \pm 1{\cdot}0$ ml. $\times$ min^{-1} $\times$ 100 ml.$^{-1}$. The flow increase produced by contralateral handgrip was markedly reduced, the maximal increase being only about 40 %($P < 0{\cdot}01$) of that without regional blockade. The time course for the flow increase was otherwise similar to that without blockade with the maximal value most often reached at about 1 min. Regional α-adrenergic blockade increased forearm blood flow at rest to $6{\cdot}2 \pm 3{\cdot}1$ ml. $\times$ min^{-1} $\times$ 100 ml.$^{-1}$ ($P < 0{\cdot}01$). Contralateral handgrip produced a further increase in blood flow which in all subjects continued towards the end of contraction. The flow was $9{\cdot}4 \pm 3{\cdot}9$ at 1 min and $12{\cdot}2 \pm 4{\cdot}9$ ml. $\times$ min^{-1} $\times$ 100 ml.$^{-1}$ at 2 min. Taken as a percentage the flow increase was about 60 % after 1 min and 100 % at the end of contraction.

Forearm vascular resistance (Fig. 3)

In the control situation without adrenergic blockade forearm vascular resistance before handgrip was 28 ± 8. Contralateral handgrip decreased

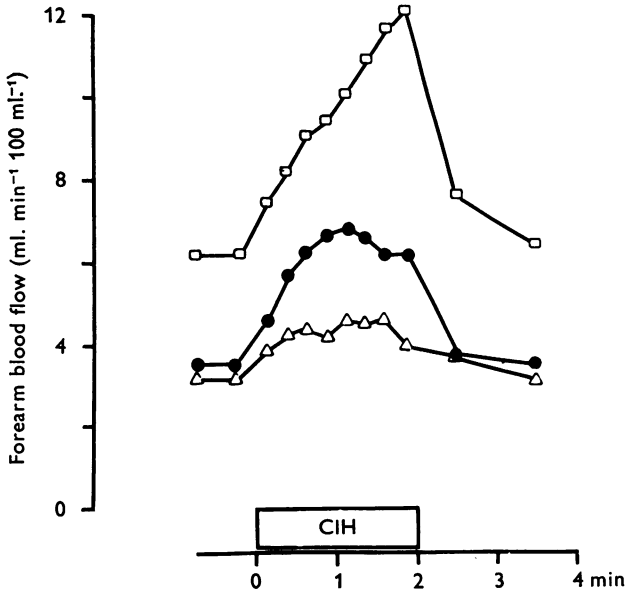

Fig. 2. Blood flow in the resting forearm during contralateral isometric handgrip without blockade, after close arterial infusion of propranolol and phentolamine, respectively. Symbols as in Fig. 1.

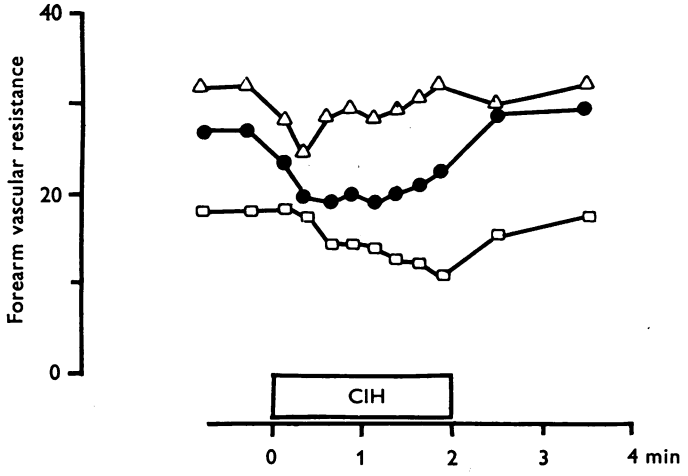

Fig. 3. Vascular resistance in the resting forearm during contralateral isometric handgrip. Symbols as in Fig. 1.

vascular resistance significantly already during the first 15 sec ($P < 0{\cdot}01$) and it decreased further to reach its lowest value, 19 ± 6 towards the end of the first min ($P < 0{\cdot}001$). It remained significantly below the value before contralateral handgrip up to 105 sec ($P < 0{\cdot}05$), and tended to approach the resting value at 120 sec. Regional β-adrenergic blockade slightly increased basal forearm vascular resistance at rest to 32 ± 10

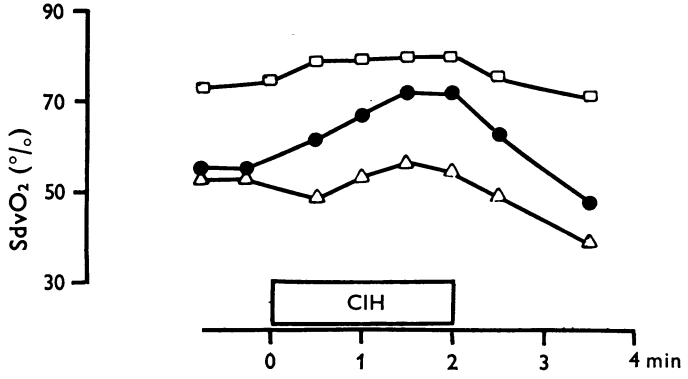

Fig. 4. Deep venous O_2 saturation ($sdvO_2$) in the resting forearm during contralateral isometric handgrip. Symbols as in Fig. 1.

($P < 0{\cdot}01$). Also during β-blockade, contralateral handgrip significantly reduced vascular resistance in the resting forearm during the first 15 sec ($P < 0{\cdot}01$). It did not decrease much further and the lowest value, 27 ± 8 ($P < 0{\cdot}001$), was recorded after about 30 sec. The percentage as well as the absolute maximal decrease was significantly smaller than in the control situation ($P < 0{\cdot}001$ and $0{\cdot}05$, respectively). Regional α-adrenergic blockade lowered forearm vascular resistance at rest to 19 ± 6 ($P < 0{\cdot}001$ compared to the control situation). During contralateral handgrip it decreased almost continuously towards the end of the contraction to $11{\cdot}5 \pm 5$ ($P < 0{\cdot}001$) at 120 sec.

Deep venous oxygen saturation (Fig. 4)

$SdvO_2$ was $55{\cdot}5 \pm 12{\cdot}8\,\%$ before contralateral handgrip in the control situation. It had increased significantly after 30 sec of contralateral handgrip ($P < 0{\cdot}05$) and continued to increase to reach a maximal value of $74{\cdot}2 \pm 12{\cdot}7\,\%$ at 90–120 sec. 90 sec after the contraction it had decreased again, reaching a value significantly below that before contraction, $48{\cdot}1 \pm 14{\cdot}5\,\%$ ($P < 0{\cdot}05$). Regional β-adrenergic blockade did not significantly affect $sdvO_2$ at rest which was $53{\cdot}7 \pm 8{\cdot}2\,\%$. After the first 30 sec of contralateral handgrip it tended to decrease ($0{\cdot}10 > P > 0{\cdot}05$) whereafter it was not significantly different from the resting value for the rest of the

contraction period. After the end of contraction $sdvO_2$ decreased significantly below the value before contraction ($P < 0{\cdot}001$). 90 sec after contraction it was $39{\cdot}7 \pm 11{\cdot}6\%$. which was also significantly lower than at the corresponding time in the control situation ($P < 0{\cdot}01$). During regional α-adrenergic blockade $sdvO_2$ was $73{\cdot}0 \pm 11\%$ at rest before contralateral handgrip and it increased continuously to $79{\cdot}9 \pm 15\%$ at the end of contraction ($P < 0{\cdot}001$). After the contraction it returned to the pre-contraction level. Unlike the control state, it never reached values below resting level.

DISCUSSION

The increase in blood flow in the resting forearm during contralateral isometric handgrip in the present study was of the same order of magnitude and followed the same time course as in a previous series of experiments, suggesting it was neurogenically mediated (Eklund *et al.* 1974). In addition, the increase in deep venous O_2 saturation indicated that the flow increase was largely due to an augmented muscle blood flow. Assuming a normal arterial O_2 saturation of 96%, the arterio-venous O_2 difference can be estimated from the measured deep vein O_2 saturations. If it is assumed that the resting forearm O_2 consumption is constant during contralateral handgrip, maximal muscle blood flow increase can then be calculated to be about 100%. Two factors might restrict the validity of this calculation. Firstly, the oxygen uptake might not be constant. Thus it could decrease if a simultaneous dilatation occurred of some arterio-venous channels ('functional shunts') and a constriction of some precapillary sphincters leading to a redistribution of the blood flow and decreased vascular surface area (cf. Rosell & Uvnäs, 1962; Renkin & Rosell, 1962). Such a mechanism would affect our discussion only quantitatively as long as the constrictor effect is not more pronounced than the dilator effect, which is rather unlikely. Secondly, since this value was obtained under conditions of changing forearm blood flow it can only be considered an approximate estimate of the increase in muscle blood flow (Zierler, 1961). Thus, the highest deep vein O_2 saturation was in most subjects recorded 15–30 sec later than the largest forearm blood flow. This time difference corresponds quite well with the transit time for blood from capillary to deep vein, since the mean transit time from brachial artery to deep veins has been shown to be in the range 15–30 sec when forearm blood flow is between resting and three times resting level (Wahren, 1966; Stjärne, Kaijser, Mathé & Birke, 1975). Therefore it seems reasonable to conclude that muscle blood flow was increased to about the same extent as total forearm blood flow. From this, theoretically, it would follow that also in the remaining tissue in the forearm (mainly skin and subcutaneous tissue) blood flow is doubled by

contralateral handgrip. However, if the hand is excluded, as in the present study, it is probable that muscle blood flow represents about 75% of resting forearm blood flow (Cooper, Edholm & Mottram 1955) and less than 25% goes to skin and subcutaneous tissue. Since skin blood flow constitutes the minor fraction of forearm blood flow, estimates of skin blood flow from total and muscle blood flow then become uncertain.

The rapidly appearing flow increase was caused, as previously described, by a marked lowering of the regional vascular resistance. The maximal decrease in resistance, which was recorded at 1 min, was more than 50% abolished by β-blockade. Thus the blood flow increase in the resting forearm on contralateral handgrip seems to be mediated, to a substantial degree, by β-adrenergic mechanisms. Since a slight reduction in resistance occurred also after β-blockade other factors might contribute, although the possibility also exists that the blockade was not complete. However, if other than β-adrenergic mechanisms contribute to the flow increase they seem to be more important in skin and subcutaneous tissues than in muscle since the increase in forearm total flow and decrease in forearm vascular resistance which remained after β-blockade was not paralleled by an increase in deep vein O_2 saturation.

It might be argued that the recorded β-adrenergically mediated vasodilatation could be produced by circulating catecholamines. Thus, adrenaline in low concentrations is shown to have a vasodilating effect in skeletal muscle which is mediated by β-receptors (Brungardt, Swan & Reynolds, 1974). However, as shown by Kozlowski *et al.* (1973) adrenaline concentration in blood increases during a comparable isometric contraction but the increase is small and appears only after the first min. Thus, in view of the rapid flow increase produced by contralateral handgrip, active neurogenic β-adrenergic vasodilatation seems to be the more likely mechanism. This contention is further supported by the rapid blood flow decrease at the end of contraction; since fractional removal of catecholamines in the lung vascular bed is only about 20%, amines released from the adrenal medulla must remain in blood perfusing the forearm at least a minute after the contraction (Stjärne *et al.* 1975).

Traditionally, adrenergic vasomotor nerve activity as well as circulating noradrenaline are considered to produce vasoconstriction by affecting preferentially α-receptors. However, vasodilation mediated by β-adrenergic effects of sympathetic nerve stimulation have in fact been described in the vascular bed of skeletal muscle, although as yet only after α-adrenergic blockade (Viveros *et al.* 1967). Furthermore noradrenaline has been shown to have vasodilator effects if administered in low doses (Brungardt *et al.* 1974). Evidence from the literature thus appears to support the existence of neurogenic adrenergic vasodilating mechanisms.

It then remains to explain the changing effect on vascular resistance with time. Several possibilities are at hand. The relative increase in resistance might be interpreted as a continuous increase in α-adrenergic relative to β-adrenergic effects since it could be abolished by regional α-adrenergic blockade with phentolamine. Several alternative or contibuting mechanisms might be responsible for such a shift. During the contraction the effort to maintain force is gradually increased and this is paralleled by an increased activity in somatomotor nerves as evidenced by increased e.m.g. activity (Clarke, Hellon & Lind, 1958). It is possible that the increase in somatomotor activity via 'irradiation' to a vasomotor centre is paralleled by an increased activity in sympathetic vasomotor fibres. Then a similar 'dose–response' relationship as discussed above (Brungardt *et al.* 1974) might apply also to adrenergic vasomotor nerve activity, to the effect that with moderately increased activity, predominantly β-receptors are stimulated, and with higher activity predominantly α-receptors. Alternatively, a shift between predominant activity in anatomically distinct β-adrenergic and α-adrenergic fibres might occur at C.N.S. level. The shift might then either be the result of an increasing somatomotor activation with parallel 'irradiation' to a vasomotor centre or it may be related to time, to the effect that *initiation* of somatomotor activity is paralleled by activity in vasodilator β-adrenergic fibres, while this activity with prolonged muscle contraction gradually fades away to be replaced by an increased activity in α-adrenergic vasoconstricting fibres.

Calculated from $sdvO_2$, muscle blood flow increase in the resting forearm under α-adrenergic blcokade was about 50% after 1 min of contralateral handgrip, i.e. of a magnitude similar to the total forearm blood flow increase. During the second minute, however, muscle blood flow, thus estimated, did not change further, whereas total flow continued to increase. A possible interpretation is that the tendency to resistance increase, which is seen normally during the second minute, is mediated by α-adrenergic mechanisms and is more pronounced in skin and subcutaneous tissue than in muscle. It must be pointed out, however, that the relevance of this argument is weakened by the difficulty of drawing conclusions from arteriovenous differences during non-steady-state conditions (Zierler, 1961). It may also be pointed out that phentolamine is considered also to have a direct relaxing effect on vascular smooth muscle not mediated by adrenergic mechanisms (Taylor *et al.* 1965). Thus the posibility cannot be excluded that the continuous decrease in resistance after phentolamine might be due to a reduced myogenic response to the rising arterial pressure during contralateral handgrip.

After the end of the contralateral handgrip total forearm blood flow in most subjects returned directly to the pre-contraction value within 1 min,

although in a few subjects it decreased below the pre-contraction value for a short period before it stabilized at initial level. Whereas the total flow decreased below the precontraction value only in some subjects, the deep vein O_2 saturation decreased in all subjects, suggesting that the muscle blood flow was decreased. This overshoot effect might have been the result of an increased myogenic tone produced by the increased arterial pressure during the contraction (cf. Folkow & Löfving, 1956). The reason why it occurred in the muscle vascular bed but not, or to a very small degree, in the skin could then be that myogenic activity plays a relatively greater role in the regulation of vascular resistance in muscle (cf. Folkow, 1964). However, the calculated decrease in muscle blood flow in the resting forearm after contralateral handgrip could be abolished by α-adrenergic blockade and it was accentuated by β-adrenergic blockade. The finding could then be explained as an effect of circulating catecholamines, which according to Kozlowski *et al.* (1973) after 2 min of handgrip have reached significant concentrations. Still it seems difficult to explain why circulating catecholamines should have more pronounced vasoconstrictor effect in muscle than in skin. Thus, from the present data it is not possible to establish the nature of the mechanisms leading to flow reduction *after* the contraction.

REFERENCES

Blair, D. A., Glover, W. E., Greenfield, A. D. M. & Roddie, I. C. (1959). Excitation of cholinergic vasodilator nerves to human skeletal muscle during emotional stress. *J. Physiol.* **148**, 633–647.

Bolme, P. & Fuxe, K. (1970). Adrenergic and cholinergic nerve terminals in skeletal muscle vessels. *Acta physiol. scand.* **78**, 52–59.

Bolme, P., Novotny, J., Uvnäs, B. & Wright, P. G. (1970). Species distribution of sympathetic cholinergic vasodilator nerves in skeletal muscle. *Acta physiol. scand.* **78**, 60–64.

Brungardt, J. M., Swan, K. G. & Reynolds, D. G. (1974). Adrenergic mechanisms in canine hindlimb circulation. *Cardiovasc. Res.* **8**, 423–429.

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.

Coles, D. R., Cooper, K. E., Mottram, R. F. & Occleshaw, J. V. (1958). The source of blood samples withdrawn from deep forearm veins via catheters passed upstream from the median cubital vein. *J. Physiol.* **142**, 323–328.

Cooper, K. E., Edholm, O. G. & Mottram, R. F. (1955). The blood flow in skin and muscle of the human forearm. *J. Physiol.* **128**, 258–267.

Delius, W., Hagbarth, A., Hongell, A. & Wallin, B. G. (1972). Manoeuvres affecting sympathetic outflow in human muscle nerves. *Acta physiol. scand.* **84**, 82–94.

Dohn, K. (1956). Plethysmographs usable during functional states recording volume changes in ml per 100 ml of extremity. *Rep. Steno. Hosp.* **6**, 147–168.

Eklund, B., Kaijser, L. & Knutsson, E. (1974). Blood flow in resting (contralateral) arm and leg during isometric contraction. *J. Physiol.* **240**, 111–124.

FOLKOW, B. (1964). Autoregulation in muscle and skin. *Circulation Res.* **15**, 19–24.

FOLKOW, B., HAEGER, K. & UVNÄS, B. (1948). Cholinergic vasodilator nerves in the sympathetic outflow to the muscles of the hind limbs of the cat. *Acta physiol scand.* **15**, 401–411

FOLKOW, B. & LÖFVING, B. (1956). The distensibility of the systemic resistance blood vessels. *Acta physiol. scand.* **38**, 37–52.

FREYSCHUSS, U. (1970). Cardiovascular adjustment to somatomotor activation. The elicitation of increments in heart rate, aortic pressure and venomotor tone with the initiation of muscle contraction. *Acta physiol. scand.* suppl. 342.

GRAF, K. & WESTERSTEN, A. (1959). Untersuchungen über Eigenschaften und Verwendungsmöglicheiten eines flexiblen Extremitätenplethysmografen. *Acta physiol. scand.* **46**, 1–18.

IDBOHRN, H. & WAHREN, J. (1964). The origin of blood withdrawn from deep forearm veins during rhythmic exercise. *Acta physiol. scand.* **61**, 301–313.

JOHNSSON, G. (1967). The effects of intra-arterially administered propranolol and H 56/28 on blood flow in the forearm. A comparative study of two β-adrenergic receptor antagonists. *Acta pharmac. tox.* **25**, 64–74.

KOZLOWSKY, S., BRZEZINSKA, Z., NAZAR, K., KOWALSKI, W. & FRANCZYK, M. (1973). Plasma catecholamines during sustained isometric exercise. *Clin. Sci.* **45**, 723–731.

LIND, A. R., TAYLOR, S. H., HUMPHREYS, P. W., KENNELLY, M. M. & DONALD, K. W. (1964). The circulatory effects of sustained voluntary muscle contraction. *Clin. Sci.* **27**, 229–244.

RENKIN, E. M. & ROSELL, S. (1962). Effects of different types of vasodilator mechanisms on vascular tonus and on transcapillary exchange of diffusible material in skeletal muscle. *Acta physiol. scand.* **54**, 241–251.

ROBINSON, B. F. & WILSON, A. G. (1968). Effect on forearm arteries and veins of attenuation of the cardiac response to leg exercise. *Clin. Sci.* **35**, 143–152.

ROSELL, S. & UVNÄS, B. (1962). Vasomotor nerve activity and oxygen uptake in skeletal muscle of the anesthetized cat. *Acta physiol. scand.* **54**, 209–222.

STJÄRNE, L., KAIJSER, L., MATHÉ, A. & BIRKE, G. (1975). Specific and unspecific removal of circulating noradrenaline in pulmonary and systemic vascular beds in man. *Acta physiol. scand.* **95**, 46–53.

TAYLOR, S. H., SUTHERLAND, G. R., MACKENZIE, G. J., STAUNTON, H. P. & DONALD K. W. (1965). The circulatory effects of phentolamine in man with particular respect to change in forearm blood flow. *Clin. Sci.* **28**, 265–284.

TUTTLE, W. W. & HORVATH, S. M. (1954). Comparison of effects of static and dynamic work on blood pressure and heart rate. *J. appl. Physiol.* **10**, 294–296.

VIVEROS, O. H., GARLICK, D. G. & RENKIN, E. M. (1968). Sympathetic beta adrenergic vasodilatation in skeletal muscle of the dog. *Am. J. Physiol.* **215**, 1218–1225.

WAHREN, J. (1966). Quantitative aspects of blood flow and oxygen uptake in the human forearm during rhythmic exercise. *Acta physiol. scand.* **67**, 269.

ZIERLER, K. L. (1961). Theory of the use of arteriovenous concentration differences for measuring metabolism in steady and non-steady states. *J. clin. Invest.* **40**, 2111–2125.