COMPARATIVE EFFECTS OF DIHYDROERGOTAMINE AND NORADRENALINE ON RESISTANCE, EXCHANGE AND CAPACITANCE FUNCTIONS IN THE PERIPHERAL CIRCULATION

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SUMMARY

1. A comparative quantitative study of the effects of dihydroergotamine (DHE) and noradrenaline (NA) on the precapillary and postcapillary resistance vessels, the precapillary 'sphincters', and the capacitance vessels was performed in a skeletal muscle and a skin region in healthy humans and in patients with orthostatic symptoms; further, the vascular effects of the drugs were analysed in muscle, skin, intestine and kidney in cats before and after sympathectomy.

2. The two drugs evoked a similar pattern of response in the cutaneous vascular bed, i.e. they both constricted resistance and capacitance vessels, increased the ratio of pre-/post-capillary resistance, but did not significantly influence precapillary sphincters. The reactions were similar in skeletal muscle for NA and also for DHE, with the important exception that the latter drug usually elicited a moderate dilator response in the muscle resistance vessels.

3. The average constrictor responses of the capacitance vessels were significantly larger for DHE than NA in skin and also in muscle despite the fact that DHE did not much affect the resistance vessels in muscle.

4. The effects of DHE on the intestinal and renal vascular circuits in the cat were comparatively small.

5. Since the constrictor effect of DHE seems confined mainly to the capacitance vessels, the drug may have beneficial effects in circulatory disorders characterized by impaired venoarterial regulation.

A thorough description of the effects on the peripheral circulation of a vasoactive drug cannot be made unless quantitative information is available about the reactions evoked in the functionally differentiated consecutive sections of the vascular beds (see Mellander & Johansson, 1968). Drug induced changes of tone in the resistance vessels influence regional blood flow, and changes of activity in the precapillary 'sphincters' determine the number of patent capillaries and therefore, the size of the functional capillary surface area available for exchange.

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Alterations of the ratio of pre-/post-capillary resistance influence hydrostatic capillary pressure and will lead to net transcapillary fluid movements, thus affecting plasma volume. Changes of tone in the capacitance vessels will result in redistributions of regional blood volume, hence modifying in an important way the venous return and cardiac filling.

Methods have been developed which permit simultaneous recordings of all these peripheral vascular functions in a tissue, and have been used, for instance, for analysing the patterns of response evoked by some vasoactive agents in experimental animals (Mellander & Johansson, 1968). The fact that these agents often elicit highly differentiated responses within the various consecutive vascular sections (Mellander, 1970) emphasizes the need for this type of study. It is evident that for vasoactive drugs used in medical practice, corresponding investigations should be performed in humans, but so far no drug seems to have been subjected to such a complete analysis of all these peripheral vascular functions in man.

In the present investigation, an attempt was made to study quantitatively the effects of dihydroergotamine (DHE), and for comparison those of noradrenaline (NA), on the pre- and post-capillary resistance vessels, precapillary sphincters, and capacitance vessels in the vascular beds of the hand (mainly skin tissue) and the calf (mainly skeletal muscle) in man. Attention was directed to DHE by some recent clinical studies (e.g. Rosmanitz, Rosmanitz & Brehm, 1964; Husmann, 1966; Lüthy, 1967) in which DHE was reported to have a beneficial effect on the pathological changes of heart rate and arterial blood pressure that occur in patients with orthostatic hypotension. Seemingly reasonable explanations for this beneficial effect of DHE have been suggested (e.g. Rosmanitz, et al., 1964), but so far without direct experimental support based on quantitative analysis of the various peripheral vascular functions.

Since a dominant feature in many types of orthostatic hypotension appears to be an abnormal pooling of blood in dependent regions in the erect posture leading to an inadequate central blood volume, beneficial effects might be expected from a drug that could evoke a fairly selective constrictor response within the capacitance vessels without much affecting the other vascular sections. The present results show that DHE elicits such a differentiated pattern of vascular response.

The mode of action of DHE with regard to its direct and indirect effects on smooth muscle has been studied extensively (e.g. Rothlin, 1947; Rothlin, Konzett & Cerletti, 1954; Aellig, 1967). DHE seems to affect vascular smooth muscle in mainly three different ways. It exerts a direct excitatory (constrictor) effect on the vascular smooth muscle, an α-adrenergic blocking action when administered in relatively large doses, and, finally, an indirect effect via a complex, usually inhibitory, action on higher autonomic nervous structures resulting for instance in a decreased vasoconstrictor fibre discharge. In an attempt to reveal to what extent these different mechanisms of DHE action were involved in the reactions of the various peripheral vascular circuits and sections, a supplementary study was performed in cats in which the effects of DHE were analysed in the vascular beds of skeletal muscle, skin, intestine and kidney before and after regional sympathectomy.

A brief preliminary report of this work has been presented previously (Mellander, 1970).

MATERIALS AND METHODS

Experiments in man

Materials. Observations were made on a total of twenty-eight humans. Nineteen of these were healthy males, 19–43 years old, mean 25 years. Four of the subjects were healthy women,
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19–22 years old, mean 20 years. In addition, investigations were carried out on five patients showing clear symptoms of orthostatic hypotension. Four of these were women, 18–59 years old, mean 43 years, and one male, 48 years old.

Technical procedures. The experiments were started in the morning and lasted for 3–4 h. Three polyethylene catheters were inserted percutaneously into different vessels as described by Bernéus, Carlsten, Holmgren & Seldinger (1954). One was introduced into the left brachial artery and was used for recording arterial blood pressure. Another was placed in a cubital vein in the left arm and was used for the administration of drugs. A third was inserted into a superficial vein on the dorsum of the right hand or, alternatively, into a vein in the right calf to permit recording of local venous pressure in either of these regions. The right hand and the right calf were then placed in water-filled temperature-regulated plethysmographs similar to the type described by Dahn (1964). Unless otherwise stated, the temperature of the water in the plethysmographs was kept at 34° and the room temperature at 23°±0-5°. The subjects were placed comfortably in the supine position and rested for about half an hour before the experiment. Sphygmomanometer cuffs were fitted to the right arm and the right thigh and were connected to the same pressure tank to permit simultaneous adjustments of venous outflow pressure in the hand and the calf. A third cuff was placed around the right lower leg distal to the calf plethysmograph. During measurement of calf blood flow, the circulation in the foot was occluded by inflating this cuff to a pressure about 50 mmHg above systolic pressure.

Arterial blood pressure was measured by an inductance manometer placed at heart level. Mean pressure was obtained by electrical integration. Venous pressure in the hand or calf was monitored from catheters, the tips of which were placed well inside the plethysmographs, and was measured by inductance manometers. Arterial and venous pressures and ECG were recorded on a direct-writing electrocardiograph (Elema, model 81). Plethysmographic tracings of changes of hand and calf volumes were followed to provide information about the capacitance function and the net transcapillary fluid movement (see below) and these changes were registered by volume piston recorders. Blood flow in these two regions was measured by conventional venous occlusion plethysmography. Cuff pressures and changes of hand and calf volumes were registered on an ink-writing recorder.

Analysis of different peripheral vascular functions. By the experimental approach mentioned above it was possible to follow the reactions in the resistance and capacitance vessels and in the precapillary sphincters, as well as the rate of net transcapillary fluid movement (cf. Mellander & Johansson, 1968). Data about the resistance function were obtained from pressure/flow recordings. By continuous measurement of volume changes in the hand and calf, it was possible to follow the shifts in regional blood content, reflecting the reactions of the capacitance vessels (abrupt and fairly rapid changes of tissue volume), as well as the rate of net fluid movements across the capillary walls (slower, continuous changes of tissue volume). These two circulatory events can be distinctly separated (for details see Mellander, 1960; Mellander & Öberg, 1967). Two different methods were used for analysing the capacitance function and they will be considered in some detail below.

When the capacitance responses are to be measured in terms of blood translocations, significant quantitative information will only be obtained by standardizing the experiments at a defined venous pressure within the physiological range (see Mellander & Johansson, 1968). This was accomplished by inflating the cuffs around the arm and thigh to a pressure of 20
mmHg so as to elevate local venous pressures just above the extravascular pressure exerted by the water in the plethysmographs. This implied that the effects of the so-called 'waterfall phenomenon' (e.g. Kjellmer, 1964) could be avoided and in addition, it produced some distension of the veins so that passive pressure dependent adjustments of the capacitance vessels were minimized (Öberg, 1967). With this cuff pressure, the transmural pressure of the veins was roughly brought back to the normal value existing in a region at heart level, and the recorded venous pressure in the two studied regions remained virtually constant during the elicitation of a capacitance response. This manoeuvre also implied that an average 'Starling fluid equilibrium' across the capillaries was established, as evidenced by the fact that the tissue volumes remained approximately constant (isovolumetric state) during control conditions at rest (see Fig. 1) Under these circumstances, this method for recording capacitance responses will provide reliable quantitative information about the amount of blood (ml/100 g tissue) expelled or mobilized from the region in response to stimuli that constrict this section of the vascular bed. Capacitance constrictor responses observed with this method will be referred to below as 'blood mobilization'. It should be emphasized that all data on 'blood mobilization' from the capacitance vessels given below were calculated from the volume records after due correction for net transcapillary fluid movement (cf. Mellander, 1960; and Fig. 4).

Contraction of the smooth muscle of the capacitance vessels is of haemodynamic significance not only by its ability to mobilize blood and thus promote venous return, but also by its ability to stiffen the walls of these vessels which enables them to resist a greater hydrostatic load than normal, and hence reduce the pooling of blood resulting from increased transmural pressure in the veins. This latter aspect of venomotor function was studied by observing the amount of blood pooled in the hand and calf in response to a standardized rise of venous outflow pressure (pressure/volume relationship of the capacitance vessels) before and after drug administration. Such information was obtained by raising the pressure in the cuffs to 50 mmHg for a period of at least 7 min which resulted in an initial rapid, and secondary slower and continuous, increase of the recorded tissue volumes. The first effect is mainly due to pooling of blood and the second to net fluid filtration into the tissue. The rate of fluid filtration is easily calculated from the latter part of the volume curve. By subtracting the amount of fluid filtered in the occlusion period from the total volume increase, a measure of the amount of pooled blood is obtained. It follows that a drug which constricts the capacitance vessels will reduce the pooling of blood in response to the standardized pressure rise compared to the corresponding value in the control period. Such capacitance effects will be referred to below as 'decreased blood pooling' and the observed decrease will be expressed as a percentage of the preceding control value.

Changes in the size of the functional capillary exchange surface produced by alterations of precapillary sphincter activity were followed by determining the capillary filtration capacity in the regions (see Mellander & Johansson, 1968; Folkow & Mellander, 1970). The filtration capacity was expressed in terms of the capillary filtration coefficient (CFC), i.e. ml fluid filtered across the capillaries per min, 100 g tissue, and mmHg transcapillary pressure gradient (e.g. Cobbold, Folkow, Kjellmer & Mellander, 1963). CFC was determined by a standardized elevation of venous outflow pressure above the level creating an isovolumetric state (for details see Mellander & Öberg, 1967).

Drug administration. l-Noradrenaline was infused intravenously with a constant rate infusion apparatus in doses ranging from 0·05 to 0·3 μg kg⁻¹ min⁻¹ during about 30 min. Dihydro-
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ergotamine-methan-sulphonate (Orstanorm®, Dihydergot®, Dihydroergotamine-Sandoz, Sandoz A.G.) was injected intravenously in a dose of 10 μg/kg bodyweight. DHE was diluted in saline (1:10 v/v) and was administered during a period of 15–30 s.

Experimental procedures. All experiments were performed with the limbs at complete rest. Most subjects received NA as well as DHE. The effects of NA were always studied first in these subjects, since the action of NA disappears rapidly upon cessation of the infusion, whereas, as will be described, the effects of DHE are maintained for at least 2 h. In some subjects, however, only the responses to DHE were studied. When both substances were given, DHE was not administered until the basal control situation after NA infusion was restored.

Heart rate (ECG) and arterial and venous pressures were followed continuously throughout the experiment. In the control periods before NA or DHE administration, hand and calf blood flows were determined repeatedly (six to ten observations). After this, the capacitance function in terms of 'blood pooling' was analysed once or usually twice, and in most cases followed by two determinations of CFC. Mean values for the different variables were calculated. When 'isovolumetric states' in the hand and calf were established (cuff pressure 20 mmHg), NA or DHE was administered; this permitted the capacitance responses in terms of 'blood mobilization' to be recorded from the beginning of drug action until a steady state was reached. From the succeeding part of the volume curve, information about net transcapillary fluid movement was obtained. In the steady state phase of drug action, blood flow, 'pooling of blood', and CFC were determined repeatedly, as described above for the control period.

At the end of the experiment, the volumes of the two studied regions were determined. The figures for tissue volume (≈ weight) given below refer to soft tissue (bone excluded). Soft tissue was considered to be 87% of total hand volume and 93% of total calf volume (bone volume determined on a medium-sized skeleton).

Experiments in cats

Experiments were performed on a total of seventeen cats, anaesthetized intravenously with a mixture of α-chloralose (50 mg/kg) and urethane (100 mg/kg). The resistance and capacitance responses and the effects on CFC of NA and DHE were studied in skeletal muscle, skin and intestine by methods modified from the ones described by Mellander (1960) which permit continuous recording of arterial inflow pressure, venous outflow pressure, regional blood flow and tissue volume. In the kidney, only the resistance function was analysed. Since the techniques used and the methods of analysing the records have been discussed in detail previously (cf. Mellander, 1960; Mellander & Johansson, 1968) reference will only be given to papers in which the preparations and the technical procedures have been described. The studies were thus performed on a calf muscle preparation (e.g. Mellander, 1966), on a skin preparation, mainly the hind paw, (Arturson & Mellander, 1964), on a segment of the jejunum (Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964), and on the kidney (e.g. Feigl, Johansson & Löfving, 1964). In most animals, observations were made in two of the above-mentioned regions at the same time. The drugs were usually administered intravenously, NA by constant infusion in doses of 0.3–1.6 μg/kg body weight, and DHE by single injection in a dose of 15 μg/kg body weight. In some animals, the drugs were given arterially close to the regions (15 μg/kg tissue), and were then administered via a short T-tube catheter which diverted flow from a proximal to a distal part of the cognate artery of the region. In some animals the
autonomic innervation was left intact throughout the experiment and in others the regional nerve fibres were severed before drug administration.

The capacitance responses (‘blood mobilization’) were expressed in % of the regional blood volume which was taken to be 2.5 ml/100 g skeletal muscle tissue, 4.0 ml/100 g skin tissue (e.g. Mellander, 1960) and 8 ml/100 g intestinal tissue (Folkow et al., 1964) in preparations with intact sympathetic innervation. The extent by which regional blood volume increased upon denervation was directly recorded in the individual experiments.

RESULTS

The results will be presented in four main sections, in which the effects of NA and DHE are described for healthy male subjects, healthy women, patients with orthostatic hypotension and animals.

In most subjects, no untoward effects of the drugs were noticed. A few of them, however, experienced minor discomfort 1–2 min after the injection of DHE in terms of slight nausea or dyspnoea and occasionally, a feeling of oppression in the chest. In no case was any change in the ECG recorded. The above-mentioned side-effects usually subsided very quickly and never lasted for more than 10 min.

Vascular effects in healthy male subjects

The time courses of the vascular responses to NA and DHE (development and duration) were studied in different ways. The capacitance response in terms of ‘blood mobilization’ was recorded in all experiments from the time of drug administration until a steady state capacitance effect was obtained. The maintenance of the vascular effects could be judged roughly by comparison of data obtained on repetitive determinations of the various vascular functions and was analysed more specifically in a few subjects by measuring, as frequently as possible, the blood flow and the capacitance response in terms of ‘blood pooling’ for a period of 2 h after the drug administration. The following conclusions could be drawn from such experiments. With regard to DHE, the vascular effects appeared 30–60 s after the start of the drug injection and steady state effects were usually reached within 8–12 min. The resistance and capacitance responses were then maintained at this level for the period of observations (2 h), except for minor random variations no greater than those observed in the control period. These slight variations were apparently due to spontaneous alterations of vasomotor activity and smooth muscle tone. The vascular effects of NA appeared within 1 min after the onset of the infusion. Steady state effects were reached within 6–10 min, and then showed only minor fluctuations. Upon cessation of the NA infusion, the vascular functions returned to the control levels within 15–20 min. Steady state vascular effects thus were elicited within some 10 min after drug administration and were then maintained at this level: For NA, during the entire infusion period, and for DHE, for at least 2 h despite the fact that this drug was applied by single injection. This implies that all vascular responses reported below, although determined at somewhat different times, can be considered steady state effects.

Effects in resistance and capacitance vessels. Table 1 summarizes control data before the administration of the drugs (usually two control periods in each subject).

NA caused a decrease in heart rate in all experiments, on the average by seven beats/min compared to the mean control value. Mean arterial pressure rose in all these experiments on
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The effects of DHE on heart rate varied: In seven experiments there was a slight decrease, in seven experiments a slight increase, and in two cases it did not change from the control level. The mean value for heart rate during the action of DHE was virtually unchanged (62 ± 8 beats/min) from the control mean value. DHE caused a rise of mean blood pressure in fifteen out of sixteen experiments to a mean value of 100 ± 12 mmHg, the average rise being 9 mmHg above mean control level (Table 2).

### Table 1. Circulatory data in man in the control period at rest (mean values ± SD)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial blood pressure (mmHg)</th>
<th>Blood flow ml 100 g tissue⁻¹ min⁻¹</th>
<th>“Blood pooling” at cuff pressure 50 mmHg ml 100 g tissue⁻¹</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy males</td>
<td>61 ± 7</td>
<td>91 ± 11</td>
<td>5.3 ± 3.0 2.5 ± 1.1</td>
<td>2.6 ± 0.8 4.6 ± 1.0</td>
<td>30</td>
</tr>
<tr>
<td>Healthy females</td>
<td>67 ± 9</td>
<td>87 ± 6</td>
<td>3.3 ± 1.5 2.0 ± 0.5</td>
<td>3.7 ± 0.7 4.7 ± 1.3</td>
<td>4</td>
</tr>
<tr>
<td>Orthostatic patients</td>
<td>79 ± 10</td>
<td>90 ± 8</td>
<td>4.3 ± 3.9 2.8 ± 1.1</td>
<td>2.7 ± 0.7 4.2 ± 1.0</td>
<td>5</td>
</tr>
</tbody>
</table>

Fig. 1. Original record of the capacitance responses in terms of ‘blood mobilization’ (decreased tissue volume) in hand (upper panel) and calf (lower panel) elicited by dihydroergotamine (DHE), 10 μg/kg i.v. The figures for ‘blood pooling’ in the capacitance vessels at cuff pressure of 50 mmHg (ml/100 g tissue), for regional resistance (peripheral resistance units, PRU), and capillary filtration coefficient (CFC), (ml min⁻¹ 100 g⁻¹ mmHg⁻¹) are also given for both regions: To the left before drug administration, and to the right under the steady state phase of drug action.
Fig. 1 is an original record of the volume in the hand and calf evoked by DHE. In the control period before drug administration the tracings show approximate isovolumetric states of the tissues, the small undulations being due to ‘vasomotion’. The constrictor response of the capacitance vessels (‘blood mobilization’) starts in the hand about 30 s, and in the calf about 90 s after the injection of DHE, as illustrated by the declining volume curves. About 8 min after the onset of the capacitance responses, the two curves again become isovolumetric, although at lower levels. The steady state constrictor responses of the capacitance vessels were reached at this point (in this particular experiment there was no net transcapillary fluid movement, see below). It can be seen that DHE caused a mobilization of about 1.6 ml of blood/100 g tissue in the hand and of 0.9 ml/100 g tissue in the calf. Local venous pressure remained constant throughout the observation period. The data on ‘blood pooling’, resistance and CFC are also given in the figure, those obtained in the control period shown to the left and those observed in the steady state phase of DHE action to the right. The amount of blood pooled decreased from 2.1 to 1.3 ml/100 g tissue in the hand, or by 38%, and from 3.8 to 2.9 ml/100 g tissue in the calf, or by 24%. In spite of these strong constrictor effects in the capacitance vessels the regional resistances (PRU) changed very little (increased by 5% in the hand and decreased by 5% in the calf). It can be seen from the volume curves that in this particular experiment where the resistances were virtually unchanged, there was no net transcapillary fluid movement (cf. Mellander & Johansson, 1968) as evidenced by the establishment of isovolumetric states of the tissues in the steady state phase of drug action. CFC, finally, was largely unaltered by DHE.

Fig. 2 summarizes the steady state responses of the resistance and capacitance vessels in the hand and calf to NA (open circles) and DHE (closed circles) observed in healthy males. In

![Graph](image-url)
Vascular effects of dihydroergotamine

In this diagram, the effects in the resistance vessels (abscissa) are plotted against the concomitantly evoked effects in the capacitance vessels (ordinate). Since in most experiments, the capacitance function was studied by two different methods, there are two diagrams on top of each other for each region; in the lower diagrams the capacitance responses were recorded in terms of ‘blood mobilization’ (ml/100 g tissue), and in the upper ones in terms of decrease of ‘blood pooling’ (per cent of control value). The thin vertical line at the zero point on the abscissa represents the control resistance before drug administration.

It can be seen from the diagram (right panel) that NA and DHE in virtually all experiments elicited constrictor responses in both the resistance vessels and the capacitance vessels of the hand. The resistance increase evoked by DHE ranged from a few per cent up to about 220% above control level. This variation may be due to different individual 'sensitivity' to the drug and to varying amounts of the drug distributed to the hand circulation via the blood stream. The dose of NA given to the different subjects (0.05–0.3 μg kg⁻¹ min⁻¹) was adjusted so as to elicit resistance responses within roughly the same range as produced by DHE. Although the constrictor effects in the resistance vessels thus can be considered roughly comparable for the two drugs, this does not seem to be true for the constrictor effects in the capacitance vessels. The results show considerable individual variation, but inspection of the points seems to indicate that at almost any given level of resistance vessel constriction, the concomitant constrictor effect in the capacitance vessels is more pronounced for DHE than NA.

The left panel of the diagram shows the simultaneous results observed in the vascular bed of the calf. It can be seen that the effects of the two drugs are quite different. NA always elicited a constriction of the resistance vessels, whereas in two thirds of the subjects DHE evoked dilator responses in these vessels. In five of the experiments, DHE caused a moderate increase of resistance. Despite these different effects of the two drugs on the resistance vessels, DHE appears to elicit more pronounced constrictions of the capacitance vessels than NA. It may further be noticed from the figure that, except for a few cases, the two different methods for recording capacitance responses have given relatively consistent results in the individual experiments.

The data for the resistance and capacitance effects of NA and DHE (Fig. 2) are summarized in Fig. 3 in which the mean values (±SEM) for all observations are calculated. In the calf, NA increased regional resistance by an average of 39% above control level, whereas the mean value for resistance during DHE administration was not much changed from the control level (−0.5%). This difference between the two drugs is significant (P<0.001). Nevertheless, the mean capacitance constrictor response was greater with DHE than NA. Thus, NA caused an average ‘blood mobilization’ of 0.6, and DHE of 1.1 ml/100 g tissue, the latter figure being significantly greater (P<0.001). ‘Pooling of blood’ decreased by 14% with NA and by 23% with DHE (P<0.02). In the hand, the mean resistance increase was somewhat higher with NA than DHE, but the difference is not statistically significant (nor was this expected since the dose of NA was adjusted to give cutaneous resistance changes similar to those of DHE). The amount of blood mobilized was 1.0 ml/100 g tissue for NA and 1.6 ml/100 g tissue for DHE. The latter value is significantly greater (P<0.005). ‘Blood pooling’ was decreased by 26% with NA and by 40% with DHE (P<0.05). The data for DHE are also presented in Table 2. The conclusion is that DHE is a more efficient constrictor of the capacitance vessels than NA in both skin and skeletal muscle, and that in skeletal muscle DHE, in contrast to NA, can elicit this constrictor response without much affecting the resistance vessels.
Regional blood volume in the leg of healthy males in the supine posture is reported to be 5.5 ml/100 g tissue (Arenander, Carlsten, Grimby, Hallberg & Westling, 1962). If this figure is used, the average capacitance response in terms of 'blood mobilization' produced by DHE can be calculated to be 20% of regional blood volume in muscle and 29% in skin.

The effects of DHE on the resistance and capacitance vessels in the forearm (mainly muscle tissue) were studied in one subject. The forearm data were found to be very similar to the mean values for the calf presented in Fig. 3 indicating that the differentiated pattern of response within resistance and capacitance vessels to DHE described above for the calf region seems to be representative of the vascular reactions in skeletal muscle in general.

DHE is believed to exert some central inhibitory action on adrenergic vasoconstrictor fibre discharge which would tend to elicit a dilator effect in the peripheral circulation. There was some indication of such an effect in the capacitance vessels in six of the studied subjects who showed a clearcut but transient increase of tissue volume (dilatation of the capacitance vessels) within 60 s after the injection of DHE. This effect which lasted for 30–60 s was only seen in the calf and not in the hand (and may also be present to some slight extent in the calf volume record of Fig. 1, which then could explain the delayed onset of the capacitance constrictor response as compared to that of the hand). DHE evoked a maintained slight dilator response in the calf
Vascular effects of dihydroergotamine

resistance vessels in the above-mentioned six subjects. It appears that a neurogenic inhibition is involved in the dilator response of the muscle resistance vessels in which it is not counter-balanced by any significant direct constrictor influence of DHE.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Calf Capacitance</th>
<th>Hand Capacitance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 16</td>
<td>+1</td>
<td>+9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>n = 16</td>
<td>n = 16</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>n = 16</td>
<td>n = 16</td>
</tr>
<tr>
<td>Resistance (%)</td>
<td>-0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>'Blood mobilized'</td>
<td>1.1</td>
<td>-23</td>
</tr>
<tr>
<td>'Blood pooling' (%)</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Healthy females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 4</td>
<td>-4</td>
<td>+10</td>
</tr>
<tr>
<td>Orthostatic patients</td>
<td>n = 5</td>
<td></td>
</tr>
<tr>
<td>n = 5</td>
<td>-2</td>
<td>+10</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>+86</td>
<td>1.6</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>1.4</td>
<td>-40</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>1.4</td>
<td>-30</td>
</tr>
<tr>
<td>Blood (%)</td>
<td>1.3</td>
<td>-39</td>
</tr>
</tbody>
</table>

In the cutaneous circulation, constrictor fibre tone might have been lower than in skeletal muscle due to the relatively high temperature of the environment in the present experiments. A possible adrenergic inhibitor effect of DHE might therefore not have been revealed in the hand resistance vessels. Therefore, three experiments were done in which vascular tone in the hand was raised reflexly by lowering room temperature to 19-20° to test if, under these circumstances, a skin dilator response could be obtained. In spite of the fact that regional resistance in the hand was markedly increased by this manoeuvre, DHE administration never caused a resistance vessel dilatation, but instead further increased resistance by an average value of 82%.

To test whether the well known α-adrenergic blocking effect of large doses of DHE was exerted by the relatively small amounts of the drug (10 μg/kg body weight) given in the present experiments, the resistance effects of NA were compared in the calf in two subjects before and after the administration of DHE. DHE per se caused virtually no resistance effects. The resistance increase caused by NA before and after DHE was, however, of the same order of magnitude indicating that the α-blocking effect of the dose of DHE used in the present experiments was negligible.

Effects on precapillary sphincters. The effects of DHE and NA on the precapillary sphincters were analysed in some of the subjects by comparing the capillary filtration coefficient in the control period and during the action of the drugs. CFC was usually affected very little, as can be seen from Table 3, in which the mean values (±SD) of all observations are given. Neither drug in the doses used caused any statistically significant change of CFC in the hand or the calf. The conclusion may be drawn that the size of the functional capillary surface area and,
hence, the activity of the precapillary sphincters was virtually unaffected by the two drugs in these experiments. Since CFC was determined only in a limited number of subjects, the ranges of the evoked resistance changes in these experiments are also shown in the table.

**TABLE 3. Effect on capillary filtration coefficient (CFC) of DHE and NA in man (mean values ±SD)**

<table>
<thead>
<tr>
<th>Region</th>
<th>CFC Control</th>
<th>DHE</th>
<th>% Change of resistance (range)</th>
<th>n</th>
<th>CFC Control</th>
<th>NA</th>
<th>% Change of resistance (range)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td>0.0061</td>
<td>0.0070</td>
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<td>8</td>
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<td>0.0060</td>
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</tr>
<tr>
<td></td>
<td>±0.0016</td>
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<td></td>
<td></td>
<td>±0.0011</td>
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<td>0.0040</td>
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<td>10</td>
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<td>0.0046</td>
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<tr>
<td></td>
<td>±0.0008</td>
<td>±0.0012</td>
<td></td>
<td></td>
<td>±0.0003</td>
<td>±0.0009</td>
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</table>

**Effects on the ratio of pre-/post-capillary resistance.** This ratio is one of the main determinants of mean hydrostatic capillary pressure and, therefore, of the fluid balance between the intravascular and extravascular compartments (see Mellander & Johansson, 1968). The effects of NA and DHE on this vascular function were analysed in the hand and calf (a total of twenty-three observations) by volumetric measurement of the rate of net transcapillary fluid movement, if any, in the phase of steady state drug action after the capacitance response was fully developed (see Fig. 1). In this particular experiment, in which the resistances of the hand and calf were not much changed, DHE caused no significant net transcapillary fluid movement as shown by the return of the volume curves to the horizontal level after the elicitation of the capacitance responses. This indicates that the ratio of pre-/post-capillary resistance, and capillary pressure, were not changed from the control values by DHE. The results were similar in other experiments in which DHE produced a dilatation of the resistance vessels. In only one of these experiments DHE led to a slight net transcapillary filtration, corresponding to an increase of capillary pressure of about 1 mmHg (see Fig. 4).

A net transcapillary absorption of extravascular fluid was, however, always observed in the experiments where DHE or NA elicited clearcut constrictor effects in the resistance vessels of the hand or calf. The fall of mean hydrostatic capillary pressure (mmHg) in these experiments could be calculated by dividing the value for the observed rate of fluid movement (ml 100 g⁻¹ min⁻¹) by the CFC value (ml min⁻¹ 100 g⁻¹ mmHg⁻¹) determined during drug action. Such data are shown in Fig. 4 in which the calculated value for the decrease of capillary pressure is plotted against the recorded increase of regional resistance in each experiment. There appears to be an approximately straight line relationship between the capillary pressure drop and the resistance increase, and the regression line shows good correlation (r = 0.90). The ordinates to the right in the diagram indicate the rates of net transcapillary fluid absorption. These findings show that when total regional resistance was increased by the drugs, they also constricted the precapillary resistance vessels relatively more than the postcapillary resistance vessels (or increased the ratio of pre-/post-capillary resistance).
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Vascular effects in healthy women

In this series of experiments which consisted of only four subjects the main attention was paid to the vascular effects of DHE. Since the effects evoked were similar to those observed in men, only the mean values of the results will be presented.

The control data for heart rate, mean arterial blood pressure, and for blood flows and 'blood pooling' in the hand and calf are presented in Table 1.

During the action of DHE, heart rate decreased by 4 beats/min and mean arterial blood pressure rose by 10 mmHg, on the average. In the calf DHE increased regional resistance in

three subjects and decreased it in one, the mean value being an 8 ± 7 (SEM) % increase above control level. The capacitance vessels always showed constrictor responses. The average 'blood mobilization' was 0.9 ± 0.2 ml/100 g tissue and the 'pooling of blood' was decreased by 28 ± 2%. In the hand, the mean resistance increase to DHE was 20 ± 12%, the 'blood mobilization' 1.4 ± 0.7 ml/100 g tissue and the decreased 'pooling of blood' 30 ± 4%. The effects on the resistance and capacitance vessels of DHE in this small series of women are thus in good agreement with those observed in men (see Table 2) with the exception of a smaller increase of resistance in the hand. NA was given to one woman in whom it constricted the resistance as well as the capacitance vessels in both the hand and calf. For a given increase of resistance the capacitance response was much smaller with NA than DHE, thus confirming the results obtained in men.

The other vascular effects were also similar in both sexes. Thus, DHE caused virtually no change of CFC in either the hand or the calf in the women. Further, transcapillary fluid ex-
change was affected in the same way as in the male subjects, i.e. there was some absorption of extra-vascular fluid when DHE increased resistance in the regions, but no net fluid exchange in the subject who showed a resistance vessel dilatation in the calf.

**Vascular effects in patients with orthostatic symptoms**

The effects of DHE were studied in five patients who showed both subjective and objective symptoms of orthostatic hypotension. Their main complaints were palpitations, dizziness, and sometimes attacks of fainting when rising from supine to erect posture. Upon shift from lying to standing position, the following changes were obtained within 10 min (mean values for all subjects): Heart rate increased by 39%, systolic blood pressure decreased by 23%, pulse pressure decreased by 44%, and diastolic pressure either increased or decreased, the average change being $-1\%$.

The vascular effects of DHE were studied in the supine position, as in the healthy subjects. The average circulatory data obtained in the control period are given in Table 1. During the action of DHE, heart rate decreased by 2 beats/min, and mean arterial blood pressure increased by 10 mmHg, on the average. DHE lowered regional resistance in the calf in two of five subjects and caused a slight increase in three, the mean change being an increase of $6\pm4\%$ above control level. The calf capacitance vessels were always constricted by DHE. On the average the amount of blood mobilized from the capacitance vessels was $1.7\pm0.2$ ml/100 g tissue and the decrease of ‘blood pooling’ was $29\pm6\%$. The corresponding mean values of the results in the hand were as follows: Resistance increase, $35\pm14\%$; ‘blood mobilization’, $1.3\pm0.3$ ml/100 g tissue; and decrease of ‘blood pooling’, $39\pm9\%$.

Comparison of these data for the resistance and capacitance functions with the corresponding figures in healthy subjects (Table 2) shows that the vascular effects caused by DHE were similar in orthostatic and normal persons.

Finally, there were virtually no effects of DHE on the capillary filtration coefficient and the effects on transepithelial fluid movement were similar to those observed in healthy subjects. Thus, the effects of DHE on precapillary sphincters and on the ratio of pre-/post-capillary resistance were also very much the same as in normal persons.

**Vascular effects in anaesthetized cats**

The main object of this study was to investigate the effects of DHE on the peripheral vascular functions in skeletal muscle, skin, intestine, and kidney before and after regional sympathectomy. DHE was usually administered intravenously in a dose of 15 μg/kg body weight. In a few experiments in which the regions were denervated, DHE was given close arterially in a dose of 15 μg/kg tissue; the results from such experiments did not differ much from the corresponding ones in which DHE was administered intravenously. The time required to reach a steady state effect of DHE in the resistance and capacitance vessels was usually quite long as in man, from 6 to 10 min both after intravenous and intra-arterial injection. The drug was usually applied only once in each experiment; when occasionally the DHE injection was repeated, this was not done until the vascular effects of the previous injection had disappeared.

Table 4 summarizes the average effects of DHE on the resistance and capacitance vessels and on CFC, expressed as a percentage of the control values at rest. Since the regional blood content in these regions has been reasonably well established under comparable experimental conditions (see Methods section), the capacitance responses were here expressed as a percentage
Vascular effects of dihydroergotamine

of these figures. In the kidney only the resistance function was studied. It can be seen that the patterns of response in skeletal muscle and skin with intact innervation were quite similar to those reported above for man, even from a quantitative point of view. (The 'blood mobilization', 16 and 27% of regional blood volume, in muscle and skin of cats should be compared with the corresponding figures, 20 and 29% in man.) After sympathectomy there was in all cases a reversal of the dilator response of the muscle resistance vessels to a constriction and the resistance increase in skin tended to be reinforced. Both regions showed constrictor responses of the capacitance vessels of similar order of magnitude as with intact nerves. In no case was CFC significantly changed from the control values by DHE. The resistance responses to DHE in the innervated intestine and kidney were always small, but variable. Gut resistance increased in three experiments (mean +14%) and decreased in two (mean −17%), giving an

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Sympathetic nerves</th>
<th>Resistance (%)</th>
<th>'Blood mobilization' in % of regional blood volume</th>
<th>CFC (%)</th>
<th>Duration of response (min)</th>
<th>n</th>
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<tr>
<td>Skeletal</td>
<td>intact</td>
<td>−8</td>
<td>16</td>
<td>±0</td>
<td>&gt;30</td>
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<td>10</td>
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<tr>
<td>Skin</td>
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<td>27</td>
<td>−2</td>
<td>&gt;30</td>
<td>4</td>
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<tr>
<td></td>
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<td>3</td>
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<td>Intestine</td>
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<td>5</td>
<td>−7</td>
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<td>5</td>
</tr>
<tr>
<td></td>
<td>denervated</td>
<td>+6</td>
<td>8</td>
<td>−4</td>
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<td>4</td>
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<tr>
<td>Kidney</td>
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<td>—</td>
<td>—</td>
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<td>6</td>
</tr>
<tr>
<td></td>
<td>denervated</td>
<td>+11</td>
<td>—</td>
<td>—</td>
<td>&lt;20</td>
<td>6</td>
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</table>

average value of +2%; kidney resistance increased in three (mean +20%) and decreased in three (mean −21%) giving, on the average, virtually no change at all. After denervation, DHE always elicited slight resistance increases in both intestine and kidney. The capacitance vessels of the gut showed slight constrictor responses both before and after denervation, whereas CFC was not much affected. The duration of the vascular responses was always longer in muscle and skin than in intestine and kidney.

NA evoked clearcut constrictions of the resistance vessels in all four regions both before and after sympathectomy and these responses were not much altered when NA infusion was repeated after DHE administration. The latter finding suggests that in the doses used DHE did not cause any significant α-adrenergic blockade.

Propranolol in a dose of 200 μg/kg body weight intravenously did not change the resistance responses to DHE, suggesting that DHE did not significantly affect β-adrenergic receptors in these vascular beds in one way or another.

DISCUSSION

The present study provides quantitative information about the reactions elicited by dihydroergotamine and noradrenaline in the precapillary and postcapillary resistance vessels, the precapillary sphincters, and the capacitance vessels of skin and skeletal muscle in man. The results
S. Mellander and I. Nordenfelt showed that the two drugs acted in a qualitatively similar way in the cutaneous vascular bed, i.e. they constricted resistance and capacitance vessels, increased the ratio of pre-/post-capillary resistance, but did not influence the precapillary sphincters. The pattern of response was similar in skeletal muscle for NA, and also for DHE, with the important exception that the latter drug usually evoked a dilator response in the muscle resistance vessels (Fig. 2). Another important difference was that the constrictor response of the capacitance vessels was quantitatively more pronounced for DHE than NA in both regions (Fig. 3). These results were confirmed in cat experiments which, further, showed that the effects of DHE on the intestinal and renal vascular circuits were relatively small (Table 4).

The effects of DHE on the resistance function in man has been studied earlier in quantitative terms, but apparently only in skin. Gatzek, Matthes & Mechelke (1949) reported increased resistance in the human ear, but some dilatation in the finger. Bluntschi & Goetz (1948) observed constrictions of resistance vessels in the toe in sympathectomized humans indicating a direct constrictor effect of DHE on the cutaneous vascular smooth muscle. A constrictor effect of DHE in the capacitance vessels was suggested by Rieckert & Pauschinger (1967) who studied pressure/volume curves of human veins.

In the present study on intact humans constriction of the resistance vessels in the hand was seen in all but one experiment, but the resistance increase was relatively moderate (up to about three times control resistance) compared to a more than hundredfold increase that can be elicited by maximal vasoconstrictor fibre activation (see Mellander & Johansson, 1968). The virtual absence of constriction, or even dilatation, of the resistance vessels in muscle tissue observed in this study suggests that the mode of action of DHE is somewhat different in muscle and skin. It seems clear from the present results that DHE is a more effective constrictor of capacitance than of resistance vessels in both muscle and skin. The amount of blood mobilized from the capacitance vessels by DHE in healthy males was on the average 1.1 ml/100 g muscle and 1.6 ml/100 g skin tissue (Table 2). The regional blood volume in the leg of healthy males has been estimated to be about 5.5 ml/100 g tissue in the supine position (Arenander et al., 1962). If this figure is used for an approximate calculation of the fraction of the regional blood volume that can be mobilized by DHE, a figure of at least 20% is obtained. This should be compared to the value for the maximum capacitance response evoked by strong vasoconstrictor fibre activation, which amounts to about 30% of regional blood volume (Mellander & Johansson, 1968). Since constrictor fibre activation leads to an associated strong constriction of the resistance vessels and, therefore, to lowered venous pressure, part of the neurogenic capacitance response is a passive phenomenon (cf. Öberg, 1967). The figures for the capacitance responses to DHE in muscle and skin are thus quite impressive in view of the fact that the concomitant resistance effects were moderate; in muscle, where resistance was hardly changed at all, the capacitance response can be considered the result of true active venoconstriction.

The following rough calculation may serve to illustrate to what extent general haemodynamics in an adult male subject (70 kg) might be influenced by the capacitance constrictor responses of DHE. Let us consider first the response in terms of ‘blood mobilization’ assuming, as suggested by some of the results above, that the average data obtained in the calf and hand are applicable to all skeletal muscle and skin regions. The volume of blood mobilized from, say, 30 kg of skeletal muscle and 2 kg of skin by DHE in the supine position, using the figures of 1.1 ml/100 g muscle and 1.6 ml/100 g skin (Table 2), would then amount to a total of about 360 ml. It is evident that such an increase of ‘central’ blood volume would influence general
cardiovascular dynamics markedly. The capacitance response in terms of decreased 'blood pooling', another aspect of venomotor function, is relevant for dependent regions in the erect posture. In a normal subject, 300–500 ml of blood is reported to be displaced into the legs upon rising (Asmussen, Christensen & Nielsen, 1939; Barbey & Brecht, 1965). The total amount of blood pooled in all dependent regions must be still larger. If by crude approximation we assume that 500 ml of blood is pooled in dependent parts in healthy subjects upon rising, and that by DHE action the average pooling is decreased by about 25% (Table 2), the 'gain for the central circulation' would be about 125 ml of blood. This gain produced by DHE might be even greater in orthostatic patients who, without treatment, are characterized by greater tendency for blood pooling and, possibly, also greater capacitance effects of DHE (Table 2).

With reservations for the above crude calculations, the constrictor responses of the capacitance vessels observed in this study are offered as a main explanation for the beneficial effects of DHE in orthostatic hypotension.

The data related to the effects of DHE and NA on the ratio of pre-/post-capillary resistance were illustrated in Fig. 4. Admittedly, the effects on net transcapillary fluid movements were small, but, nevertheless, not negligible in experiments where the drugs evoked constrictions of the resistance vessels. An arbitrary example (taken within the range of responses shown in Fig. 4) may serve to illustrate this point. Let us assume that DHE raised resistance in all muscles (30 kg) by 25%, and in all skin (2 kg) by 100% above control levels and that, as shown in results section, these effects will last for at least 1 h. With an average fall of the capillary pressure of 1.5 mmHg in skeletal muscle at this resistance increase (see regression line), the total amount of fluid absorbed from the extravascular space in this tissue would be about 110 ml/h. In the skin, with an average capillary pressure drop of 5 mmHg, fluid absorption would occur at a rate of about 35 ml/h. The seemingly small effects on the ratio of pre-/post-capillary resistance of DHE in muscle and skin might thus, in this case, theoretically lead to an increase of plasma volume in the supine posture by about 150 ml in a period of 1 hour.

The capillary filtration coefficient was not significantly changed by DHE or NA in the doses given. CFC reflects both the capillary surface area available for exchange and the permeability of the capillary membranes. The results can therefore, most likely, be taken to indicate that neither of these two factors were altered by the drugs (cf. Mellander & Johansson, 1968; Folkow & Mellander, 1970). It follows that the precapillary sphincters, which determine the size of the functional capillary surface area, were virtually unaffected. The finding that CFC was not changed by DHE suggests that capillary function and, hence, tissue nutrition was not impaired in skin and muscle. This seems to be an important observation in view of the well-known toxic effects on the microcirculation caused by its parent compound, ergotamine, which can result in the development of gangrene.

Comparison of the results obtained in the experiments on cats with innervated and denervated vascular beds (Table 4) may permit the following conclusions about the modes of action of DHE. The constrictor effects of DHE are mainly, or entirely, due to a direct excitatory action on the vascular smooth muscle effectors; the slight dilator responses noted in the resistance vessels of skeletal muscle, intestine and kidney with intact autonomic nerves can be related to a central inhibitory action of DHE on autonomic nervous structures resulting in decreased sympathetic constrictor fibre discharge. In no case were dilator effects elicited in these resistance vessels after sympathectomy and the constrictions of the cutaneous resistance vessels seemed to be somewhat reinforced after denervation (Table 4). This latter finding, and the
fact that, in the intact human, the capacitance vessels of muscle sometimes showed initial, but transient, dilatation before the development of the strong constrictor response in the steady state phase of DHE action (see results section) may suggest that some central inhibitory action of DHE on adrenergic constrictor fibre discharge was present in most vascular circuits and sections. A steady state net dilator effect of such an action, however, seemed to be detectable only in those sections where the counterbalancing direct constrictor effect of DHE was weak.

No significant $\alpha$-adrenergic blocking effect on the vascular smooth muscle of DHE in the doses used was revealed in the present studies on humans and cats. Yet a minor $\alpha$-blocking effect cannot be entirely ruled out (cf. Aellig, 1967). It might further be possible that DHE by a direct action or by an indirect effect via release of adrenaline from the adrenal medullae, could have exerted some stimulatory action on $\beta$-adrenergic receptors. It is known that the dilator effects of $\beta$-receptor stimulating agents are confined to precapillary vessels mainly, at least in skeletal muscle (see Mellander & Johansson, 1968). Further, adrenaline is the only substance for which a pattern of response has been described which resembles that elicited by DHE: adrenaline can be applied in doses which cause a dilatation of resistance vessels and a constriction of capacitance vessels in skeletal muscle (Mellander, 1960). Yet, any significant $\beta$-adrenergic stimulatory action of DHE seemed to be refuted by the finding that the vascular responses were unchanged after the administration of propranolol.

It can be concluded from the present experiments in man and animals that DHE has a preferential and strong constrictor action on the capacitance vessels in skin and skeletal muscle tissues without much affecting the resistance vessels in skeletal muscle, intestine or kidney, or the precapillary sphincters in muscle, skin, or intestine. A theoretical basis for suggesting the use of the drug in circulatory disorders characterized by impaired vasomotor regulation of the capacitance function may thus be established. Before too far-reaching conclusions be drawn, however, further studies are required in which, for instance, the effects of DHE on the central circulation are analysed, including measurements of cardiac output, stroke volume, etc. Such studies are in progress.

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