Comparison of the Reflex Reactivity of Skin and Muscle Veins in the Human Forearm

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ABSTRACT To determine the relative participation of skin and muscle capacitance beds of the forearm in venomotor reflexes, epinephrine iontophoresis was combined with forearm plethysmography so that the volume of muscle veins could be estimated simultaneously with the volume of cutaneous veins, at a constant venous pressure. With this technique not only are the cutaneous veins markedly constricted but they also are prevented from filling since skin blood flow is abolished. In 10 normal subjects, the venous volume in the elevated control forearm at a congesting pressure of 30 mm Hg (VV[30]) was 3.16 ±0.30 SEM cc/100 cc, while in the iontophoresed arm it was 2.54 ±0.31 cc/100 cc. Thus the forearm cutaneous VV[30] was 1.62 cc/100 cc. With a deep breath, ice to the forehead, and leg exercise, and cutaneous VV[30] decreased 19.8% ($P < 0.01$), 36.6% ($P < 0.01$), and 32.6% ($P < 0.02$), respectively, whereas the muscle VV[30] was not altered significantly. Similar results were observed using the isolated forearm technique and a deep muscle vein. The infusion of epinephrine intra-arterially did not decrease reflex venomotor reactivity until cutaneous blood flow was completely suppressed, indicating that the inability of the veins to react in the iontophoresed arm was not the result of epinephrine diffusion into the muscle bed. Thus, these results indicate that, in the forearm, only cutaneous veins participate in venomotor reflexes. Further, since the forearm is principally composed of skeletal muscle and the hand skin, an explanation is provided for the observation that veins of the forearm, studied as a whole, appear less reactive to stimuli than veins of the hand. An explanation also is provided for fainting which occurs during motionless standing despite intense venoconstriction, thereby emphasizing the importance of the skeletal muscle pump in the legs in preventing postural syncope.

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INTRODUCTION

It is well established that the distensibility of the capacitance vessels can be diminished actively through reflexes mediated by the sympathetic nervous system (1–10); the traditional view is that this constriction occurs equally in all components of the peripheral venous system. Recently, however, studies in experimental animals have suggested that there is a different relative responsiveness of certain venous segments to nerve stimulation. Thus, it has been observed by Webb-Peploe and Shepherd that the distal segment of canine saphenous vein is more reactive to electrical stimulation of the lumbar sympathetic chain than the segment proximal to the entrance of the first deep muscle vein (11). This finding led us to consider the possibility that the venous beds of skin and skeletal muscle in man might demonstrate differential reflex venoconstriction. In order to examine the effects of sympathetic stimulation on the distensibility of these capacitance systems, epinephrine iontophoresis (12–16) was employed so that the dynamics of muscle veins could be measured simultaneously with those of cutaneous veins, at a constant venous pressure or venous volume. During iontophoresis, epinephrine is selectively deposited in the skin of the forearm, thereby causing an effective suppression of skin blood flow as well as an intense cutaneous venoconstriction. In this manner, plethysmographic measurements of the forearm, which has undergone iontophoresis, are those of the capacitance bed in muscle, whereas simultaneous measurements on the untreated forearm reflect both the skin and muscle veins; the difference

between the dynamics of the two forearms provides an assessment of cutaneous venomotor response.

METHODS

Studies were performed in the recumbent position in 10 normal male subjects between the ages of 21 and 39 yr. Venous reactivity in the forearm induced by reflex sympathetic stimulation was studied by two methods. In the first or equilibration technique (1, 8, 17), carried out in all subjects, the venous volume of the forearm at a congesting pressure of 30 mm Hg (VV[30]) was measured with a mercury-in-rubber strain gauge plethysmograph (18, 19). In this method, venous occlusion was produced by suddenly inflating a sphygmomanometric cuff, 13 cm wide, placed around the upper arm to a pressure of 30 mm Hg; equilibration of venous pressure with cuff pressure was permitted for 3 min at which time the venous volume remained constant. Before venous congestion, it was measured by elevation of the forearms that the venous pressures of both arms were equal and less than 1 mm Hg. The intervention was then applied and the induced changes in venous volume were taken as a measure of venomotor reactivity, a decrease of limb volume indicating venoconstriction.

The second method, the isolated forearm technique (3, 9, 20–22), was performed in four subjects; the upper arm cuff was inflated to a level exceeding systolic arterial pressure and the forearm venous pressure was measured through a 14 cm PE50 catheter passed percutaneously retrograde from the antecubital vein into a deep muscle vein. Since the volume of the forearm was maintained constant by the occluding cuff, any change in venous pressure represented an alteration in the compliance of the forearm venous bed. Before carrying out measurements of venous tone with either method, the hand was excluded from the circulation by the inflation of a wrist cuff to suprasystolic pressure (23).

Epinephrine iontophoresis (12–16) was performed by wrapping the arm, which had been cleansed with acetone and ether, in a gauze bandage soaked with epinephrine hydrocholoride, 1:2000 (pH 4.5). This was covered by aluminum foil which served as the positive electrode and was secured by an elastic bandage. The leg served as the negative electrode and was similiarly wrapped, except that saline replaced the epinephrine solution. Complete iontophoresis occurred with a current of 20 ma applied for 20 min (16).

Reflex venoconstriction was elicited by having the subject take a deep breath, calculate a mathematical problem, perform supine leg exercise with a bicycle ergometer for 1–3 min at 330 ft lb/min, and by applying ice to the forehead for 1 min (10, 24, 25). During all interventions employing both the equilibration and isolated forearm techniques, the changes in venous compliance in the iontophoresed forearm were compared with those in the control, simultaneously recorded, contralateral forearm. In the equilibration method, at a constant venous pressure, the difference between the volumes of the two forearms allowed quantitative determination of cutaneous venous volume. In the isolated forearm technique, at a constant volume, changes in venous reactivity in the skin were reflected by the differential change in venous pressure of the control and treated forearms.

In the forearm of two subjects, epinephrine was infused into the brachial artery at a rate of 1, 2, and 4 μg/min. Infusion of the agent was maintained at each level for 5 min to allow achievement of a stable state; there were no waiting periods between each infusion. Forearm blood flow was measured by the venous occlusion technique as described in previous reports (26) at 15-sec intervals during the infusion. In addition, before and during each level of intra-arterial epinehprine infusion, venomotor reactivity in response to a deep breath was determined for the treated forearm by comparing the changes in its venous volume by the equilibration method with that measured simultaneously in the contralateral forearm. A period of 15 min then was permitted to elapse so that the forearm vascular dynamics could return to stable control values. In the forearm which had undergone epinephrine infusion, iontophoresis with this substance was then performed as described above and the effect of epinephrine infusion was redetermined on muscle blood flow and muscle venous volume in an identical manner as before iontophoresis. Therefore, during intra-arterial epinephrine infusion, it was possible to relate the loss of reflex venomotor activity to the extent of venous and arteriolar constriction of both the skin and muscle vascular beds (27). The infusion rate at which reflex venous constriction could no longer be elicited was found to represent the concentration of administered catecholamine necessary to arrest skin blood flow and prevent filling of the cutaneous venous compartment.

RESULTS

Equilibration technique. At rest in the supine position the average VV[30] of the 10 subjects' control arm was 4.16 ±0.30 cc/100 cc; the VV[30] of the arm in which epinephrine iontophoresis was performed was 2.54 ±0.31 cc/100 cc. Fig. 1 is a representative tracing demonstrating the effects of sympathetically mediated venomotor stimuli on venous volume at equilibration, measured simultaneously in both arms. A deep breath, ice applied to the forehead, and leg exercise produced a profound effect on the control forearm, causing, respectively, an immediate and significant decrease in VV[30] to 3.69 ±0.17, ($P < 0.01$), 3.61 ±0.21, ($P < 0.01$), and 3.54 ±0.27 ($P < 0.02$) cc/100 cc. In contrast, in the epinephrine iontrophoresed forearm there was little or no response ($P > 0.2$). These data obtained from each subject are shown in Figs. 2–4. When VV[30] of the treated forearm, representing the volume of the muscle capacitance bed, was subtracted from that of the control forearm, an approximation of skin VV[30] was obtained. A deep breath, ice applied to the forehead, and leg exercise resulted, respectivly, in reductions of cutaneous VV[30] of 19.8, 36.6, and 32.6%, whereas there was no significant change in muscle VV[30] (Fig. 5).

Isolated forearm technique. When the volume of the forearm was held constant by arterial occlusion and the changes in venous pressure were used as an index of venomotor activity, it was shown in four subjects that upon taking a deep breath and commencing leg exercise, there was a rapid increase in venous pressure in the isolated but untreated control forearm, which signified an elevation in venous tone (Fig. 6). In contrast, in the forearm in which epinephrine iontophoresis was performed, the venous pressure did not change in the isolated forearm venous compartment (Fig. 6). Utilizing the isolated forearm method in two subjects venocon-

strictor activity was shown to be similar in both forearms before epinephrine iontophoresis. This venomotor response was reduced markedly in the treated forearm as compared with the control forearm immediately after iontophoresis, and returned toward normal 2 hr after iontophoresis was completed (Fig. 7).

Intra-arterial epinephrine. When the dose of epinephrine infused directly into the brachial artery was increased sequentially in two subjects, the responses of both subjects were similar. Fig. 8 depicts the responses of one of the subjects. The forearm blood flow and VV[30] decreased progressively as the dose of epinephrine was increased. Venous reactivity was unaltered at the lowest infusion rate of 1 μg/min of epinephrine even though a generalized venoconstriction had occurred in the infused forearm. However, when the rate of infusion was increased to 2 μg/min, venous reactivity was abolished. It was observed in both subjects that the dose of epinephrine which resulted in the loss of venous reactivity to sympathetic stimulation was the same as that which caused skin blood flow to cease, i.e., 2 μg/min.

DISCUSSION

The most important finding of this study is the previously unrecognized observation that the veins in the forearm muscular bed in man are unreactive to sympathetic reflex venomotor stimuli, whereas marked venoconstriction occurs in the cutaneous veins of the forearm. This conclusion is supported in this investigation by the determination of forearm venous tone utilizing two different, sensitive techniques. In the first, changes in the distensibility of the venous system were sensed by measuring the volume of blood contained within the capacitance vessels of the forearm at constant venous pressure. Thus, a reduction in venous volume at a constant venous pressure of 30 mm Hg indicated diminished compliance of the venous bed and, thereby, an elevation of venous tone or venoconstriction. This method for the study of venous tone is an adaptation of the standard equilibration technique establishing the pressure-volume characteristics of the capacitance bed of the leg described by Litter and Wood (17). Importantly, this method is applicable for the quantitative study of ve-

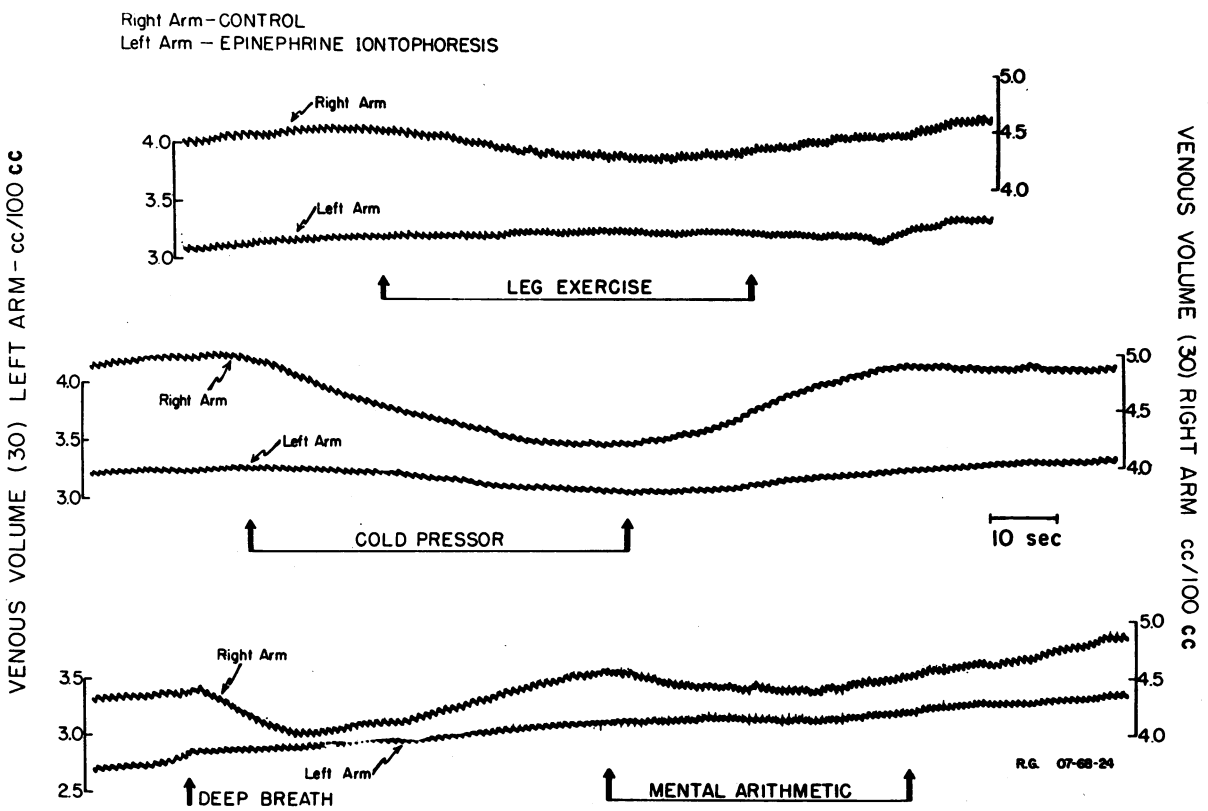

FIGURE 1 The response of the forearm venous volume to the stimuli of leg exercise, ice to the forehead (cold pressor), a deep breath, and mental arithmetic. The venous volume was measured after equilibration at a cuff pressure of 30 mm Hg. Simultaneous measurements were made in both forearms, the left having undergone prior epinephrine iontophoresis to suppress skin blood flow. A decrease in venous volume represents venoconstriction.

nous distensibility. In the present investigation, it was consistently observed that the veins in the control forearm constricted normally in response to a number of sympathetic stimuli: a deep breath, ice applied to the forehead, leg exercise, and mental arithmetic (Fig. 1–4). In contrast, simultaneously in the opposite forearm in which the skin circulation was suppressed by epinephrine iontophoresis, the capacitance vessels were observed to be completely unresponsive to the same stimuli (Fig. 1–4). Since the cutaneous vessels are markedly constricted by epinephrine, there is intense venoconstriction in the skin and cutaneous blood flow is abolished. Thus, the lack of venous reactivity in the treated forearm was interpreted to be entirely due to the unresponsiveness of the muscle capacitance vessels.

These findings that only the cutaneous veins in the forearm respond to sympathetic stimulation are confirmed in the present study by the use of the second method for the assessment of forearm venomotor activity, the isolated forearm technique. In this method, the forearm is isolated from the circulation by suprasystolic arterial occlusion of the upper arm as described by Wallace (20) and recently modified by Samueloff, Bevegård, and Shepherd (9). Since the volume of the capacitance vessels in the isolated forearm remains constant, venomotor reactivity is reflected by changes in venous pressure in the occluded segment; thus, an increase in venous pressure to a stimulus indicates venoconstriction. It is important to point out that this method allows the sensitive determination of qualitative changes in venous tone and is not suitable for calculations of absolute alterations in venous compliance (9). In the present investigation, as assessed by the isolated forearm technique, the veins in the control forearm constricted normally to the sympathetic stimuli of a deep breath and leg exercise, whereas the veins in the iontophoresed forearm were unresponsive, indicating that venoconstriction occurred only in the capacitance vessels in the skin (Fig. 6). The catheter through which the venous pressure was determined from the isolated forearm was placed in a deep muscle vein in both the control forearm and the forearm which underwent iontophoresis; therefore, the procedure of iontophoresis itself could not have affected this measurement. Moreover, it was shown that the response of these veins to sympathetic stimulation was nearly equal to the control arm before iontophoresis and returned toward normal when the effect of the epinephrine was dissipated (Fig.

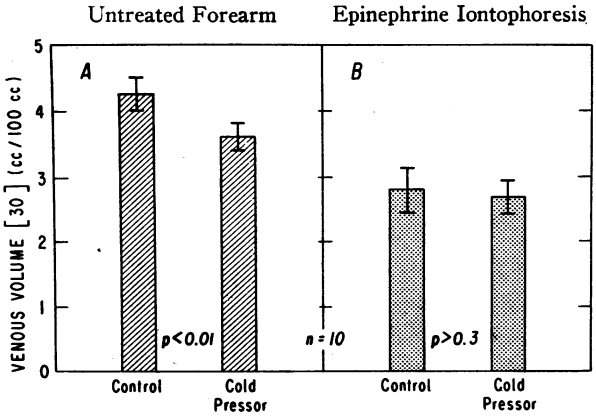

FIGURE 3 The response of the forearm venous volume (±SEM) to the application of ice to the forehead (cold pressor) measured simultaneously in the control forearm, A, and the opposite forearm on which epinephrine iontophoresis had been performed, B. Venous volume was measured after equilibration at a cuff pressure of 30 mm Hg.

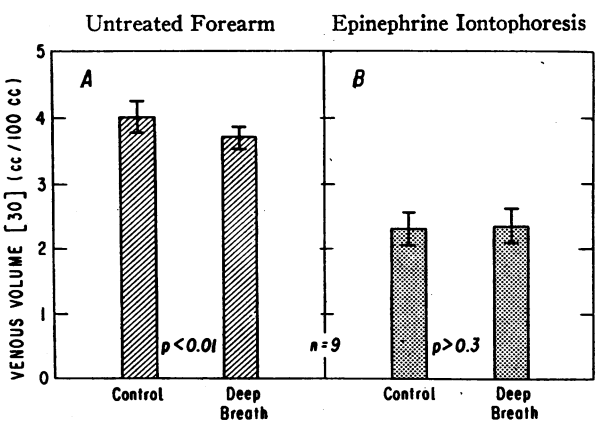

FIGURE 2 The response of the forearm venous volume (±SEM) to a deep breath measured simultaneously in the control forearm, A, and the opposite forearm on which epinephrine iontophoresis had been performed, B. Venous volume was measured after equilibration at a cuff pressure of 30 mm Hg.

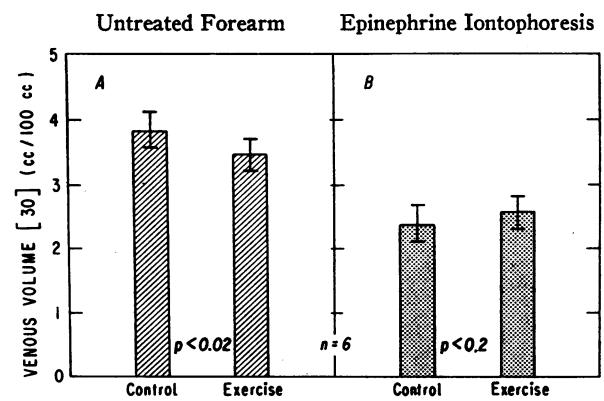

FIGURE 4 The response of the forearm venous volume (±SEM) to leg exercise measured simultaneously in the control forearm, A, and the opposite forearm on which epinephrine iontophoresis had been performed, B. Venous volume was measured after equilibration at a cuff pressure of 30 mm Hg.

7), findings indicating that the rise in venous pressure produced by the interventions were the result of venoconstriction in the cutaneous veins. Differences in the intensity of the response of the veins of the control arm to a deep breath seen in Fig. 7 are undoubtedly due to variations in the magnitude of the deep breath. Thus, the results obtained from both the equilibration and isolated forearm techniques clearly indicate that reflex venomotor reactivity takes place in the skin of the forearm but not in the skeletal muscle.

The technique of epinephrine iontophoresis provides a reliable means for effectively suppressing the cutaneous circulation (12–16). In the treated arm, the cutaneous veins are constricted and essentially empty since the epinephrine deposited in the skin produces marked vasoconstriction leading to the abolition of blood flow in the skin. The fact that retrograde filling of the cutaneous veins did not occur has been demonstrated by Cooper, Edholm, and Mottram, who showed the incised skin was bloodless after epinephrine iontophoresis (12). In the present study, epinephrine iontophoresis reduced the forearm VV[30] 40% below that of the untreated control forearm (Fig. 2–4). Thus, it appears that the VV[30] in the treated forearm provides an estimation of the volume of the capacitance bed in muscle, and the difference between it and the VV[30] of the control forearm allows approximation of the VV[30] of the venous bed in skin. Since the iontophoresed and control forearms were studied at the same time, the VV[30] of

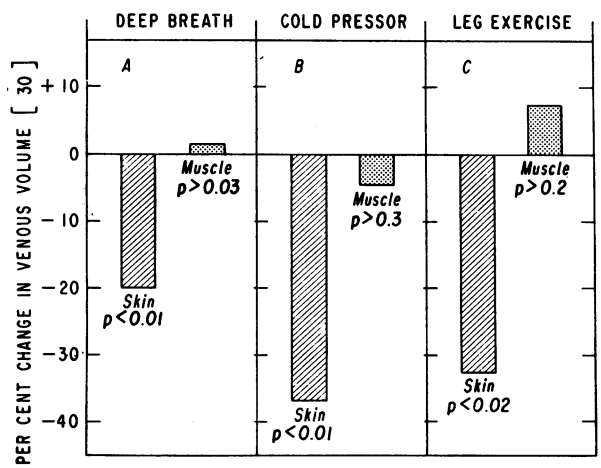

FIGURE 5 The per cent change in the venous volume of the forearm skin and muscle veins induced by a deep breath, A, application of ice to the forehead (cold pressor), B, and leg exercise, C. Venous volume was measured after equilibration at a cuff pressure of 30 mm Hg. Muscle venous volume was considered to be the venous volume of the iontophoresed forearm. Skin venous volume was considered to be the difference between the venous volume measured simultaneously in the control forearm and the forearm on which epinephrine iontophoresis was performed.

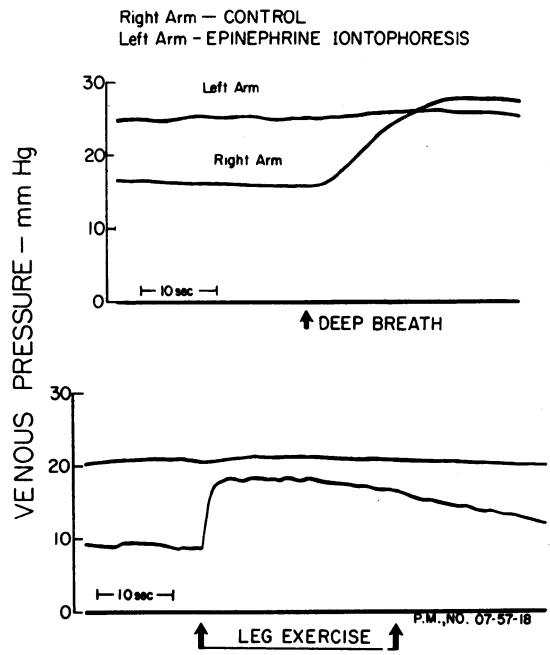

FIGURE 6 The response of the forearm venous pressure to a deep breath, upper panel, and leg exercise, bottom panel, measured from a deep muscle vein simultaneously from a control and iontophoresed forearm, after the forearms were isolated from the circulation by the inflation of upper arm cuffs to suprasystolic pressure.

both skin and muscle could be measured simultaneously. In addition, it is clear that the cutaneous VV[30] was the only venous compartment which diminished in response to the reflex venomotor stimuli, the per cent change of the cutaneous VV[30] being quite pronounced (Fig. 5).

In order to exclude the possibility that during iontophoresis diffusion of epinephrine from skin to muscle was not responsible for the veins in muscle being unreactive to nerve stimulation, epinephrine was administered intra-arterially into one forearm which had not undergone epinehprine iontophoresis. In this manner, the effect of exogenously administered epinephrine on venomotor reflexes could be determined for the entire forearm. When 1 μg/min of epinephrine was infused intra-arterially, venomotor reactivity to the stimulus of a deep breath was exactly the same as that measured simultaneously in the opposite untreated forearm. Venomotor reactivity thus was considered to be 100% (Fig. 8 A). Since the intra-arterial epinephrine was reaching both skin and muscle veins and venous reflexes were unaltered, it is unlikely that the loss of venomotor reflexes in the previous studies after epinephrine iontophoresis was due to a small amount of iontophoresis epinephrine which may have reached the muscle veins by diffusion. Rather it seems more likely

to conclude that epinephrine iontophoresis caused an abolition of venomotor reflexes by abolishing skin blood flow. Evidence to support this contention was provided by examining the effects of a higher dose of intra-arterial epinephrine on venomotor reactivity. It was noted that when the dose of infused epinephrine was increased to 2 μg/min, venomotor reactivity was nearly abolished. The reason why it was abolished was explored further

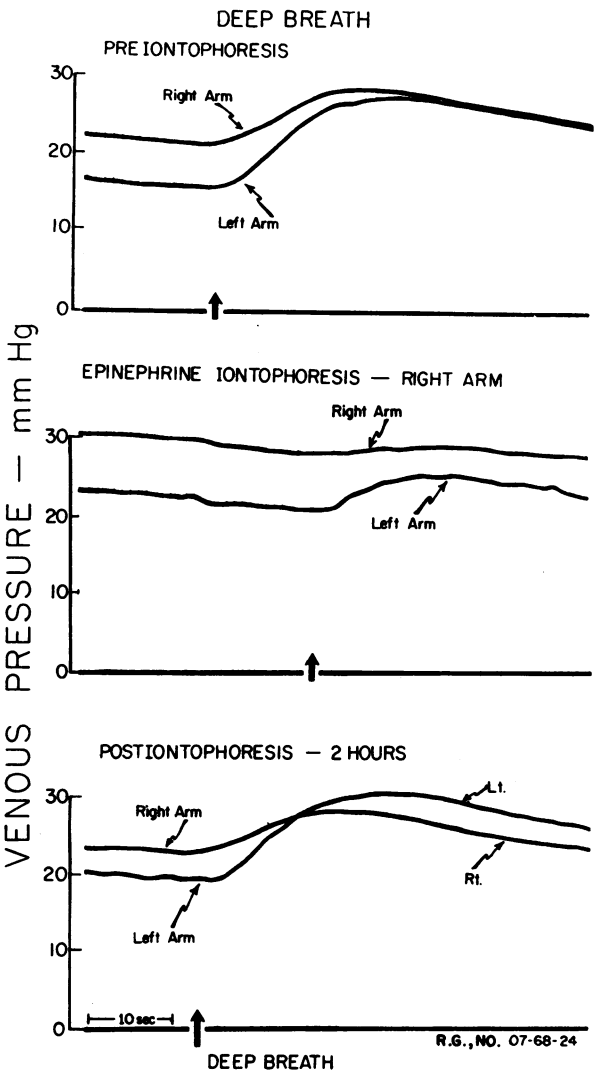

FIGURE 7 The response to a deep breath of the venous pressure measured from a deep muscle vein simultaneously from both forearms which were isolated from the circulation by inflation of upper arm cuffs to suprasystolic pressure. The venomotor reactivity of the left forearm (control) is compared with that of the right forearm before epinephrine iontophoresis of the right forearm (top panel). Venomotor reactivity is again compared after right forearm iontophoresis (middle panel), and after the effects of iontophoresis have begun to dissipate (bottom panel).

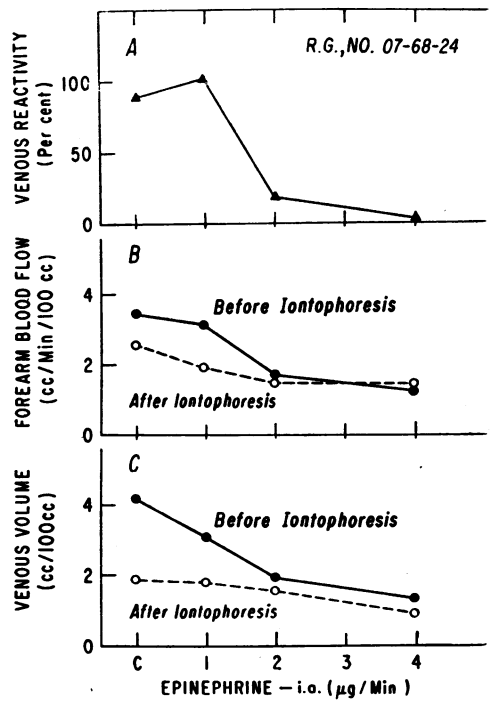

FIGURE 8 The effect of an epinephrine infusion into the brachial artery on venomotor reactivity, A, forearm blood flow, B, and forearm venous volume measured after equilibration at a cuff pressure of 30 mm Hg, C. A. Venous reactivity was determined before epinephrine iontophoresis by comparing the change in venous volume of both forearms measured simultaneously in response to a deep breath. The change in venous volume of the forearm receiving the intraarterial epinephrine infusion is expressed in relation to the change in the venous volume of the control forearm to the same stimulus, assuming that the control forearm is 100% reactive. After epinephrine iontophoresis venous reactivity was lost even before the intra-arterial epinephrine infusion and is, therefore, not shown in this panel. B. The forearm blood flow response to the epinephrine infusion was determined before (closed circles) and after (open circles) epinephrine iontophoresis of the same forearm. C. The response of the venous volume to the infused epinephrine after equilibration at a congesting pressure of 30 mm Hg was determined before (closed circles) and after (open circles) epinephrine iontophoresis of the same forearm. Epinephrine-i.a. = intra-arterial epinephrine.

by determining what the various levels of intra-arterial epinephrine had done to the blood flow and venous volume of the skin and muscle vascular beds. To accomplish this, epinephrine iontophoresis was performed on the same arm that had received the intra-arterial epinephrine. After skin blood flow was abolished by iontophoresis, the various levels of intra-arterial epinephrine infusion were repeated to determine their effects on muscle blood flow and muscle venous volume (Fig. 8 B, C). The effects of intraarterial epinephrine on skin blood flow and skin venous volume, therefore, could be

established by subtraction of the values in the iontophoresed forearm from those in the control forearm. Thus, it was observed that the dose of intra-arterial epinephrine which caused cessation of skin blood flow was the same that caused loss of venomotor reactivity, i.e., 2 μg/min. Therefore, venomotor reactivity was dependent on skin blood flow; when skin blood flow was abolished by two independent methods, epinephrine iontophoresis and intra-arterial epinephrine infusion, venomotor reactivity was lost. It was further shown that when skin venous volume was decreased by the epinephrine infusion of 1 μg/min, the skin veins were still completely reactive. Thus, it is unlikely that diffusion of iontophoresed epinephrine from skin to muscle could have accounted for the absence of venous reactivity in skeletal muscle; even if small amounts of the substance did enter the muscle bed, it appears that epinephrine would not have altered venous reflexes even if the muscle veins were capable of responding to reflex stimulation.

Therefore, from the observations obtained in this study, it is concluded that the venous bed of the skin in the forearm in man constricts to a wide variety of stimuli known to produce venoconstriction, whereas the capacitance vessels in skeletal muscle in the forearm do not participate in venomotor reflexes. These findings are consistent with the recent demonstration by Abboud and Eckstein who have demonstrated that the increase in resistance to venous outflow from the paw of the dog to nerve stimulation is considerably greater than the rise in venous resistance in the muscular portions of its foreleg (28). Moreover, these investigators have shown in the foreleg of the dog that the content of norepinephrine in the cephalic and metacarpal veins which drain the paw and skin is significantly higher than the concentration of the neurotransmitter in the brachial vein which drains principally skeletal muscle (29). Similarly, utilizing a fluorescent staining technique for the demonstration of norepinephrine in tissues, Fuxe and Sedvall have shown absence of catecholamines in the walls of veins in skeletal muscle, whereas norepinephrine was abundant in arterioles in corresponding muscle (30).

Further, since the forearm is principally composed of skeletal muscle and the hand skin, an explanation is provided for the observation that veins of the forearm, studied as a whole, appear less reactive to adrenergic stimuli than veins of the hand (9). In fact, the results of this study suggest that the venous pressure rise observed in the deep muscle vein of the isolated forearm was caused entirely by a shift of blood from the cutaneous venous compartment. Although the total volume of blood in the forearm veins may remain constant with this technique, it is proposed that the amount of blood in a single vein or venous segment does not appear to remain constant.

It is important to point out that not all sympathetic reflexes appear to be equally capable of achieving venoconstriction in cutaneous veins; thus baroreceptor stimulation produced by reductions of arterial pressure in the physiologic range have not been shown to induce measurable reflex changes in venous tone in the forearm and hand in man (25), while baroreceptor-mediated reflexes in response to similar changes in arterial pressure have been demonstrated in certain venous compartments in the abdominal viscera in animals (31). However, severe hypotension, such as that observed in vasovagal syncope in man, apparently is able to elicit cutaneous venoconstriction (32). It is of interest to consider the present findings of the lack of reflex venoconstriction in skeletal muscle in view of the effectiveness of venous return to the heart from the legs. It appears that the muscle pump is more important in supporting venous return than sympathetic venoconstriction, since postural syncope will occur when the limbs are immobile despite intense sympathetic venoconstriction (32). Finally, the finding of a different relative reflex responsiveness in certain venous segments is in keeping with the demonstration of unequal reactivity in the arterioles of skin and muscle of the limbs. Thus, a greater arteriolar constrictor response is elicited in the cutaneous resistance vessels than that in the arterioles in skeletal muscle (33).

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