Effects of Bradykinin on Forearm Venous Tone and Vascular Resistance in Man

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It is now well established that the endogenous nonapeptide bradykinin has important effects on the circulatory system and, in addition, may play a role in many physiologic and pathologic clinical conditions. Since its discovery in 1948, it has been shown in animals and man that bradykinin reduces systemic arterial pressure, increases limb blood flow, and elevates cardiac output. Little information is available, however, concerning the actions of this interesting vasoactive substance on the capacitance vessels of the systemic circulation either in experimental animals or in man. This paper describes studies on the effects of bradykinin on venous tone in the forearms of normal subjects and adds some information concerning its actions on the arteriolar bed of the forearm.

Methods

Nine normal male volunteer subjects, with ages ranging from 18 to 38 years, were studied in the recumbent position. An acute venous occlusion plethysmographic technique, employing the Whitney mercury-in-rubber strain gauge plethysmograph placed on the midforearm, was used to measure forearm blood flow and to estimate venous tone as described in detail elsewhere.

Venous pressure was measured through a 14 cm PE50 catheter introduced into a large vein at the wrist and advanced so that its tip lay just distal to the mercury-in-rubber gauge. The forearm was elevated so that the initial venous pressure was exactly zero. Arterial pressure was measured through an indwelling arterial needle placed into the brachial artery of the opposite forearm. A sphygmomanometric cuff was placed around the wrist and was inflated just before each venous occlusion to a level exceeding systolic arterial pressure. A sphygmomanometric cuff, 13 cm wide, was placed around the upper arm, and forearm venous occlusion was produced by inflating this cuff suddenly to a pressure of 30 mm Hg, i.e., below the diastolic arterial pressure.

Forearm blood flow was calculated from the change of forearm circumference during venous occlusion and was expressed in ml/100 g tissue/min. Vascular resistance in the forearm was calculated as the ratio of mean arterial pressure to forearm blood flow and was expressed in units of \( \frac{\text{mm Hg}}{\text{ml/100 g/min}} \). This calculation neglected venous pressure because the resting venous pressure was zero and its rise was small during the short period of occlusion. The pressure-volume characteristics of the capacitance vessels were calculated by determining the ratio of the increment in venous pressure to the increment in forearm volume which occurred in the 10 seconds following inflation of the venous occluding cuff, and were expressed in units of mm Hg/ml (fig. 1).

Since both pressure and volume rose in an almost linear fashion immediately and throughout the brief occlusion, this ratio was not altered significantly by the precise time during the first 30 seconds of occlusion at which the measurements were made. This ratio has also been used by Sharpey-Schafer to express the pressure-volume characteristics of the venous bed. This alteration of forearm volume, that accompanies obstruction to venous outflow appears to be due principally to filling of the distensible postcapillary capacitance bed because of: a) the large magnitude of change of the forearm circumference which occurred, b) the observation that there is no appreciable increase in resistance to flow in the arteriolar bed during the occlusion to low pressure for short duration, and c) the estimate that only 25% of the total blood volume is contained in the entire prevenous bed.

In addition to the acute occlusion method, an equilibration technique was employed in all 9 subjects to evaluate instantaneous changes in tone of the capacitance vessels of the forearm induced by bradykinin. The forearm was elevated so that the transmural venous pressure fell to zero, and the wrist cuff was inflated to a suprasystolic level. In this method, the venous oc...
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Three segments of records from one subject. Tracing on the left (A) was obtained during the control period, that in the middle (B) was recorded two-thirds of a minute later, and that on the right (C) was recorded one and one-third minutes after the injection of 25 μg of synthetic bradykinin. MAP: mean arterial pressure. PLETH: refers to the forearm plethysmographic tracing. VP: forearm venous pressure. The numbers below the tracing indicate the variables which were measured or calculated. HR: heart rate. FBF: forearm blood flow. FVR: forearm vascular resistance. FVT: forearm venous tone. Note in panel C that the rise of pressure in the veins is less steep while the rise in the plethysmographic tracing is more rapid than during the control period (A).

<table>
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FIGURE 1

Incluing cuff was inflated rapidly to 30 mm Hg, and equilibration of venous pressure and forearm circumference was permitted for two minutes. Under these conditions, the veins were distended, forearm venous pressure remaining stable at 30 mm Hg, and flow into this capacitance vessel reservoir was equal to that leaving it. The drug was then administered and the induced changes in venous volume were continuously assessed by measuring forearm circumference with the plethysmograph. The record of plethysmographic deflections after equilibration was reached provided, therefore, a continuous assessment of venous tone (fig. 2), a decrease of limb circumference indicating venoconstriction and an increase signifying venodilatation. This estimation of venous tone neglects the small increment in forearm volume consequent to transudation of fluid into the interstitial space.

Following placement of the catheter and needles, 15 minutes were permitted to elapse in order that the subjects might reach a stable state. Four control venous occlusion curves were obtained at one-half minute intervals in order to determine basal forearm blood flow and forearm venous tone. Synthetic bradykinin* 0.4 μg/kg, representing doses ranging from 20 to 35 μg, was suddenly injected intravenously in the opposite forearm. The chemical and biologic identity between natural and synthetic bradykinin has been established.20 Venous occlusion curves were recorded at 20-second intervals over the next three minutes. After a 15-minute waiting period, the effects of bradykinin on venous tone were assessed by the equilibration technique. After venous occlusion was maintained for two minutes, bradykinin was injected in the same quantity and manner as described above and a continuous record of changes in forearm circumference was obtained.

In five of these subjects the actions of bradykinin were studied during the control state and after adrenergic blockade had been induced by the administration of guanethidine. The latter drug was administered orally in maximum daily doses ranging from 50 to 150 mg/day for seven to ten days. At the time of the second study, evidence that adrenergic blockade had been

*Obtained from Sandoz Pharmaceuticals, Hanover, New Jersey.

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achieved included postural hypotension, abolition of the post-Valsalva overshoot of systolic arterial pressure, and absence of an increase of forearm vascular resistance and venous tone during the cold pressor test.23

Results
I. ACUTE OCCLUSION TECHNIQUE: CONTROLS AND BRADYKININ
The values for mean arterial pressure, forearm blood flow, forearm vascular resistance, and forearm venous tone during the control period in the nine normal subjects are summarized in figures 3 and 4. Considerable scatter was found in these control values from the several subjects, but in any given subject the four measurements prior to the administration of bradykinin showed little variation. Figures 3 and 4 show also the effects of bradykinin on mean systemic arterial pressure, forearm blood flow, forearm vascular resistance, and venous tone, expressed as percentage of changes from the control. After the administration of bradykinin in all of the subjects, mean arterial pressure declined ($P < 0.01$), while forearm blood flow was augmented ($P < 0.01$). Hence, the calculated forearm vascular resistance declined ($P < 0.01$) to an average value which was 33% below the average value during the control period. In all nine subjects, venous tone initially rose ($P < 0.02$), with the peak value averaging 38% above the average control value, but after one minute declined ($P < 0.01$) in all of the subjects to an average value of 24% below the average control value.

II. ACUTE OCCLUSION TECHNIQUE: GUANETHIDINE AND BRADYKININ
In three of the nine subjects, after treatment with guanethidine, the effects of bradykinin were determined again by the acute occlusion technique. Guanethidine administration lowered the values for forearm vascular resistance and venous tone during the control state prior to the administration of bradykinin. The extent of the reduction of forearm vascular resistance produced by bradykinin was essen-

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**FIGURE 2**

Plethysmographic tracing for estimating venous tone by the equilibration method following the injection of bradykinin, top (A) before guanethidine and bottom (B) after adrenergic blockade by guanethidine. The venous occluding cuff pressure and the forearm venous pressure are both 30 mm Hg but recorded at different sensitivities. Note in panel A that following bradykinin, while forearm venous pressure remained stable the forearm volume decreased, and then increased, showing constriction and dilatation respectively of the capacitance vessels. During guanethidine (B) only dilatation occurred. For abbreviations see legend of figure 1.

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Average change (± SEM) of mean arterial pressure (top) and forearm blood flow (bottom), following bradykinin, expressed as percentage of changes from the control values. Data added to each graph illustrate actual measurements during the control period for the nine subjects. For explanation see text. Average SEM: standard error of the mean of the four measurements during the control period carried out in any one subject, averaged for the nine subjects, and expressed as a percentage of the mean.

Initially the same before and after guanethidine (fig. 5A). However, pretreatment with guanethidine altered markedly the response of venous tone to the administration of bradykinin. During guanethidine treatment, venoconstriction was not produced in any of the three subjects by bradykinin and only venodilatation was observed (fig. 5B).

III. EQUILIBRATION TECHNIQUE: BRADYKININ

In all nine subjects, the effects of brady-

kinin on venous tone were also determined by the equilibration method. In this method, the drug was administered while forearm venous pressure and circumference were measured.
Average effects of bradykinin determined by the acute occlusion method in three subjects. Forearm vascular resistance (A) and forearm venous tone (B) before treatment with guanethidine (solid dots, solid line) and after guanethidine (open circles, broken lines).

continuously after equilibration of these variables had been achieved. The effects of bradykinin on venous tone expressed as percentage of changes from the control are shown in figure 6A. As observed with the acute occlusion technique, in all of the subjects, venous tone increased initially (P < 0.01), but this was followed by a decline of venous tone (P < 0.02) (figs. 2 and 6). Shortly after the fall in arterial pressure had begun, a decrease in forearm volume occurred, indicating that venoconstriction had occurred. Following the nadir of forearm volume at one minute, the volume rose steadily and, by one and one-half minutes after injection, the forearm volume was greater than before administration, indicating that venodilatation had taken place (figs. 2 and 6).

IV. EQUILIBRATION TECHNIQUE: GUANETHIDINE AND BRADYKININ

In five of the nine subjects, after treatment with guanethidine, the effects of bradykinin were determined again by the equilibration technique. As observed with the acute occlusion technique, guanethidine administration lowered the value for forearm venous tone during the control state prior to the administration of bradykinin. Again, as noted with the acute occlusion technique, during guanethidine treatment the administration of bradykinin did not result in an initial venoconstric-
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Discussion

It was observed in normal subjects that bradykinin reduced systemic arterial pressure and simultaneously increased forearm blood flow, findings which indicate that bradykinin dilated the resistance vessels of the forearm (figs. 1, 3 and 4). The reduction of systemic arterial pressure was most marked at 20 seconds after injection, and the increase of forearm blood flow rose to a peak at 80 seconds (fig. 3). The ratio of the rise of forearm venous pressure to forearm volume increased initially and then declined following bradykinin, suggesting that constriction and then dilatation of the capacitance vessels occurred (figs. 1 and 4). This sequence of venoconstriction followed by venodilatation was substantiated further by the equilibration method for estimating venous tone in that forearm volume decreased initially and then increased following bradykinin (figs. 2 and 6A).

This study has confirmed earlier conclusions\(^1\)-\(^9\) that bradykinin dilates the arteriolar bed of the forearm by direct action, because the calculated forearm vascular resistance fell in the presence of a reduced systemic arterial pressure.\(^{30}\) The view that bradykinin has a direct dilating effect on arteriolar smooth muscle is supported further in this study by the observation that forearm vascular resistance declined markedly in the subjects pretreated with the antiadrenergic agent, guanethidine (fig. 5A). This agrees with the observations of Rocha e Silva et al.\(^{31}\) that the sympatholytic agent, dibenzyline, and the catecholamine-depleting drug, reserpine, potentiated the duration of the vasodilator effect of bradykinin in the anesthetized cat. The observations that bradykinin lowers the vascular resistance of the human forearm and also the total systemic vascular resistance\(^4\)-\(^9\) provides an explanation not only for the reduction of systemic arterial pressure but also, in part, for the increase of the cardiac output noted by other investigators.\(^4\)-\(^9\)\(,\)\(^10\) It appears likely that this elevation of cardiac output is not only due to the direct positive inotropic actions of bradykinin,\(^10\)-\(^32\) but also that compensatory mechanisms are important, such as the decrease in resistance offered to ventricular ejection and to reflex influences on heart rate and ventricular contractility mediated through the baroreceptors.\(^{33}\)

The changes in the tone of the capacitance vessels of the forearm following bradykinin were more complex than those of the resistance vessels. It was noted that the change which occurred first after the administration of the drug was venoconstriction which coincided with the fall in systemic mean arterial pressure (figs. 1, 2, 4, and 6). Following this brief phase of increased venous tone, the duration of which was the same or slightly longer than the period of reduced arterial pressure, venodilatation was consistently observed. In order to clarify these findings, five of the subjects were studied before and after treatment with the antiadrenergic drug, guanethidine. In these subjects the reflex arteriolar and venous constriction which occurs during the cold pressor test,\(^{23}\) and the post-Valsalva systolic pressure overshoot\(^{23}\) had been abolished. In these subjects with adrenergic blockade, the administration of bradykinin elicited a fall of systemic arterial pressure that was essentially identical to that seen before guanethidine. However, an increase of venous tone was no longer produced; only a reduction of venous tone was observed (figs. 5B and 6B).

It is postulated that this initial effect is indirect and is due to reflex vеноconstriction secondary to reduction of arterial pressure, and that the direct effect of bradykinin on the capacitance vessels is that of mild dilatation. Therefore, the direct effects of the drug on the systemic vascular smooth muscle of both the forearm arterial and venous beds are similar, i.e., vasodilatation. In this connection it is also pertinent that bradykinin has been shown to produce active dilatation of vascular beds other than that of skeletal muscles, i.e., the cutaneous,\(^9\) the cerebral,\(^{34}\) the coronary,\(^{35}\) the renal,\(^{36}\) and the pulmonary\(^4\)-\(^37\) beds. These findings on venous tone agree with those of Burch and DePasquale\(^{38}\) who found that bradykinin increased the volume...
of the veins of the finger. These changes were interpreted, in most part, as a result of constriction of the arteriovenous anastomoses of the finger which increased effective flow to the digit and therefore increased digital volume because less blood was diverted from the finger. Our observations on venous tone also agree with the findings of Kontos et al., who found that bradykinin increased the distensibility of the hand veins.

The duration of the vascular effect of bradykinin following the injection was very brief and persisted for less than three to four minutes. It was also noted in the course of these studies that a cutaneous flush appeared consistently following the injection of bradykinin. The onset and duration of this flush corresponded generally to the period of the decline of forearm vascular resistance. Although the intravenous administration of bradykinin is associated sometimes with local pain, this was observed infrequently in our subjects.

Summary

The effects of intravenous injections of synthetic bradykinin on the vascular dynamics of the forearm were studied in nine normal subjects. A plethysmographic technique was used to measure forearm blood flow and to estimate forearm venous tone. Bradykinin decreased mean systemic arterial pressure, elevated forearm blood flow, and reduced calculated forearm vascular resistance and also venous tone. The venodilatation was preceded by brief venoconstriction which was prevented in five subjects pretreated with the anti-adrenergic agent, guanethidine. It is postulated (a) that this venoconstriction is one of the compensatory reflex actions that accompany reduction of systemic arterial pressure, and (b) that the prime effect of bradykinin on both the arterial and the venous beds of the forearm is a direct vasodilatation.

References


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