General and Regional Circulatory Effects of Synthetic Bradykinin in Man

By Hermes A. Kontos, M.D., Joseph H. Magee, M.D., William Shapiro, M.D., and John L. Patterson, Jr., M.D.

Bradykinin is a potent vasodilator in several animal species. The circulatory effects of bradykinin in man have been less extensively studied. Fox et al. observed that intra-arterial or intravenous administration of bradykinin increased blood flow to the hand and forearm. These investigators also found that blood flow to the skin of the hand, forearm, face, and neck increased during the administration of bradykinin. Burch and DePasquale reported that intra-arterial injection of bradykinin produced digital vascular responses similar to those seen during reactive hyperemia. They concluded that bradykinin selectively closed digital arteriovenous anastomoses. Gersmeyer and Spitzbarth found that single intravenous injections of 50 to 100 μg of bradykinin caused reduction in arterial blood pressure, acceleration of heart rate, increase in cardiac output and stroke volume, and fall in systemic vascular resistance. Comparable doses injected into the superior vena cava or pulmonary artery increased pulmonary arterial pressure. Injections of bradykinin into the femoral artery caused increased blood flow to the calf and rise in skin temperature. Saameli and Eskes reported that intravenous infusions of 0.25 to 0.5 μg of bradykinin per minute per kilogram body weight lowered arterial blood pressure and accelerated heart rate.

The present investigation was concerned with the general circulatory effects of synthetic bradykinin in man and with its effects on the vascular beds of the kidney and upper extremity.

Methods

Forty experiments were performed on 19 healthy volunteers ranging in age from 22 to 47 years (mean age 29 years). The weight of these subjects ranged from 46.8 to 83.6 kg (mean weight 63 kg). All subjects were studied in the postabsorptive state, while lying recumbent on a table.

A solution containing 25 μg of bradykinin/ml of isotonic saline, prepared immediately before the experiment, was used for intravenous infusion at rates of 25 and 40 μg/min. The duration of the infusion varied from 10 to 45 minutes. In a small number of experiments 0.2 μg/min of bradykinin in a solution containing 1 μg/ml were infused into the brachial artery near the elbow.

Cardiac output was determined by the dyedilution method utilizing indocyanine green. A known amount of dye was injected in less than one second through a calibrated syringe into an antecubital vein and as rapidly as possible flushed into the central circulation with 10 ml of isotonic saline. Brachial arterial blood was withdrawn at the rate of 19.4 ml/min by means of an automatic withdrawal pump through an indwelling Cournand no. 18 arterial needle connected to a cuvette densitometer by means of polyethylene tubing. Cardiac output was calculated from dye curves after they were replotted on semilogarithmic paper. Determinations of cardiac output were made before the administration of bradykinin and during the tenth minute of the infusion. Brachial arterial blood pressure was measured with a Statham P-23D strain gauge. Mean arterial blood pressure was obtained by electronic integration. Systemic vascular resistance was calculated.

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ed from the cardiac output and mean arterial blood pressure, assuming a mean right atrial pressure equal to zero.

Oxygen consumption was measured by timed collection of expired gas in Douglas bags and subsequent determination of its composition with the Scholander micrometer gas analyzer.7

Blood flow to the hand or forearm was determined by venous occlusion plethysmography using a water-filled plethysmograph at a temperature of 32°C. When forearm blood flow was measured, the circulation to the hand was excluded by inflating a wrist cuff to a pressure exceeding 200 mm Hg. A series of control measurements were made at 30-second intervals. Measurements were repeated at 30-second intervals during the infusion of bradykinin.

In certain experiments in which, during the administration of bradykinin, an increase in forearm blood flow occurred, the contribution of vasodilatation in forearm skeletal muscle to the increase in total forearm blood flow was examined by determining the oxygen content of deep forearm venous blood. Venous blood was obtained from a polyethylene catheter introduced upstream into a deep antecubital vein of the opposite limb as described by Mottram.8 Two or three samples were obtained prior to the infusion of bradykinin and a similar number between the fifth and tenth minutes of the infusion. Circulation to the hand was arrested five minutes prior to control blood sampling and throughout the infusion of bradykinin. Oxygen content of blood samples was determined by the method of Van Slyke and Neill.9

The distensibility of hand veins was determined by a method used by Sharpey-Schafer10 in the forearm and modified by Watson11 for use in the hand. A polyethylene catheter was introduced into a vein at the wrist and advanced distally until it passed at least one venous valve. The hand was then placed in the plethysmograph above heart level. The venous catheter was kept patent by the slow infusion of heparinized saline given between measurements. Venous pressure was measured with a Statham P-23D strain gauge, placed at the height of the water level in the plethysmograph chimney. In the absence of venous occlusion, the pressure exerted by the water column in the plethysmograph (11 cm of water) on the dorsum of the hand was higher than the venous pressure, so that the venous distending (transmural) pressure was close to zero. Simultaneous recordings of venous pressure and hand volume were made following the application of 40 mm Hg pressure at the wrist with a cuff. The increase in hand volume was plotted against the corresponding venous distending pressure. Venous distensibility is represented by the slope of the resulting volume-pressure diagram. Since the volume-pres-
Circulatory Effects of Bradykinin

Selection periods were obtained between the 15th and 45th minutes of the infusion. The concentration of inulin in plasma and urine was measured by the method of Young and Raisz and that of PAH by the method of Smith et al.

Results

Figure 1 shows a typical experiment illustrating the effects of intravenous infusions of bradykinin on arterial blood pressure and heart rate. During the first few minutes of the infusion, systolic and diastolic blood pressures decreased while heart rate accelerated. Subsequently, both arterial blood pressure and heart rate returned toward preinfusion levels. During the tenth minute of bradykinin infusion there was an increase in cardiac output and stroke volume and a decrease in systemic vascular resistance; changes in heart rate and mean arterial blood pressure were not significant (table 1).

The administration of bradykinin had no significant effect on total body oxygen consumption (table 1). During the infusion of 25 μg/min of bradykinin, hand blood flow increased while changes in forearm blood flow were statistically insignificant. Infusion of a higher dose of bradykinin (40 μg/min) produced an increase in forearm blood flow. During infusion of 40 μg/min of bradykinin the oxygen content of deep forearm venous blood decreased in three subjects and increased in one; the mean decrease was not statistically significant (table 1).

Renal clearance of inulin and glomerular filtration fraction were slightly decreased during infusion of bradykinin. There was no significant alteration in urine flow or PAH clearance.

Intra-arterial administration of 1 μg of bradykinin caused an increase in hand volume which always outlasted the circulatory effects, sometimes for several minutes. Since in these experiments the hand was above heart level and was subjected to an external pressure of 11 cm of water, the increase in hand volume could not be due to accumulation of blood in

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<th>Circulatory Effects of Bradykinin</th>
<th>N</th>
<th>C</th>
<th>E</th>
<th>D</th>
<th>P</th>
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<tbody>
<tr>
<td>I. Effects of intravenous infusions of 25 μg/min</td>
<td></td>
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<td></td>
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<tr>
<td>Cardiac output, liter/min</td>
<td>9</td>
<td>6.41±0.45</td>
<td>9.34±0.71</td>
<td>2.92±0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>9</td>
<td>88.3±3.7</td>
<td>88.3±3.7</td>
<td>0</td>
<td>n.s.</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>9</td>
<td>64.6±2.6</td>
<td>73.0±5.3</td>
<td>8.4±1.3</td>
<td>n.s.</td>
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<tr>
<td>Stroke volume, ml/beat</td>
<td>9</td>
<td>199.8±7.3</td>
<td>132.1±3.6</td>
<td>34.9±9.6</td>
<td>&lt;0.01</td>
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<tr>
<td>Systemic vascular resistance, mm Hg/liter/min</td>
<td>9</td>
<td>14.19±0.90</td>
<td>9.92±0.82</td>
<td>4.27±0.62</td>
<td>&lt;0.001</td>
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<tr>
<td>Oxygen consumption, ml/min</td>
<td>5</td>
<td>192.8±6.5</td>
<td>192.8±6.5</td>
<td>0</td>
<td>n.s.</td>
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<tr>
<td>Hand blood flow, ml/min/100 ml</td>
<td>10</td>
<td>7.83±1.21</td>
<td>12.88±1.77</td>
<td>5.05±0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Forearm blood flow, ml/min/100 ml</td>
<td>6</td>
<td>3.77±0.58</td>
<td>3.90±0.65</td>
<td>0.73±0.39</td>
<td>n.s.</td>
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<tr>
<td>Venous distensibility, ml/mm Hg</td>
<td>9</td>
<td>0.21±0.054</td>
<td>0.26±0.054</td>
<td>0.054±0.004</td>
<td>&lt;0.001</td>
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<tr>
<td>Urine flow, ml/min</td>
<td>5</td>
<td>16.7±1.1</td>
<td>14.2±2.1</td>
<td>2.5±1.7</td>
<td>n.s.</td>
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<tr>
<td>PAH clearance, ml/min</td>
<td>5</td>
<td>646.1±85.7</td>
<td>662.5±98.7</td>
<td>16.4±0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insulin clearance, ml/min</td>
<td>5</td>
<td>126.1±12.5</td>
<td>111.6±11.7</td>
<td>14.5±3.7</td>
<td>&lt;0.02</td>
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<tr>
<td>Filtration fraction, per cent</td>
<td>5</td>
<td>19.84±0.76</td>
<td>17.39±1.25</td>
<td>2.4±0.7</td>
<td>&lt;0.05</td>
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<tr>
<td>II. Effects of intravenous infusions of 40 μg/min</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm blood flow, ml/min/100 ml</td>
<td>7</td>
<td>2.26±0.38</td>
<td>3.73±0.59</td>
<td>1.17±0.24</td>
<td>&lt;0.01</td>
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<tr>
<td>Oxygen content deep forearm venous blood, ml/100 ml</td>
<td>4</td>
<td>11.23±1.04</td>
<td>9.07±1.35</td>
<td>1.56±0.93</td>
<td>n.s.</td>
</tr>
<tr>
<td>Venous distensibility, ml/mm Hg</td>
<td>5</td>
<td>0.27±0.022</td>
<td>0.47±0.063</td>
<td>0.20±0.054</td>
<td>&lt;0.02</td>
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<tr>
<td>Hand blood flow, ml/min/100 ml</td>
<td>5</td>
<td>3.98±0.42</td>
<td>7.08±1.0</td>
<td>3.08±0.66</td>
<td>&lt;0.001</td>
</tr>
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Note: All values represent mean plus standard error. N = number of subjects, C = control value, E = experimental value, D = difference between control and experimental mean values, P = refers to statistical comparison of difference between control and experimental mean values to zero, n.s. = not significant.
the veins. Neither dilatation of arteries nor dilatation of capillaries could account for the increase in volume for the latter was still present after vasodilatation had subsided; we conclude that bradykinin led to formation of edema. With doses exceeding 10 μg there was visible edema. In two subjects, the intra-arterial administration of 1 to 10 μg of bradykinin produced an increase in hematocrit ratio of the venous effluent from the hand ranging from 0.2 to 2.6%. With intravenous infusions of 25 μg/min or intra-arterial infusions of 0.2 μg/min of bradykinin there was no demonstrable evidence of edema formation.

An increase in venous distensibility was observed during intravenous infusions of 25 μg/min or intra-arterial infusions of 0.2 μg/min of bradykinin (fig. 2).

CLINICAL OBSERVATIONS

Slight burning pain at the site of bradykinin infusion was experienced by all subjects. This rarely persisted for more than one to two minutes. A sensation of flushing, followed immediately by intense diffuse erythema of the face, neck, and upper chest was observed in all instances. In some cases there was mild associated dizziness. Slight erythema of the hand was also seen in some cases. The facial erythema coincided with the fall in arterial blood pressure. Erythema was most intense during the first few minutes of the infusion and was later replaced by patchy erythema of diminished intensity.

Discussion

Our observations on the general circulatory effects of bradykinin are in agreement with findings of previous investigators. The fall in arterial blood pressure and reduction in systemic vascular resistance are consistent with known vasodilating properties of bradykinin. The initial cardiac acceleration was probably related to baroreceptor activity, secondary to the fall in arterial blood pressure. Increase in cardiac output can reasonably be explained as a response to decreased systemic vascular resistance, but the possibility of autonomic or direct cardiac effects of bradykinin cannot be excluded. The rise in arterial blood pressure toward preinfusion levels, following the initial hypotensive period, was probably related to compensatory vasoconstriction in some vascular beds. The general circulatory effects of bradykinin resemble changes seen following acute opening of a large arteriovenous fistula. As in other hyperkinetic circulatory states, the increase in cardiac output during administration of bradykinin was brought about mainly by increased stroke volume, thus lending further support to the view that "an increased stroke volume is the keystone to the hyperkinetic circulatory state."

The present observations and those of others 1-4 indicate that bradykinin is a powerful vasodilator of cutaneous blood vessels in man. The flush and increased blood flow to the hand indicate that skin vasodilatation must account for at least part of the observed decrease in systemic vascular resistance. The contribution of cutaneous vasodilatation to the fall in systemic vascular resistance is difficult to estimate because of the variable degree of bradykinin-induced vasodilatation in different skin regions, as judged by variations in the intensity of the flush. By this criterion, vessels of the skin of the face, neck, and upper chest appear to be the most responsive to
bradykinin. The greater response of cutaneous vessels of the face and neck to bradykinin has also been noted by Fox et al. 2

Failure of forearm blood flow to increase significantly during infusion of 25 µg/min of bradykinin, and the relatively small increase in hand blood flow seen under these circumstances, indicate that the bradykinin-induced cutaneous vasodilatation was far from the maximum possible. If the maximum cutaneous blood flow in man is taken as 1.8 to 2 liter/min/square meter of body surface area, 18, 19 then the observed increase in cardiac output during the infusion of 25 µg/min of bradykinin cannot be accounted for entirely by cutaneous vasodilatation. Since such doses of bradykinin do not increase blood flow to skeletal muscle or renal blood flow, it may be inferred that an increase in blood flow through the cerebral, coronary or splanchnic vascular beds occurred.

Our observations on the oxygen content of deep venous forearm blood suggest that the increase in total forearm blood flow during the intravenous infusion of 40 µg/min of bradykinin was due entirely to skin vasodilatation. In fact, the decreased oxygen content in three of the subjects indicated that blood flow to forearm skeletal muscle decreased during intravenous administration of bradykinin.

The increased venous distensibility suggests that bradykinin dilates veins of the hand. This view is at variance with the conclusions of Guth et al. 20 These investigators found that administration of bradykinin caused a decrease in venous outflow and an increase in weight of the perfused rabbit's ear and of several other perfused preparations. They ascribed these effects to venoconstriction with secondary passive dilatation of capillaries. Their results are not in accord with previous observations 1, 21-25 and their experiments have been criticized by Hilton. 24

The accumulation of edema fluid might also explain the findings of Burch and DePasquale. 3 Large doses of bradykinin were used by these authors (10 µg in 50% of their experiments). In their experiments, as in ours, the increases in volume outlasted the circulatory effects and could have been due to edema formation rather than to selective closure of arteriovenous shunts.

Guth et al. 20 also observed constriction of small vessels, believed to be venules, following intravenous administration of 10 to 20 µg of bradykinin. Since this effect coincided with decreased arterial blood pressure, it is possible that the observed vasoconstriction resulted from reflexes initiated by the fall in blood pressure, 25 rather than from direct action of bradykinin on the blood vessels involved.

Infusion of bradykinin had no consistent effect on renal blood flow. Glomerular filtration rate fell slightly with a concomitant slight decrease in filtration fraction. Webster 21 observed increased renal plasma flow following direct injection of Kallidin-10 into a renal artery; in contrast, there were no effects following intravenous injections, suggesting that rapid inactivation of this peptide precludes any important renal effect following remote injections. The present studies are in agreement with respect to bradykinin, and indicate that doses sufficient to cause systemic vasodilatation do not cause important changes in the renal circulation.

Summary

The general and regional circulatory effects of synthetic bradykinin were investigated in 19 healthy volunteers. During intravenous infusion of bradykinin (25 µg/min) mean arterial pressure decreased initially, but returned to control levels within a few minutes. Heart rate increased during the hypotensive period, but subsequently returned toward preinfusion levels. Cardiac output increased, mainly as a result of increased stroke volume, and systemic vascular resistance decreased. Blood flow to hand increased during such infusions of bradykinin, but blood flow to forearm was not altered significantly. Intravenous infusions of 40 µg/min produced an increase in blood flow to the forearm, resulting solely from cutaneous vasodilatation in most subjects. The distensibility of hand veins increased both during intravenous infusions of 25 µg/min and during infusions of 0.2 µg/min into the bra-
chial artery. Renal clearance of inulin was slightly decreased during infusion of 25 μg/min bradykinin; there was no detectable change of PAH clearance.

Acknowledgment

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References

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