Bradykinin, Digital Blood Flow, and the Arteriovenous Anastomoses

By George E. Burch, M.D., and Nicholas P. DePasquale, M.D.

During studies on the anticoagulating properties of snake venom, Rocha e Silva and associates discovered the vasoactive polypeptide, bradykinin. The substance was called bradykinin because, in contrast to histamine and acetylcholine, it stimulated smooth muscle to contract after a latent period and because the contraction was gradual. The substance received little attention until recently when it was isolated in the pure state, synthesized, and its chemical structure confirmed. Animal experimentation subsequently showed that bradykinin had five important pharmacological properties, namely, smooth muscle stimulation, vasodilatation, increase in capillary permeability, migration of leukocytes, and stimulation of pain fibers.

Only a few studies of this interesting substance have been carried out in man. Fox and Hilton showed that the perfusate from the subcutaneous space of the forearm of human subjects contained much larger amounts of bradykinin after reflex induction of sweating than prior to the onset of sweating. They concluded that the sweat glands contain a bradykinin-releasing enzyme and that the vasodilatation associated with sweating may be due to bradykinin. Herxheimer and Schachter have shown that the intracutaneous injection of bradykinin in man increases capillary permeability to dyes of high molecular weight.

Studies in this laboratory (G. E. Burch and N. P. DePasquale, unpublished observations) have indicated that bradykinin results in an increase in the volume of an intracutaneous bleb, but not in erythema.

Recently, Fox et al. published an abstract in which they reported that bradykinin increased the blood flow to the human forearm and hand. However, they failed to present details concerning the mechanism for the increased blood flow.

Because of the marked potency and important physiological actions of bradykinin on the circulation, it was decided to study, in detail, the influence of this substance on human digital blood flow.

Methods

The digital rheoplethysmogram (RPG) was recorded for 10 subjects ranging in age from 18 to 67 years (mean, 48 years). Six of the subjects were female and four were male, eight being Negro, and two, white. The RPG was recorded for the second right finger tip (2RF) and the third right finger tip (3RF). Details of the rheoplethysmographic technique used in this laboratory have been presented previously.

The material used in this study was a synthetic nonapeptide* which has the same structural formula and pharmacological properties as natural bradykinin. The synthetic bradykinin in doses which varied from 1.0 to 10 μg. was injected directly into the right brachial artery.

Results

The results are summarized in tables 1 and 2 and in figures 1 through 6.

GENERAL RESPONSES

Intra-arterial injection of bradykinin was associated with pain in all subjects. The pain was localized to the right arm and involved the entire extremity distal to the site of injection.

*Supplied by Dr. R. Bircher of Sandoz Pharmaceuticals.
Figure 1A
Digital rheoplethysmogram showing the digital vascular responses to intra-arterial injection of bradykinin (A) under control conditions and (B, facing page) 60 seconds after arterial injection of 2.0 μg. bradykinin. See text for details.

Injection in the antecubital fossa. The pain was usually most intense at the site of injection but in several subjects was most intense in the finger tips. The pain was described as burning by all subjects. The onset of the pain occurred within 30 seconds of injection. It reached a maximal intensity at about 45 seconds and disappeared completely in about 60 to 120 seconds. A residual sensation of warmth, which lasted from 120 to 180 seconds, was present in the finger tips. Although the intensity of the pain was related to dosage, even a dose of 1.0 μg. always produced pain. There was no tachyphylaxis of the pain response to intra-arterial injection of bradykinin.

A flush response was noted in all subjects. The intensity of the flush varied temporally and directly with the pain response so that the flush was most intense when the pain was most intense. In seven subjects, the flush was localized to the hand and arm distal to the
site of injection. However, in three subjects the flush was also observed in the blush area of the head and neck but not in the contralateral arm. The flush was always most intense in the hand and was associated with an increase in the skin temperature of the digits and forearm as measured with thermocouples.

This increase in skin temperature was always greater in the digits than in the forearm.

CHANGES IN CARDIAC RATE AND BLOOD PRESSURE

Intra-arterial injection of bradykinin had essentially no effect on the cardiac rate (table 1). The systolic blood pressure decreased 5
to 10 mm Hg immediately after the injection of bradykinin in five subjects. Complete recovery of the blood pressure occurred within 35 to 50 seconds. In four subjects, no change in the level of the arterial blood pressure was noted even when 10 μg. of bradykinin were given. In one subject, a biphasic response consisting of a fall followed by a slight rise in the level of the arterial pressure was noted. This response began almost immediately after the injection of bradykinin with a decrease in the systolic pressure of about 20 mm Hg and a decrease in the diastolic pressure of about 10 mm Hg. After an interval of about 25 seconds, the systolic and diastolic pressures rose to levels which were slightly higher than the preinjection levels.

CHANGES IN THE TIME COURSE OF DIGITAL INFLOW (IV)

The mean rate of digital blood flow during a single cardiac cycle decreased in seven subjects and increased in three. The mean rate...
of inflow decreased more during the diastolic than during the systolic phase of the pulse cycle, the decrease in the mean being 84 per cent ($P < 0.02$) for diastole and 28 per cent ($P > 0.5$) for systole (table 1, fig. 1).

**CHANGES IN RATE OF BASAL FLOW**

The basal pulsatile flow decreased in seven subjects and increased in three subjects (table 1). The mean decrease in basal flow was 48 per cent ($P < 0.02$). Maximal pulsatile flow decreased in six subjects and increased in four subjects, with a mean decrease of 10 per cent ($P > 0.5$).

**CHANGES IN THE TIME COURSE OF DIGITAL OUTFLOW ($O_v$)**

In the seven subjects in whom the mean rate of digital inflow decreased, the simultaneous curves of inflow ($I_v$) and outflow ($O_v$) were widely separated temporally (figs. 1 and 2). This separation was due primarily to a "lag" in the outflow curve. Since outflow must equal inflow during the pulse cycle when the circulation is at equilibrium, the quantitative mean rates of digital outflow for a single pulse cycle were essentially the same as for inflow.

**CHANGES IN THE TIME COURSE OF THE DIGITAL PULSE ($D_v$)**

The height of the digital volume pulse wave ($D_v$) increased in nine subjects and decreased in one subject after the intra-arterial injection of bradykinin. The total volume of the
TABLE 1
Certain Quantitative Digital (Right Index Finger Tip) Rheoplethysmographic Data for Man Before and After Ipsilateral Intra-arterial (Brachial) Administration of Bradykinin

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Pulse flow (cu. mm./5 cc. part/sec.)</th>
<th>Maximal pulse flow (cu. mm./5 cc. part/sec.)</th>
<th>Mean rate of inflow (cu. mm./5 cc. part/sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>% Change</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>0.50 0.88</td>
<td>7 7 +4 133</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.98 0.82</td>
<td>22 48 +26 118</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0.83 0.78</td>
<td>43 19 -24 -56</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0.72 0.65</td>
<td>32 20 -12 -38</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.80 0.72</td>
<td>55 0 -55 -100</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0.74 0.88</td>
<td>15 28 +13 87</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.88 0.87</td>
<td>30 8 -22 -73</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0.60 0.60</td>
<td>107 74 -33 -31</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0.95 0.95</td>
<td>58 3 -55 -95</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0.80 0.76</td>
<td>32 3 -29 -91</td>
</tr>
<tr>
<td>Mean</td>
<td>0.81 0.79</td>
<td>40 21 -19 -48</td>
<td></td>
</tr>
</tbody>
</table>

Influence of intradigital injection of bradykinin on the volume curve of the artifact for the same subject shown in figures 1 and 5.
BRADYKININ AND DIGITAL FLOW

FIGURE 4

RPG showing increase in digital volume following arterial injection of bradykinin. The digital volume reaches a maximum in about 90 seconds and decreases to its control level in about 500 seconds after injection.

TABLE 2

Summary of Digital Vascular Responses to Intra-arterial Injection of Bradykinin

<table>
<thead>
<tr>
<th>Response Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Flushing of the digit.</td>
</tr>
<tr>
<td>2. Increase in warmth of the digit.</td>
</tr>
<tr>
<td>3. Increase in magnitude of the volume pulse wave (Dv).</td>
</tr>
<tr>
<td>4. Decrease in the rate with which the volume pulse wave (Dv) reached its peak.</td>
</tr>
<tr>
<td>5. Change in contour of the volume pulse wave often with disappearance of the dicrotic notch.</td>
</tr>
<tr>
<td>6. Decrease in digital inflow volume (Iv).</td>
</tr>
<tr>
<td>7. Lag in the time-course curve of volume of outflow (Ov).</td>
</tr>
<tr>
<td>8. Decrease in basal rate of flow.</td>
</tr>
<tr>
<td>9. Increase in resistance to flow.</td>
</tr>
<tr>
<td>10. Increase in total volume of the digit.</td>
</tr>
<tr>
<td>11. Quick &quot;overfilling&quot; of the digital collecting vessels.</td>
</tr>
<tr>
<td>12. Decrease in magnitude of the volume artifact.</td>
</tr>
<tr>
<td>13. Lengthening of the time interval between the onset of the brachial artery pulse wave and the digital volume pulse wave.</td>
</tr>
<tr>
<td>14. Little change in arterial blood pressure.</td>
</tr>
<tr>
<td>15. No change in heart rate.</td>
</tr>
<tr>
<td>16. No indirect evidence of change in cardiac output or stroke volume.</td>
</tr>
</tbody>
</table>

of the digital pulse wave was decreased by bradykinin, so that the peak of Dv occurred later after the injection of bradykinin than before injection.

CHANGES IN THE TIME COURSE OF THE ARTIFACT (Av)

The volume time course of the artifact recorded during the period of maximal response to bradykinin was of less magnitude than that recorded during the control period. After recovery, the volume curve of the artifact returned to control levels and configuration (fig. 3).

CHANGES IN TOTAL DIGITAL VOLUME

In all subjects, the injection of bradykinin was followed by a marked increase in total digital volume (fig. 4). This increase in digital volume began within 15 seconds of the injection of bradykinin, reached a maximum within 60 to 100 seconds, and returned to control levels within 300 to 500 seconds. Thus, the volume change occurred earlier and lasted longer than the pain and flush responses.

Discussion

Studies performed in this laboratory many years ago11 showed that during reactive hyperemia there was an increase in total digital volume, an increase in the skin temperature of the digit, a decrease in the time course of digital inflow, a decrease in basal pulsatile flow, and a decrease in the time course of the volume artifact. The digital vascular responses due to the intra-arterial injection of bradykinin (fig. 1) are almost precisely the same in every respect as those of reactive hyperemia (fig. 5), and in both instances are different from the responses observed under any other conditions.

The digital vascular responses to the ipsilateral intra-arterial (brachial) injection of bradykinin are summarized in table 2. These
findings can best be explained by selective constriction of the arteriovenous anastomoses with dilatation of the capillaries, venules, and veins. As a result of constriction of the A-V anastomoses, the "effective" blood flow to digital tissues and the total volume of the digit increase, even though the total digital flow decreases (fig. 6). This decrease in total digital inflow volume \(I_v\), as well as in the basal pulsatile flow, is due to increased resistance in arterioles, capillaries, and collecting (capacitance) vessels as a result of an increase in the number of functioning capillaries and distention of the collecting vessels with blood. The decrease in digital inflow volume is greater for diastole than for systole, because during systole the vis a tergo better overcomes the resistance within the small vessels. The increase in "effective" blood flow through the small vessels supplying the tissues results in a rise in the digital skin temperature and a flush. Since the arteriovenous

*FIGURE 5A*

Digital RPG for the same subject shown in figures 1 and 3 (A) under control conditions and (B, facing page) after restoration of circulation to the digit which had been arrested at the brachium for 18 minutes. Note similarity between the digital vascular responses to reactive hyperemia and to bradykinin (fig. 1).
anastomoses are constricted, blood is no longer readily shunted out of the digit, resulting in a delay or "lag" in the time-course curve of digital outflow. The increased resistance in the collecting vessels reduces the amount of blood which can be displaced into the digit during the recording of the volume artifact and at least in part explains the reduction in the magnitude of the volume artifact during the peak response to bradykinin. The increase in the interval between the anaerotic limb of the brachial artery pulse wave and the anaerotic limb of the volume pulse wave, as well as the decrease in the slope of the anaerotic limb of the volume pulse wave during the response to bradykinin, is explained by increased resistance to flow through the small vessels and collecting vessels of the digit.

The precise similarity of the digital vascular responses during reactive hyperemia and after the injection of bradykinin suggests that reactive hyperemia may be due to the release of bradykinin and that the digital vascular responses to reactive hyperemia are due primarily to constriction of the A-V shunts. Subjects in whom both bradykinin administration and reactive hyperemia were studied reported that the pain following bradykinin
Acidification of plasma in vivo activates bradykinogen. However, whether or not the pH changes resulting from the accumulation of acid metabolites during ischemia are of sufficient magnitude to release bradykinin is not known. Studies in animals suggest that bradykinin is produced in glandular tissues to regulate local blood flow according to secretory activity and metabolic requirements. It is possible that the release of bradykinin in the digits during ischemia is also a local regulatory phenomenon governed in part by the effects of anoxia. By closing the A-V anastomoses and reducing the "waste" of blood through these "leaks," the "effective" blood flow to the cells is increased. It may even be speculated that the glomus body, the function of which has never been understood, may release the bradykinin-forming enzyme in response to local ischemia. Furthermore, the glomus bodies which contain large A-V shunts may be sensitive to bradykinin and, in turn, regulate "effective" blood flow to the tissues in response to bradykinin.

The property of bradykinin to constrict selectively the arteriovenous anastomoses provides an important tool for the investigation of these structures. Other studies in this laboratory of the dermal vascular responses to intracutaneous and subcutaneous injections of bradykinin in man show the polypeptide to produce relatively little active dilatation of the small vessels. Therefore, the dermal flush and increase in temperature must be in large part due to passive response to the deviation of digital flow to the small peripheral vessels in response to constriction of the A-V shunts.

Although the injection of bradykinin produced pain in each subject, the digital vascular responses observed with bradykinin could not be explained on this basis for reasons previously described.

Summary
Bradykinin injected ipsilaterally into the brachial artery has been shown rheoplethysmographically to produce digital vascular changes which are the same as those observed in reactive hyperemia. The changes seem to be due to a selective constriction of the A-V shunts with dilatation of the arterioles, capillaries, venules, and veins. These vessels seem to dilate largely in passive response to the constriction of the A-V shunts.

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