Effects of Bradykinin on the Systemic and Coronary Vascular Bed of the Intact Dog


Bradykinin is a polypeptide and one of the plasma kinins. First described in 1949, the pure product was isolated in 1960 and its identity with the original crude mixture established. It has vasodilator properties, stimulates smooth muscle, increases capillary permeability, and causes pain. It has been shown to increase blood flow through the forearm and skin of humans, and reduces resistance in the isolated perfused dog-lung preparation. Recently, bradykinin (among other substances) has been shown to diffuse from the skin of scalded rats.

There is no integrated study of the general and coronary hemodynamic effects of bradykinin in the intact animal. Therefore, the following reports the results of such a study.

Methods

The subjects were eight dogs, weighing 10 to 20 Kg., not selected by age, sex, or breed. Anesthesia was secured by the subcutaneous injection of morphine sulfate (3 mg./Kg.), followed after one hour by Dial-urethanc-Nembutal* (0.25 ml./Kg., I.V.); utilizing fluoroscopy and by way of the neck veins, a cardiac catheter was placed in a main branch of the pulmonary artery and in the coronary sinus. A Cournand needle was placed percutaneously in each femoral artery. Pressures from these sites (except coronary sinus), were measured by a strain gauge and recorded on a direct-writing instrument. Mean pressures were derived by electrical integration.

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*Courtesy Ciba Pty., Australia. It contains Dial, 100 mg./ml.; monothyleurea and urethane, each 400 mg./ml.; Nembutal, 60 mg./ml., was used as a 1:1 diluent.

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One hour after the intravenous anesthetic, cardiac output was measured by the Fick principle, followed shortly by measurement of coronary flow by the nitrous oxide saturation method. The details of techniques used have been reported previously. Recently, bradykinin (among other substances) has been shown to diffuse from the skin of scalded rats.

Some 20 minutes after the control study had been done, synthetic bradykinin* was given. The average dose was 0.05 mg./Kg. This was dissolved in 20 ml. of 0.9 per cent saline and given by continuous intravenous infusion over a period of 20 minutes; during this time, cardiac output and coronary flow were again measured. Monitoring of rate and pressure revealed a steady state of tachycardia and hypotension during the study period. Tachyphylaxis was apparently avoided by this method of administration.

At the end of the experiment, the animal was killed and the heart excised. Left ventricular weight was measured as previously described. This figure was used directly to calculate myocardial oxygen consumption and efficiency. Works and resistances were calculated by accepted formulae.

Results

The figures given are group means with standard deviations. Comparisons were made by the Student t-test: statistical (as opposed to physiological) significance was accepted at the 5 per cent level.

GENERAL METABOLISM (TABLE 1)

Respiratory rate and minute volumes increased. The definite increase in carbon dioxide production was associated with a significant increase in whole-body respiratory quotient. Arterial oxygen content increased significantly; thus, whole-body oxygen extraction narrowed. Less definite, although similar, trends were recorded for carbon dioxide values.

PRESSURE-WORK RESPONSES (TABLE 2)

The trend to increased oxygen consumption, when associated with the decrease in

*Courtesy of Sandoz Pty., Australia.
arteriovenous oxygen difference, led to a definite increase in cardiac output. The tachycardia associated with the drug outstripped this output increase; thus, stroke volume declined.

There were statistically significant decreases in the femoral and pulmonary arterial mean pressures. The recorded increases in left and right ventricular works were statistically insignificant. Vascular resistance decreased in the greater and lesser circulations.

**CORONARY HEMODYNAMICS (TABLE 3)**

Bradykinin was associated with a definite increase in coronary blood flow; calculated coronary vascular resistance definitely decreased. The parallel increase in coronary flow and heart rate resulted in maintenance of coronary flow per heart beat. There was an increase in the rate of coronary flow for each unit of left ventricular work done.

**MYOCARDIAL METABOLISM (O₂ AND CO₂) AND CARDIAC EFFICIENCY (TABLE 4)**

Coronary sinus oxygen content and myocardial oxygen extraction were unchanged. The increases in cardiac carbon dioxide production (coronary sinus — arterial CO₂), and cardiac respiratory quotient were trends only. There was a definite increase in cardiac oxygen consumption, whether determined as
BRADYKININ ON CORONARY CIRCULATION

**Table 3**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (ml./100 Gm. heart/min.)</td>
<td>96 ± 13</td>
<td>139 ± 37†</td>
</tr>
<tr>
<td>Coronary flow per beat (ml.)</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>Coronary vascular resistance (units)</td>
<td>1.2 ± 0.17</td>
<td>0.6 ± 0.13†</td>
</tr>
<tr>
<td>Ratio, coronary flow/left ventricular work</td>
<td>29 ± 11</td>
<td>39 ± 16†</td>
</tr>
</tbody>
</table>

*Figures are means with S.D.
†P value of change 0.05 or less.

**Table 4**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial O₂ content (flow; vol. %)</td>
<td>15.6 ± 2.0</td>
<td>16.1 ± 3.0</td>
</tr>
<tr>
<td>Coronary sinus O₂ content (vol. %)</td>
<td>4.4 ± 1.8</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>Δ arterial-coronary sinus O₂ (vol. %)</td>
<td>11.2 ± 1.0</td>
<td>11.9 ± 1.3</td>
</tr>
<tr>
<td>Coronary sinus CO₂ (vol. %)</td>
<td>50.4 ± 6.0</td>
<td>56.4 ± 5.0</td>
</tr>
<tr>
<td>Arterial CO₂ content (vol. %)</td>
<td>50.9 ± 6.4</td>
<td>46.9 ± 4.5†</td>
</tr>
<tr>
<td>Δ coronary sinus-arterial CO₂ (vol. %)</td>
<td>8.5 ± 2.7</td>
<td>9.5 ± 3.0</td>
</tr>
<tr>
<td>Cardiac respiratory quotient</td>
<td>0.75 ± 0.15</td>
<td>0.80 ± 0.10</td>
</tr>
<tr>
<td>Cardiac metabolic rate—O₂ (ml./100 Gm. heart/min.)</td>
<td>10.6 ± 2.0</td>
<td>10.6 ± 5.5†</td>
</tr>
<tr>
<td>Cardiac metabolic rate—CO₂ (ml./100 Gm. heart/min.)</td>
<td>8.5 ± 3.6</td>
<td>13.8 ± 6.2†</td>
</tr>
<tr>
<td>Left ventricular O₂ consumption† (ml/min.)</td>
<td>50 ± 38</td>
<td>97 ± 49†</td>
</tr>
<tr>
<td>Stroke left ventricular O₂ consumption† (ml.)</td>
<td>0.70 ± 0.05</td>
<td>0.60 ± 0.30†</td>
</tr>
<tr>
<td>Index of efficiency (left ventricular work/C.M.R.O₂)</td>
<td>0.35 ± 0.15</td>
<td>0.25 ± 0.09†</td>
</tr>
<tr>
<td>Mechanical efficiency (% by Joules' Law)‡</td>
<td>31 ± 10</td>
<td>22 ± 9†</td>
</tr>
</tbody>
</table>

*Figures are means with S.D.
†P value of change 0.05 or less.
‡Derived from wet-weight of left ventricle.

In the circumstances of this study, bradykinin increased respiratory rate and air exchange. Unlike the results reported by Waaler, no definite change in tidal volume was found. This discrepancy was possibly due to the difference in the experimental method. There was no definite evidence in the present study of the bronchoconstrictor effect reported in guinea pigs. The respiratory stimulus associated with bradykinin explains to some extent the decreases in arterial and mixed venous carbon dioxide. The decrease in whole-body oxygen extraction appeared to be an important association with the increase in cardiac output; since bradykinin increased forearm flow in man, it is likely that peripheral vasodilatation explains, in part at least, the increase in cardiac output recorded here.

The depression of systemic blood pressure was in keeping with that found in other species; this fall was not the primary association with the reduction in peripheral resistance. The increase in cardiac output was also important. Similarly, the relationship of increased flow and decreased pressure served to explain the decline in total pulmonary resistance. This trend was similar to, but perhaps greater than, that reported in the isolated perfused dog-lung preparation.

The increase in cardiac output was roughly paralleled by the increase in coronary blood flow; the increase in coronary blood flow and the decline in perfusion are associated significantly to decrease coronary vascular resistance. Apart from minor changes in arte-
rial carbon dioxide content, the increases of cardiac oxygen and carbon dioxide metabolism were a function of the increased coronary blood flow. As already noted, the increase in left ventricular work was not statistically significant; thus, cardiac efficiency decreased, whether assessed directly or indirectly (index of efficiency), or on a flow-work relationship.

This increase in coronary blood flow, without change in cardiac oxygen extraction, but with increase in cardiac oxygen usage and decline in efficiency, has been recorded when the heart rate is increased by a pacemaker. In the present study, there was a good correlation (correlation coefficient \( R = 0.5, P = 0.02 \)) between rate and coronary flow. Clearly, this relationship would also exist between rate and cardiac oxygen metabolism. Other factors which are said to relate to coronary flow or cardiac oxygen consumption are increase in left ventricular work and the product of heart rate and mean systemic pressure. In this study, left ventricular work could not be so related \( (R = 0.12) \), but the product \( (\text{rate} \times \text{mean arterial blood pressure}) \) gave a significant correlation \( (R = 0.7, P < 0.01) \). These relationships are, of course, associative and not necessarily causal, but the role of increased heart rate is probably of importance in the explanation of the increase in coronary flow.

Some of the actions of bradykinin have been compared with those of histamine, acetylcholine, and serotonin. Certainly, the two latter increase coronary blood flow, but the concomitant increase in coronary sinus oxygen content is unlike the effect of bradykinin. The stimulant effect of bradykinin upon cardiac output is at variance with the effect of serotonin for the same factor; histamine is said to decrease cardiac output. Thus, there are some differences in the cardiovascular effects of bradykinin when compared with serotonin, histamine, and acetylcholine.

The circulatory depression due to some types of snake venom or injected trypsin has been associated with the release of bradykinin. If this is so, it is perhaps possible that other circulatory measurements, e.g., coronary flow or cardiac efficiency, are affected in the manner shown in the present study.

### Summary

Bradykinin, in the circumstances of this study, increased heart rate, cardiac output, and coronary blood flow. Systemic, pulmonary, and coronary vascular resistances decreased; these changes were not entirely due to the decrease in systemic and pulmonary arterial pressures. The changes in myocardial oxygen and carbon dioxide metabolism were mostly related to the increase in coronary blood flow. Bradykinin was found to be associated with a decrease in cardiac efficiency.

### References

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