An acute pressure rise in the vascularly isolated carotid sinus causes a decrease in total peripheral resistance and a bradycardia which lead to a fall in arterial pressure. A shift in posture that raises blood pressure at the carotid bifurcation elicits a similar reflex response. Stimulation of most of the other baroreceptor areas of the systemic arterial and cardiopulmonary systems produces a depressor response and bradycardia. However, none of these baroreceptor areas prevents the development of experimental or clinical hypertension, and there is evidence that in chronic experimental hypertension, the carotid sinus nerves carry a normal nerve-impulse pattern to the central nervous system in response to high carotid sinus pressure. It is also a fact that hypertensive animals and humans have normal heart rates under basal conditions.

The present work was designed to find out exactly how long it takes the baroreceptor reflex mechanism to adjust to a continuous pressure elevation. One report sheds some light on this subject: Kubicek et al. have shown that the pulse rate had returned to normal at the end of a 20-hour period of elevated pressure due to splanchnic nerve stimulation. Thus, adjustment of the cardiac part of the reflex mechanism occurs in less than 20 hours.

This paper is a report of a group of experiments done in the intact conscious rabbit to observe the effect of a continuously elevated arterial pressure on reflex bradycardia specifically, when baroreceptor areas are continuously stimulated, we want to know: (a) the rate of adjustment and (b) the sensitivity of the cardiac reflex mechanism. We studied the problem by elevating arterial pressure with the infusion of angiotensin, and the criterion for adjustment was the return toward the control heart rate while arterial pressure was still high.

**Methods**

Rabbits were anesthetized with ether or sodium thiopental, 30 mg./Kg., intravenously. A 0.062-inch O.D. polyethylene tube was tied into the femoral artery, and after the animal was placed in a small wire cage, where it sat or lay quietly throughout the experiment, an electrical transducer was attached to the tube. Pressure was recorded for 15 to 30 seconds every one or two minutes throughout the entire experiment on the Sanborn Twin-Viso recorder. Five thousand units of heparin were administered every hour to prevent clotting. Venous or right heart pressure was measured in a few experiments along with arterial pressures.

Control pressure readings were taken until we were sure the animal had recovered completely from the anesthetic. The ear was anesthetized with 2 per cent procaine, and then room-temperature saline was infused into the marginal ear vein from a Harvard constant infusion pump for one-half to one hour or until pressure and heart rate variations were minimal, at which time the infusion of angiotensin was started. Dosage ranged from 0.6 to 4.7 μg./Kg./min. The total volume of saline and angiotensin infused into an animal was kept minimal by using infusion rates of 0.039 to 0.062 ml./min.

Heart rate was obtained by counting the pulse record to within half a beat for six seconds and multiplying by 10. Systolic and diastolic pressures could be read to within ± 2.5 mm. Hg. In those experiments where mean pressure is reported, the values were obtained from an electrical mean pressure integrator. The heart rate and blood pressure

*We are indebted to Dr. William Wagner of CIBA Pharmaceuticals for his generous supply of synthetic angiotensin (CIBA Hypertensin: val. 5-angiotensin II).*
were plotted on graph paper for each minute and then averaged for five-minute periods and re-plotted. Angiotensin infusions were maintained for different lengths of time, ranging from 30 minutes to 8 hours in 17 animals.

**Results**

If the heart rate changed during the control period, because of the diminishing effect of anesthesia or infusion of saline, the control period was extended until heart rate variations were minimal for at least 15 minutes before angiotensin was infused. If an animal seemed jumpy or nervous, 2 per cent procaine was injected into the femoral area. However, most rabbits showed no sign of discomfort.

When angiotensin was infused, pressure rose at variable rates and reached a plateau within 5 to 40 minutes, average 19 minutes. The average diastolic pressure plateau was 21 mm Hg, range 8 to 32, above control pressure. The heart began to slow simultaneously with the rise in pressure and gradually stopped slowing as the pressure plateau was approached.

Figure 1 (no. 12) is a plot of minute blood pressure and heart rate values from an animal whose heart rate began to rise within five minutes of initial slowing. The minute
values are used to illustrate how extremely sensitive the reflex mechanism may be to minute, rapid pressure changes. Here they were caused by momentarily stopping the infusion to refill the angiotensin syringe, denoted by R in figure 1. Figure 2 (no. 68) is a plot of five-minute averages from an animal whose heart rate did not start to rise for 25 minutes after the initial slowing but then did so very rapidly. In contrast, the heart rate in figure 3 (no. 64) stayed slow for 80 minutes and then rose slowly. The differences in rate of restoration of heart rate cannot be attributed to differences in anesthetics, e.g., both nos. 64 and 68 had thiopental for the placement of femoral catheters. The cardiac reflex mechanism in rabbit no. 410 (fig. 4) showed no adjustment during more than a seven-hour period of elevated pressure. The infusion was finally stopped because the animal became refractory to angiotensin; a 10-fold increase in infusion rate could not keep the blood pressure up. This refractoriness to angiotensin occurred sooner in some other animals.

Three of the 17 animals did not show any heart rate increase by the time infusion was terminated at 36 or 60 minutes and 7½ hours (fig. 4), respectively. A fourth animal with a fluctuating heart rate is discussed later. Data from the 13 animals that showed adjustment of the reflex bradycardia are presented in table 1.

The greatest amount of slowing took place in the first 10 minutes of infusion, with less slowing and a leveling off in the second 10-minute period. The term "initial drop" (table 1, column 3) refers to the total drop in heart rate that occurred by the end of the first 20 minutes of infusion. The sensitivity of the cardiac reflex mechanism (column 2) was determined by dividing the drop in heart rate by the increase in diastolic pressure. Since the blood pressure did not increase at a constant rate, sensitivity was calculated for both the first and second 10-minute periods and then averaged for each of six animals. For the remaining seven, reflex sensitivity was determined from the first 10-minute period only since these animals showed no further pressure increase; the pressure either fell slightly or did not change.

Five to 120 minutes, average 37 minutes (table 1, column 3), after the initial drop, the heart rate began to rise toward the control value at rates ranging from 1.2 to 6.0 per cent of the initial drop per minute (column 4). These rates of rise are based on the slope of the line best fitted to the one-minute plotted heart rate values.

In some experiments, pressure could not be maintained at the initial plateau value, and it gradually decreased at maximum rates of 3 mm. Hg and 8 mm. Hg per 10 minutes for diastolic and systolic, respectively. Often, systolic pressure decreased without a change in diastolic. Although any decrease in pressure was undesirable for the purpose of this study, diminishing bradycardia could not be attributed solely to these rates of pressure decrease since there was no correlation between them and the rates of rise in heart rate. Moreover, in some experiments, the heart rate rose in the presence of constant and even increasing arterial pressure (fig. 2).

After the rise in heart rate had started, 50 per cent of the initial drop* had been restored within 2 to 30 minutes, average 16 minutes. As shown in figure 5, this time between start of heart rate rise and 50 per cent restoration of the initial drop bore a definite relationship to the sensitivity of the reflex response. The more sensitive the initial reflex cardiac response was, the longer it took to restore 50 per cent of the initial drop once the rate had started to rise. The exact time in each case depended on both the rate of rise and the amount of initial slowing. These two parameters would then be related to sensitivity. The sensitivity was directly related to the amount of initial slowing (data not shown). The values in table 1 show some indication of an inverse relationship between sensitivity (column 2) and the

*Since all experiments were not run until the heart returned to its control rate, we have used 50 per cent restoration of the initial drop as the basis for comparing animals.

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TABLE 1
Adjustment of Reflex Bradycardia During Angiotensin Infusion

<table>
<thead>
<tr>
<th>Animal number</th>
<th>SENSITIVITY Heart rate drop/mm. Hg increase in diastolic pressure</th>
<th>Minutes from initial drop in heart rate to start of rise*</th>
<th>RATE OF RISE*% of initial drop/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.57</td>
<td>10</td>
<td>6.0</td>
</tr>
<tr>
<td>16†</td>
<td>1.8</td>
<td>5</td>
<td>4.4</td>
</tr>
<tr>
<td>68†</td>
<td>2.1</td>
<td>20</td>
<td>5.5</td>
</tr>
<tr>
<td>74†</td>
<td>2.3</td>
<td>55</td>
<td>1.9</td>
</tr>
<tr>
<td>28</td>
<td>2.8</td>
<td>20</td>
<td>5.6</td>
</tr>
<tr>
<td>61</td>
<td>2.8</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>31†</td>
<td>3.1</td>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td>64</td>
<td>3.5</td>
<td>80</td>
<td>1.3</td>
</tr>
<tr>
<td>72†</td>
<td>3.7</td>
<td>35</td>
<td>1.3</td>
</tr>
<tr>
<td>65†</td>
<td>4.7</td>
<td>105</td>
<td>1.2</td>
</tr>
<tr>
<td>9</td>
<td>4.8</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td>12</td>
<td>5.4</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>66</td>
<td>9.4</td>
<td>120</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Means</strong></td>
<td><strong>37</strong></td>
<td><strong>2.8</strong></td>
<td></td>
</tr>
</tbody>
</table>

*See text for explanation.
†Animals whose cardiac reflex sensitivity was averaged from the first and second 10-minute periods of infusion. See text.

rate at which bradycardia diminished (column 4), i.e., the first seven animals had sensitivity values at or below 3.1 and their heart rates rose 1.9 to 6.0 per cent of the initial drop per minute, while the others, at or above 3.5, had rises of 1.2 to 1.6 per cent of the initial drop per minute.

Although there was a tendency for those with a long time between initial drop and start of heart rate rise (column 3) to have the slower rates of rise (column 4), this was not consistent. As a result, the total time from initial drop to 50 per cent restoration was not related either to sensitivity or to the amount of initial slowing.

Out of the 13 animals whose cardiac reflex mechanism adjusted during the infusion, 11 developed a tachycardia when the angiotensin infusion was stopped. Moreover, the amount of overshoot above control heart rate was directly related to the amount of restoration of heart rate that had occurred during infusion as shown in figure 6. The two rabbits without postinfusion tachycardia had total rate restorations during the infusion of only 20 to 35 beats, and when the infusion was stopped, heart rates rose to control values but did not overshoot. The overshoot values plotted in figure 7 were those obtained at or above control pressure, 5 to 15 minutes after angiotensin was stopped in 9 of the 11 rabbits. Unfortunately, the other two had postinfusion hypotension during this time and so were not plotted.

The experiments in which venous or right ventricle pressures were recorded showed that these pressures sometimes rose momentarily when the heart first slowed and then stayed at normal values throughout the angiotensin infusion.

Discussion
Angiotensin was the pressor agent of choice for the present study, because it does not directly affect the heart rate. In our labora-
tery, when angiotensin was added to the blood of a heart-lung preparation with flow limited to the coronaries, no change in rate was ever observed (unpublished observation). Secondly, unlike norepinephrine, angiotensin does not cause a depressor reflex when applied locally to the carotid sinus. The present data show that the initial drop in heart rate, resulting from a moderate elevation of arterial pressure, persisted for 5 to 120 minutes in 13 rabbits. At the end of these times and with pressure still high, the heart rate began to rise, and bradycardia diminished at rates ranging from 1.2 to 6.0 per cent of the initial drop per minute. Kubieck et al. found that pulse rate had returned to normal after 20 hours of elevated arterial pressure produced by splanchnic nerve stimulation. We had six animals whose initial heart rate drops were restored 80 to 100 per cent by the time the infusion was stopped. The average time between initial drop to start of heart rate rise for these six was 23 minutes, range 5 to 80 minutes. After the rise started, the average time to attain 80 to 100 per cent restoration of heart rate was 27 minutes, range 15 to 45 minutes. Therefore, following initial slowing, it took an average total time of 50 minutes for the heart rate to return to or almost to its control rate while arterial pressure was elevated.

The rate of return toward control heart rate was fairly continuous with the exception of two animals. One, not included in "Results," showed a series of rises and falls in heart rate during a three-hour infusion as shown in figure 7. This response may be a rare instance of alternating fatigue and recovery of the mechanism responsible for bradycardia. The other rabbit's heart rate leveled off for two hours after 50 per cent restoration of the initial drop, and then began to rise again at twice the original rate.

When their 20-hour period of splanchnic nerve stimulation was over, Kubieck et al. also noted a definite tachycardia that persisted for a few hours. They interpreted the sharp increase in pulse rate as an accommodation to the higher pressure by the reflex mechanism and an attempt to maintain the elevated pressure. We found a direct relationship between the extent of postinfusion tachycardia and the amount of restoration of heart rate attained while pressure was elevated. We take this as indirect evidence of a definite resetting or change to a new level of activity by the reflex mechanism. McCubbin claimed that the pattern of impulse activity from the carotid sinus nerve of dogs was unchanged during six hours of elevated pressure elicited by angiotensin infusion. If we can assume that this applies to rabbits, the diminishing bradycardia or resetting of the reflex mechanism during elevation of arterial pressure was not due to a change in receptor areas during the infusion period, but rather to a change either within the central nervous system or in the reflex pathways themselves.
system (CNS) or on the effector side of the reflex pathway. Except for McCubbin's report, the only direct observations of which we are aware were made within a 10-minute period, and they show that baroreceptors adapt so quickly they could not account for the adjustment of heart rate we observed. For example, a study of single carotid sinus baroreceptor units showed they adapt to a steady pressure within seconds of its application, i.e., there is not a gradual decrease in nerve discharge once a steady pressure is established. Bronk stated that upon elevating carotid sinus pressure, sympathetic nerve activity to the heart disappeared but within a matter of seconds could reappear.

It is less likely that adjustment of reflex bradycardia was initiated from the effector side of the reflex than in the CNS. Preliminary studies in our laboratory show that if blood pressure is kept constant and the peripheral vagus nerve stimulated continuously for an hour, the heart remains slow and constant.

There was the possibility that reflexes from the right side of the heart could have caused a rise in the heart rate during angiotensin infusions. However, venous pressure did not rise except sometimes momentarily during initial slowing. The subsequent rise in heart rate was not associated with elevated venous or right heart pressures.

We did not find any correlation between either sensitivity of the initial cardiac response or magnitude of slowing and the time of maintenance of the initial bradycardia, i.e., time between initial drop in heart rate and start of rise. However, once heart rate began to rise, the rate of return toward control was inversely related to sensitivity (table 1). The more sensitive the reflex mechanism, the longer it took to restore 50 per cent of the initial drop in heart rate. Bradycardia starts to be reversed at some unpredictable time, probably by the CNS, but the rate of reversal depends on the effectiveness of the cardiac reflex slowing mechanism.

In a recent article, Nishith et al. report that a single injection of angiotensin into anesthetized dogs had a direct effect on the cardioaccelerator center that is masked at first by the buffer nerve reflex effect. An immediate tachycardia was observed in sinoaortic denervated dogs. We have made the same observation in two of three sinoaortic denervated rabbits with a short continuous infusion of angiotensin. However, we also injected angiotensin directly into an internal carotid artery distal to the sinus and without impeding blood flow of two normal rabbits. There was no effect on heart rate until the material reached the general circulation to cause a rise in arterial pressure and an accompanying bradycardia. None of the heart rate changes in the present work were related to the rate of infusion or to total dosage of angiotensin. Moreover, even if angiotensin had a cardioaccelerator action under these experimental conditions, it would still not invalidate the conclusion that restoration of heart rate resulted from adjustment of the reflex mechanism, since this would have to occur before the angiotensin-tachycardia effect could appear.

Summary

Angiotensin was infused into intact, conscious rabbits to produce a continuous, moderate elevation of arterial pressure. The reflex cardiac rate response was studied. Within two hours of initial drop in heart rate, average time 37 minutes for 13 rabbits, the heart rate began to rise. The rates of rise were between 1.2 and 6.0 per cent of the initial drop per minute. Thus, in the presence of elevated arterial pressure, the cardiac reflex mechanism can adjust so that heart rate reaches control values within an average time of one hour in most animals. One additional animal showed no tendency for adjustment in over seven hours of infusion. The time between start of heart rate rise and restoration of 50 per cent of the initial drop was directly related to the sensitivity of the initial reflex response, i.e., heart rate drop per mm. Hg increase in diastolic pressure. Most of the animals developed a postinfusion tachycardia.
which was directly related to the amount of increase in heart rate attained by the end of the infusion. We conclude that in the presence of continuously elevated arterial pressure, the reflex cardiac slowing mechanism can adjust within a relatively short time, and the evidence that this represents a resetting of the mechanism within the central nervous system is discussed.

References

Book Review

This monograph contains the papers and discussion during a recent symposium held in London. The following polypeptides are discussed: oxytocin, vasopressin, angiotensin, substance P, bradykinin, and anaphylatoxin. Each substance is discussed in terms of its discovery, chemical isolation, synthesis (for some), and effects on smooth muscles and blood vessels. Several vascular phenomena are described: reactive hyperemia, peptone shock, hyperemia of the salivary gland during increased activity, vasocostriction from purified angiotensin, vasodilatation from bradykinin. The index of this monograph is also a useful compilation of the names and synonyms of polypeptides that have been described to be biologically active.
Adjustment of Reflex Bradycardia to Elevated Arterial Pressure in Conscious Rabbits
Natalie Alexander and Marjorie De Cuir

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