Reflex Regulation of Arterial Pressure during Sleep in Man

A QUANTITATIVE METHOD OF ASSESSING BAROREFLEX SENSITIVITY

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ABSTRACT

The control of arterial pressure during sleep was studied in 13 untreated, unsedated subjects aged 20 to 46, including 7 with hypertension. Arterial pressure was measured directly. A transient rise of arterial pressure up to 30 mm Hg was produced by the sudden intravenous injection of 0.25 to 2 μg of angiotensin. Linear plots were obtained in 10 of 13 subjects when the systolic pressures of successive pulses during the pressure rise were plotted against the pulse intervals which began the next beat. The relationship was disturbed by movement or arousal, and was better when pulse intervals falling in inspiration were discarded.

The slope of the line (milliseconds of cardiac slowing per millimeter rise in systolic pressure) in the awake subject ranged from 2 to 15.5 msec/mm Hg, and from 4.5 to 28.9 during sleep. Reflex sensitivity was highest in dreaming sleep. In 7 of 10 subjects, baroreflex sensitivity increased significantly during sleep; in 6, the prevailing arterial pressure was inversely correlated with the baroreflex sensitivity. The pressure appeared to be the dependent variable. It is concluded that the baroreceptor reflex arc can be rapidly reset, particularly during sleep. The lower arterial pressures during sleep may be actively maintained in some subjects by increased baroreflex sensitivity.

ADDITIONAL KEY WORDS: angiotensin, baroreflex resetting, dreams, hypertension, vagus, heart rate control

The methods so far available for testing buffer reflex function in man have been so crude that it has been impossible to estimate the sensitivity or activity of these reflexes. Regniers (1) claimed they were inactive in human hypertension, because occluding the carotids below the sinuses had no influence on arterial pressure or heart rate, but he took no precautions to ensure that the carotids were in fact occluded. When this was done, Gammon (2) and Pickering and associates (3) found a rise in arterial pressure and pulse rate in healthy, nephritic, and hypertensive subjects, but a quantitative assessment was impossible. The reflex responses of heart rate to being tilted on a table were later shown to be smaller in subjects with higher pressures and absent in those with malignant hypertension. Bevegard and Shepherd (4) investigated the influence of transmural pressure on the carotid baroreceptors in man and demonstrated the activity of the reflex at rest and during exercise.

The need for a more accurate method has long been evident to those interested in the mechanism of persistent hypertension in man. We wished to investigate also the fall of arterial pressure found in sleep (5, 6). Among the many separate mechanisms exerting control upon blood pressure, those most influen-
tial in regulating its short-term behavior are the baroreceptor, or buffer, reflexes. Do these function in the same way in the sleeping as in the waking subject? If so, how is it that despite the much lower arterial pressure, the heart rate does not increase but slows. The afferent nerve impulses responsible for reflex baroreceptor regulation of heart rate and vasomotor activity arise in the arterial tree near the heart, notably in the carotid sinuses and aortic arch (7). The effects of these impulses depend on their subsequent course in the brain stem, a structure known to be the site of marked changes of nervous activity during sleep (8) and dreams (9). Does sleep, then, alter the function of these reflexes in any way? Do they thus contribute to the maintenance of the lower arterial pressure of sleep? We have attempted to answer these questions using a new method of assessing baroreflex function.

Methods

The method is based on the observation that the rise of arterial pressure following a single, quick intravenous injection of angiotensin is accompanied by cardiac slowing. This cardiac slowing seems, on the evidence outlined in the discussion, to be due to a reflex from the baroreceptors. We found a linear relationship between systolic blood pressure and pulse interval during the transient pressure changes produced by angiotensin injections. We studied 13 volunteer subjects aged 20 to 46 years; two were normal and 11 were said by their referring physicians to have raised blood pressure or pulse interval. However, in 4 of these 11 we found normal arterial pressures (mean arterial pressure). However, in 4 of these 11 we found normal arterial pressures (mean arterial pressure at or below 100 mm Hg) during our three-night observation period, and we have therefore called them normal in this report. (We will subsequently refer to H or N for hypertensive or normotensive subjects, e.g. H3, N4.) None of the subjects was receiving any medication. Each lay on a hospital bed and was studied in the laboratory before, during, and after sleep, between approximately 9:30 PM and 6:30 AM on three successive nights. Most of the subjects engaged in their normal activities during the intervening days.

On the first night, the blood pressure was measured every 5 min by an automatic cuff recorder (5). On the second night this was repeated, with the addition of five channels of electroencephalographic (EEG) records. On the third night, the EEG was again recorded, but the blood pressure was measured directly.

In each subject a polyethylene cannula, 1 mm i.d., was inserted into a brachial artery by a modified Seldinger technique and pushed 10 cm into the artery. The cannula was connected by 1.2 m of 1.5 mm (i.d.) polyvinyl pressure tubing (capacity 2 ml) to a strain gauge (Consolidated Electrodynamics) fixed at the level of the sternal angle. The arterial cannula was flushed frequently via a three-way stopcock with heparinized saline solution. The signals were amplified by a Grass model 6A1 low-level d-c amplifier and inscribed on curvilinear paper using a Grass polygraph at a paper speed of 30 mm/sec. Mean pressures were obtained by electrical damping. The arterial pressure gauge was calibrated against a standard mercury manometer. The frequency response of the catheter-manometer system was tested dynamically. At 5 cps the amplitude was 105% of that at 1 cps. The system resonated at 18 cps when the amplitude was 182% of that at 1 cps. A saw-toothed waveform was followed faithfully up to 3 cps. The electrocardiogram (ECG) was monitored in each subject from two precordial electrodes. The rate and approximate depth of respiration were recorded from a rubber stethograph about the chest connected to a Grass PT5 strain gauge.

A medium-sized Intracath (C.R. Bard, Inc., Murray Hill, N. J.) polyethylene cannula was inserted 15 cm into the antecubital vein on the same side. The cannula was connected to 1.2 m of polyethylene tubing, 1.5 mm i.d., leading to a three-way tap; this allowed the subject limited arm movement. Injections (up to 1 ml) were immediately flushed in with 4 ml of saline. The beginning and end of the flush, which lasted 5 to 8 seconds, were signaled on the record. Similar injections and flushings with saline not containing angiotensin were given in all subjects in order to control volume and temperature effects, but were without effect on blood pressure or pulse interval. Each subject was tested for sensitivity by injecting serially graded doses of 0.25 μg of angiotensin until the dose was reached which produced a rise of systolic pressure of 25 to 35 mm Hg or an obvious increase in pulse interval (when there was usually a smaller pressure rise). This dose was usually 0.5 to 1.0 μg. Five channels of EEG were recorded from felt-padded disc electrodes of the silver/silver chloride type, with solid silver connections. These were held in position with collodion-impregnated strips of gauze in a placement pattern especially adapted to recording the major diagnostic features of the sleep EEG. Standard electrode positions Fp1-C4, C1-O2, T1-
O2, Fz-Cz, Cz-Pz, were employed, as defined by
the International 10-20 system of electrode
placement. Electroencephalograms were recorded
with Grass model 6 A5 D amplifiers at a sensi-
tivity of 7.5 \mu V/mm, a low linear frequency
setting of 1 cps (time constant, 0.12 seconds)
and a high linear frequency setting of 70 cps
(so that the pen deflection of a 70-cycle input
signal was within 20% of the deflection of a 10-
cycle input signal of the same voltage). The
last two control settings served to minimize
sweat artifact and muscle potential interference,
respectively. Eye movements were registered by
a separate, identical amplifier as changes in
potential between two silver electrodes placed
1 cm lateral, and 1 cm inferior, to the outer
canthus of each eye. Under these circumstances
movements of the eyes, and thus of the source
of the corneoretinal potential (cornea-positive,
-0.1 v), produced relative changes in potential
between the two electrodes. These were re-
corded at a time constant setting of 0.12
seconds. Electron!ogram potentials from the plat-
ysma muscle were recorded on a separate chan-
nel from a pair of silver electrodes held in
place under the chin. Sleep stages were defined
in accord with the criteria for adults given by
Gastaut and Broughton (10).

Results

As a measure of the response to a pressure
change, the pulse interval was chosen, since
this could be measured accurately by the
R-R interval on the ECG, without disturbing
the sleeping subject. As a measure of stimulus,
the systolic, diastolic, pulse, and mean pres-
sures, and the rate of rise of pressure (11, 12)
were available. We chose systolic pressure;
pulse pressure did not regularly change with
angiotensin. We have not examined the rela-
tionship to the rate of rise of pressure.

The latency of the reflex response in man
was unknown, but animal studies suggested
it was between one and two beats (13). We
therefore proceeded empirically to plot sep-
arately the systolic pressure and pulse pres-
sures of successive arterial pulses against their
respective, preceding, coincident, and several
succeeding cardiac (pulse) intervals (the latter being measured as R-R intervals in the
ECG record). We found that the results of
each pressor test could be expressed as a
straight line with greatest consistency when the
systolic pressures of successive arterial

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pulses were plotted (as abscissa) against
those pulse intervals which began with the
next beat (as ordinate). Similar plots employ-
ing earlier or later pulse intervals gave a poorer statistical correlation. There was no corre-
lution between the value of the pulse pressure
and the duration of succeeding cardiac inter-
vals. This appeared to result, at least in part,
from the fact that pulse pressure increased
much less consistently than systolic pressure
during the pressor responses to intravenously
injected angiotensin. In 2 subjects, angio-
tensin raised systolic and diastolic pressures
by equal amounts so that the pulse pressure
throughout the response remained constant.

The same portion of each pressor response—
the 20- to 30-second period from the start of
the rise of pressure to just before peak pres-
sure—was selected for analysis and compar-
ison in each subject; the regression coefficient
(slope), and the correlation coefficient and its
P value were calculated for each line by the
method of least squares. Responses that were
interrupted by body movement, or fluctuation
in the depth of sleep showed a large scatter
of points. In these instances, a low correlation
coefficient resulted, and those showing a P
value greater than 0.05 were discarded. The
slope (regression coefficient) is used as an
expression of baroreflex sensitivity, and ex-
presses the increase in pulse interval per
millimeter rise in systolic pressure. The exact
dose of angiotensin used was not important;
larger doses caused a greater pressure rise
and prolonged the plotted line but did not
alter its slope. Heart rate is influenced by
respiration (12, 14) and a better correlation
between systolic pressure and succeeding pulse
interval was obtained when each response
was analyzed with discrimination between
pulse intervals occurring in inspiration and
expiration. Pulse intervals that began in in-
spiration or in which more than half fell
during inspiration were not plotted. The im-
provement in correlation obtained by this
discrimination varied from subject to subject.

For purposes of comparison of reflex re-
sponses at different times in the same sub-
ject and between different subjects, we took
### Table 1

**Data from Response to a Representative Angiotensin Injection (Subject N5)**

<table>
<thead>
<tr>
<th>Systolic pressure (mm Hg)</th>
<th>R-R interval (msec)</th>
<th>Systolic pressure (mm Hg)</th>
<th>R-R interval (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expiration</strong></td>
<td></td>
<td><strong>Expiration</strong></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>670</td>
<td>99</td>
<td>660</td>
</tr>
<tr>
<td>100</td>
<td>650</td>
<td>102</td>
<td>670</td>
</tr>
<tr>
<td>104</td>
<td>690</td>
<td>106</td>
<td>720</td>
</tr>
<tr>
<td>(Injection here)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>700</td>
<td>97</td>
<td>700</td>
</tr>
<tr>
<td>97</td>
<td>710</td>
<td>96</td>
<td>700</td>
</tr>
<tr>
<td>(End of flush)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>660</td>
<td>96</td>
<td>670</td>
</tr>
<tr>
<td>99</td>
<td>660</td>
<td>100</td>
<td>680</td>
</tr>
<tr>
<td><strong>Inspiration</strong></td>
<td></td>
<td><strong>Inspiration</strong></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>670</td>
<td>102</td>
<td>660</td>
</tr>
<tr>
<td>101</td>
<td>650</td>
<td>104</td>
<td>680</td>
</tr>
<tr>
<td>103</td>
<td>660</td>
<td>104</td>
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<td>103</td>
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<td>108</td>
<td>730</td>
<td>107</td>
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<td>107</td>
<td>770</td>
<td>108</td>
<td>750</td>
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<td>(End of flush)</td>
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<tr>
<td>112</td>
<td>780</td>
<td>112</td>
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<tr>
<td>111</td>
<td>830</td>
<td>111</td>
<td>790</td>
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<td>110</td>
<td>800</td>
<td>110</td>
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<tr>
<td>108</td>
<td>770</td>
<td>108</td>
<td>760</td>
</tr>
<tr>
<td>115</td>
<td>810</td>
<td>115</td>
<td>840</td>
</tr>
</tbody>
</table>

Slope = 15.64; r = 0.926 (See Fig. 1).

Measurements in boldface are those plotted in Figure 1.

The slope of the plotted line (i.e., the increase in pulse interval for each millimeter rise in systolic pressure) as indicative of the sensitivity of the baroreceptor heart rate reflex. Representative data showing the method of correlation, plotting, and calculation of a regression line for a typical response are set out in Table 1 and Figure 1. Figure 2 illustrates another typical plotted response and shows the respiratory modulation of reflex bradycardia. The scatter of points representing inspiratory pulse intervals was greater and the slope of their regression line a little smaller. Figure 3 illustrates a larger scatter of inspiratory points and an additional feature of the plotted responses. Later points in the response—toward the peak of the rise in pressure—tended to depart rather suddenly from the regularly linear relation observed between earlier points. This may have been due to release of adrenal catecholamines (15) or to central stimulation of sympathetic activity (16). This is why the earliest portion of each response was selected for comparison with other responses in each subject. Figure 4 shows the actual recording.
Subject N5. Response to 1.5 μg angiotensin in stage 4 sleep. This is the plot of the pressures designated in Table 1.

Of that portion of the response from which the line of Figure 3 was calculated and the method of obtaining the plotted point. Some difficulty was encountered during stage 2 sleep. This stage is characterized by marked electroencephalographic activity and the frequent interruption of an otherwise regular trace by sharp wave vertex transients known as K complexes. These are accompanied by manifestations of sympathetic discharge in man (17). When such a K complex occurred during a recorded response, the regularly linear relationship between pulse interval and systolic pressure was abolished at the point of its occurrence (Fig. 5). A similar problem was met with tests performed during rapid eye movement (dreaming) sleep, when there were frequent phasic bursts of tachycardia and other signs of massive sympathetic discharge.

In only 1 subject (H6) of the 13 studied was it impossible to obtain reflex cardiac slowing with the stimulus used. He had a systolic arterial pressure of 170 mm Hg and showed no bradycardia when the pressure was raised a further 30 mm Hg. Another subject (N6) was excluded after a mild febrile reaction developed following injections through a catheter which probably contained pyrogens. It was possible to obtain rectilinear plots of baroreceptor reflex sensitivity in 10 of the 11 remaining subjects (Table 2). In 1 subject with coarctation of the aorta (H7), the response was curvilinear, convex to the left, and we therefore could not obtain any
Subject H3. Response to 0.5 µg angiotensin in stage 4 sleep. Plot as in Figure 2. Note the linear arrangement of expiratory points in contrast to the much more scattered pulse intervals in the inspiratory phase of respiration. The dotted line connects late points in the response which may reflect adaptation of the reflex, a delayed effect of angiotensin on the heart rate, or both.

quantitative information. In 4 subjects not included in this report we considered the arterial pressure to be too high to raise further and therefore did not proceed with baroreflex testing by this method. We tested the reflex sensitivity in the 10 subjects in Table 2 by repeated injections of angiotensin. No tests were done for at least 30 min after the initial cannulation. Injections were given before, during, and after sleep. The number of injections per subject ranged from 7 to 34. No tachyphylaxis was seen in the pressor effect of angiotensin, but the dosage was small (not more than 3 µg and usually 0.5 to 1 µg) and was not repeated until the pressure had fallen again to control values (usually 1 to 2 minutes).1

1A table giving the timing, dose, and responses to all injections in the 10 subjects has been deposited as Document no. NAPS-00169 with the National Auxiliary Publications Service of the American Society for Information Sciences, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, N. Y. 10001. A copy may be secured by citing the Document number and remitting either $1.00 for a microfiche copy or $3.00 for a photo copy. Advance payment is required. Make checks or money order payable to ASIS-NAPS.

Polygraphic recording of the response plotted in Figure 3. Records from above down. Channels 1, 2, 3, 5 and 6 show the continuous slow waves of the EEG at stage 4 sleep. Channel 4 records eye movements, (EOG); Channel 7 is an electromyogram (EMG); Channel 8, the ECG, shows the length in hundredths of a second of plotted R-R intervals above the record, and those of the inspiratory pulse intervals (below record) omitted from the plot (Fig. 3); Channel 9 records arterial pressure; value of respective systolic pressures are shown under each pulse wave; Channel 10 shows respiration, inspiration downwards; vertical bars demarcate inspiratory from expiratory portions of each respiratory cycle. Note that the section of the polygraphic record illustrated here includes only the first five of the seven plotted points of Figure 3.

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The results, comparing the average reflex sensitivity both before and after sleep with that during sleep, are summarized in Table 2. The sensitivity of the baroreflex arc changed significantly during sleep in 8 of 10 subjects. In 7 of 10 the sensitivity increased with sleep; in 2 subjects the slope increased during sleep but not to a statistically significant degree; and in subject H5 the sensitivity decreased.

The averaged values in Table 2 conceal in some cases a considerable variation in sensitivity in what is ostensibly the same state of waking or sleep. The reasons for this are not entirely clear. The results of tests which are temporally related (within about 30 min)
and in the same EEG state are closely similar.

The consistency of the results which it is possible to achieve in some subjects may be seen in Figure 6, which shows all the results during one night in one subject (H3).

Correlation with Stage of Sleep.—There were no consistent differences in the slope of the responses recorded in stages 2, 3, and 4 of synchronized sleep. Stage 1, at the onset of sleep, usually lasted too briefly to allow testing. There was, however, a distinct pattern associated with dreaming sleep, during which the most marked increases in slope were seen. Six of the seven subjects in whom it was possible to obtain measurable responses in dreaming sleep showed the greatest intensity of reflex bradycardia of the night in this phase. This finding was itself not consistent, however; some responses, though increased over waking values, were no steeper than those seen during synchronized sleep. In two subjects (H4 and N5), the only definite increase in reflex sensitivity was seen in dreaming sleep.

In some subjects, increases in reflex sensitivity occurred in single responses some minutes just before sleep (Fig. 6).

Correlation of Reflex Sensitivity with R-R Intervals of the ECG.—The average value of 10 consecutive expiratory pulse intervals in
Subject N5. Stage 2 sleep. Control angiotensin injection at 0338 produced sharp rise in pressure and reflex bradycardia. At 0340-30 in the recovery period, slow infusion of angiotensin was begun; rate of infusion was adjusted so as to maintain blood pressure at the presleep level of 110/60 mm Hg. At 0343-20, a second injection of angiotensin produced a further sharp rise in pressure and additional slowing of the heart. Infusion was stopped; blood pressure returned to the previous low value of stage 2 sleep (88/44) within 2 minutes. A third and final injection (postinfusion control) at 0350:30 completed the experiment. The values or reflex sensitivity for the three injections were 19.6, 36.7 and 21.9, respectively. Thus, although the second injection of angiotensin produced small absolute changes of pressure and heart rate, the degree of cardiac slowing per unit rise of pressure was not diminished, but, if anything, increased.

the period immediately before injection was determined in each subject. This was correlated with the value of the slope of the reflex response to the subsequent injection. In 6 of 10 subjects, the greatest reflex sensitivity was coincident with the lowest resting heart

**TABLE 2**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Awake</th>
<th>Asleep</th>
<th>Dreaming</th>
<th>Mean of slopes</th>
<th>df</th>
<th>P</th>
<th>Regression of BP on slope</th>
<th>df</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>N1</td>
<td>4.93</td>
<td>12.01</td>
<td></td>
<td></td>
<td>4</td>
<td>&lt; 0.025</td>
<td>-0.627</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>N2</td>
<td>5.05</td>
<td>7.19</td>
<td></td>
<td></td>
<td>26</td>
<td>&lt; 0.05</td>
<td>-0.60</td>
<td>26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N3</td>
<td>15.45</td>
<td>28.89</td>
<td></td>
<td></td>
<td>13</td>
<td>&lt; 0.001</td>
<td>-0.77</td>
<td>13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>N4</td>
<td>2.26</td>
<td>4.54</td>
<td></td>
<td></td>
<td>10</td>
<td>&lt; 0.005</td>
<td>-0.65</td>
<td>9</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>N5</td>
<td>14.12</td>
<td>19.15</td>
<td></td>
<td>39.05</td>
<td>22</td>
<td>NS</td>
<td>-0.22</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>H1</td>
<td>2.20</td>
<td>4.73</td>
<td></td>
<td></td>
<td>3</td>
<td>NS</td>
<td>-0.766</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>H2</td>
<td>2.66</td>
<td>5.36</td>
<td></td>
<td></td>
<td>11</td>
<td>&lt; 0.025</td>
<td>-0.716</td>
<td>11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>H3</td>
<td>4.53</td>
<td>18.57</td>
<td></td>
<td></td>
<td>18</td>
<td>&lt; 0.001</td>
<td>-0.83</td>
<td>15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>H4</td>
<td>5.12</td>
<td>3.52</td>
<td></td>
<td></td>
<td>17</td>
<td>NS</td>
<td>-0.12</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>H5</td>
<td>2.00</td>
<td>0.70</td>
<td></td>
<td>7.54</td>
<td>9</td>
<td>NS</td>
<td>+0.85</td>
<td>9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

df = degrees of freedom; ns = not significant.

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rate. In 2 other subjects (N2 and N4), the correlation was less striking; in the remaining 2 subjects (N5 and H4), no correlation was apparent.

Correlation of Reflex Sensitivity with Mean Arterial Pressure.—Seven of the subjects showed a significant relationship between preinjection mean arterial pressure and the sensitivity of the subsequent reflex response (Table 2). This was an inverse correlation in 6 of the 7 (Fig. 7).

This relationship between initial arterial pressure and reflex sensitivity raised the question whether the raised sensitivity observed in sleep was a simple consequence of reduced pressure. Accordingly, after testing the reflex in sleep, the arterial pressure was raised to the waking level by a continuous infusion of angiotensin, and the reflex was again tested as before by a superimposed rapid injection of angiotensin (Fig. 8). This was done in 5 subjects and the reflex sensitivity was unchanged from or greater than that obtained just before the infusion.

Discussion

It is critical to the argument presented here that the bradycardia following the intravenous injection of angiotensin is of reflex origin. The evidence that this is so is very strong. Atropine has been shown to reduce the cardiac slowing and to increase the rise of arterial pressure in response to angiotensin in man (18, 19), suggesting that the bradycardia is of vagal origin. Several studies have failed to demonstrate any direct negative chronotropic effect of angiotensin on the myocardium or the sinus node (20, 21). No bradycardia followed a rise in pressure when angiotensin was injected in 2 subjects with autonomic dysfunction (P. Sleight and J. D. Bristow, unpublished observations). There is also the theoretical possibility that angiotensin could produce bradycardia by a vagally mediated central effect. However, in dogs, the bradycardia following a pressor response to angiotensin was abolished by severance of the buffer nerves, while leaving both vagi intact (22). After this procedure, in fact, angiotensin produced a delayed tachycardia.

It is possible that the bradycardia might have been caused by chemoreceptor stimulation, perhaps as a result of vasoconstriction in the carotid and aortic bodies. However, if this were the case, one might have expected increases in the rate or depth of respiration, and these were not seen. Furthermore, we have examined the baroreflex sensitivity by this method in waking subjects breathing differing gas mixtures, and find that these maneuvers usually change the position of the line but not the slopes, except in hypoxia, where the slope is flatter, i.e. pulse intervals shorter. (J. D. Bristow and others, unpublished observations in this laboratory.) It has been assumed then that the bradycardia following injection of angiotensin in these studies is a reflex originating in the aortic and carotid baroreceptors. It is also very probable that this effect is mediated, at least in part, by the vagus nerves.

Of the four reflex effects of baroreceptor stimulation—arterial dilatation, venous dilatation, reduction in force of cardiac contraction, and reduction in heart rate—the last is by far the easiest to measure precisely.

The close correlation of systolic pressure with the R-R interval of the succeeding cardiac cycle suggests that in man the latency of the heart rate reflex is very short. This agrees with Jewett's (13) estimate in the dog in which the shortest reflex time (from afferent stimulation until vagal discharge) was 80 msec.

Heart rate is also influenced by respiration. The justification for selecting expiratory rather than inspiratory points for analysis was empirical—they showed the greatest uniformity. The fact that the slopes of lines calculated from inspiratory points were smaller suggests that the reflex response to an increase in pressure may be attended by enhancement of sinus arrhythmia, an observation made some time ago by Schweitzer (23).

As we have pointed out, there is some variability in responses in the same subject during states ostensibly similar. Some of this variability may result from imprecision of the points at the lower end of the line compared...
with the later points. This is due to two fac-
tors: (1) There appears to be in some cases a
threshold of pressure below which pressure
variations are tolerated without immediate ac-
tivation of reflex slowing. (2) In the period
before the pressure rise there is some sponta-
near variation in pressure, without change
in pulse interval; if the end of such a sponta-
near rise coincides with the beginning of the
provoked rise there may be some in-
creased scatter at the beginning of the line
which may differ in two instances and result
in differing slopes when the regression line is
calculated. It is also possible, of course, that
other factors in addition to sleep may alter
the blood pressure-heart rate relationship
and account for some variability in response—for
example, differing states of activation of the
reticular formation not revealed by the EEC.
For these reasons we are on much surer
ground when we have a large number of tests
at any particular state of sleep or wakeful-
ness.

These plots of a beat-to-beat relationship
between pulse interval and systolic arterial
pressure during an evoked rise of the latter,
bear a striking relationship to the static endo-
sinus pressure-heart rate plots of Koch (24).

**Results during Sleep.**—The linearity of the
plot of R-R interval against systolic pressure
was not altered by sleep, but the slope of the
line changed significantly in 8 of 10 subjects.
In 7 subjects the slope increased and in the
other (H5) it decreased.

This could have been due to either (1) a
true change in sensitivity of the whole of the
baroreflex arc or (2) a change in another com-
ponent of the stimulus apart from the sys-
tolic pressure—for example, the pulse pres-
sure or rate of rise of pressure might have
changed during sleep, compared with that
during waking. We examined these latter
possibilities in the subjects in whom there
was a striking increase of slope during sleep,
but could find no evidence for them.

It appeared, therefore, that the blood pres-
sure-heart rate reflex had an increased sen-
sitivity during sleep in some, but not all, sub-
jects. There was also a significant correlation
between the sensitivity of the reflex and the
arterial pressure prevailing at the time of
each test (Table 2). In 5 of the subjects,
this correlation was quite striking. The ques-
tion arose whether mean pressure or reflex
sensitivity was the dependent variable. Was it
possible that reduction of the background
mean pressure basically altered the sensitivity
of mechanoreceptors to a given rise in pres-
sure? The recent studies of Christensen et al.
(25), suggested that this was so in the dog.
If their model is correct, the threshold of baro-
receptors would have a “following” property,
varying directly as the prevailing mean pres-
sure; and the sensitivity or responsiveness of
receptors would be increased at lower pres-
sures. This offers an attractive explanation of
some of the findings of the present study:
the increased sensitivity of the reflex during
sleep might thus be explained by a change oc-
curring in the receptors alone, by “following”
or “clamping” the lower blood pressures of
sleep. However, the angiotensin infusion ex-
periments do not support this explanation for
our subjects; when the lower pressures of
sleep were raised back to about the levels of
the subject awake, the reflex sensitivity did
not decrease, but remained unchanged or
even increased.

It appears likely that the increased gain of
the reflex arc in sleep is due to changes in the
central nervous system, and there is some
support for this view from animal experi-
ments (26-29). It is not unreasonable to sup-
pose that fluctuations in the level of arousal
might in turn alter the activity of baroreceptor
reflexes, and of other autonomic mechani-
isms. Hughelin and Bonvallet (30) have
shown in the cat that as vigilance decreased
in falling asleep there was a diminution of
cortical inhibition of the reticular system. Fa-
cilitation of several autonomic functions oc-
curs during sleep (31, 32), and there is evi-
dence from the present study for further
central facilitation of responses recorded dur-
ing dreaming sleep.

In 6 subjects, the degree of slowing per
unit rise of pressure was directly correlated
with the average preinjection pulse interval.
Thus the greater reflex bradycardia during sleep was superimposed upon an already low heart rate; the steepest responses were recorded at the lowest resting heart rates. This observation contrasts with the findings of Warner and Cox (33), and of Alexander and De Cuir (34), who noted that the value of the initial heart rate influenced the magnitude of a subsequently induced reflex bradycardia in the opposite direction. The latter workers suggested that an already high "vagal tone" reduced the magnitude of reflex bradycardia, since subsequently induced changes of "vagal tone" would be relatively much smaller. The work of Warner and Cox suggested that this might be a generalized working rule in heart rate control. If it is, and if the mechanism holds for man, then the present findings may be said to add further evidence of an overriding effect of sleep itself, reversing the relationship predicted by these studies.

Whatever its origin, this increase in baroreflex sensitivity in sleep favors the active maintenance of lower arterial pressures during sleep. Pressures normally maintained when persons are awake evoke bradycardia in sleep. This stronger "braking" effect on the heart in sleep must result in a more active resistance to influences tending to elevate blood pressure—for example, the pressor effect that has been shown to follow a K-complex, the apparently massive sympathetic discharges that accompany myoclonic jerks in dreaming sleep, or the frequent movements which accompany changes in the level of sleep throughout the night.

It is interesting to contrast the mechanisms we have outlined for regulating the peaks of arterial pressure during the night with that described by Guazzi and associates (35). They described very severe falls in arterial blood pressure, particularly during sleep with rapid eye movements in cats that were subjected to denervation of their carotid bodies. The falls in pressure were very much less when the chemoreceptors were preserved, but baroreceptors were deafferented instead. This mechanism would seem to be one which regulates the troughs of arterial pressure. In any case, there is obviously a species difference since we did not see consistent falls in arterial pressure during sleep with rapid eye movements in man.

The method developed in these experiments provides a tool for assessing possible changes of reflex regulation of arterial pressure under various physiological and pathological conditions. The method was designed primarily to detect any change in reflex sensitivity which might accompany the onset of sleep in man—a change which could conceivably take place within a short space of time (1 or 2 minutes). The experimental test had thus to be both quickly repeatable, and reliably reproducible. Finally, it was essential that the experimental test used could be carried out so as not to disturb the subjects. The method outlined here satisfied these requirements: it did not disturb waking subjects or change the EEG level when they were sleeping.

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BAROREFLEX SENSITIVITY IN MAN ASLEEP AND AWAKE


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