Hemodynamic Patterns during Desynchronized Sleep in Intact Cats and in Cats with Sinoaortic Deafferentation

By Takao Kumazawa, M.D., Giorgio Baccelli, M.D., Maurizio Guazzi, M.D., Giuseppe Mancia, M.D., and Alberto Zanchetti, M.D.

ABSTRACT

In unanesthetized, unrestrained cats, placed in a sound-attenuated cage, stroke volume and cardiac output were continuously monitored by an electromagnetic flow transducer chronically implanted around the ascending aorta, arterial pressure was measured by means of a femoral catheter connected to a strain-gauge transducer, and heart rate by a cardiotachograph. Total resistance was computed by dividing arterial pressure by cardiac output. Electroencephalograms, cervical electromyogram, and ocular movements were also monitored to obtain evidence of naturally occurring sleep. In animals with intact sinoaortic reflexes the fall in arterial pressure occurring during desynchronized sleep was associated with a small decrease in cardiac output and a relatively greater reduction in total resistance. After sinoaortic deafferentation, the conspicuously exaggerated fall in arterial pressure occurring during the same type of sleep was almost entirely due to a parallel exaggeration of the reduction in total resistance; changes in cardiac output were only slightly greater than before deafferentation. Only in the few episodes of desynchronized sleep in which extreme hypotension was accompanied by signs of cerebral anoxia, did cardiac output greatly decrease; in these cases, calculated resistance was found to increase. Both small and large changes in cardiac output were independent of heart innervation.

ADDITIONAL KEY WORDS

- arterial pressure
- cardiac output
- total peripheral resistance
- cardiac innervation
- venous return
- resistance vessels
- capacitance vessels
- sympathetic vasoconstrictor activity
- baroceptive reflexes
- chemoeptive reflexes

The cat's sleep is a suitable condition in which to study cardiovascular control, and possibly neurogenic mechanisms, since it is a true behavioral state without experimental biases such as anesthesia, cerebral transection, electrical stimulation of the brain, or forced immobilization. We have already reported that blood pressure falls more markedly during desynchronized sleep (a state of sleep characterized by a desynchronized electroencephalogram and rapid eye movements, and associated with dreaming in man [1, 2]) than during sleep with a synchronized electroencephalogram (3); that the hypotensive effect of desynchronized sleep is strikingly exaggerated by sinoaortic deafferentation, to the point that episodes of transient cerebral anoxia sometimes occur (3); and that this exaggerated hypotension is due to the absence of the buffering action of chemoeptive impulses from the carotid and aortic bodies (4). In the desynchronized sleep of the cat, hypotension is commonly accompanied by bradycardia, but it is largely independent of changes in heart rate and, more generally, of neural influences upon the heart, as hypoten-
sion is still observed after bradycardia has been blocked by methylatropine and even after bilateral stelllectomy and surgical interruption of the vagal innervation of the heart (5).

Our previous experiments, however, do not provide sufficient information on hemodynamics during sleep. Even if neural influences upon the heart appear of minor importance for inducing sleep hypotension, this observation does not rule out the possibility of changes in cardiac output. Influences on peripheral vessels during desynchronized sleep might concern only or predominantly resistance vessels, but they might also involve capacitance vessels, thus affecting cardiac output independently of direct influences upon the heart. Cardiac output might also be affected by non-neural influences such as changes in coronary blood flow or arterial hypoxia.

The experiments reported here have been aimed at answering some of these questions, by simultaneously recording or calculating systolic, diastolic, and mean arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance in cats during natural sleep. The present report is limited to data obtained during the desynchronized stage of sleep.

**Methods**

The observations reported here were made in eleven cats, four of which were studied with intact sinoaortic reflexes, six after sinoaortic deafferentation, and one both before and after deafferentation. Sinoaortic deafferentation was performed under pentobarbital anesthesia, 30 mg/kg ip. The carotid sinus areas were denervated by cutting both carotid sinus nerves, identified at their origin from the glossopharyngeal nerve, and carefully stripping the carotid sinus walls. The effectiveness of denervation was confirmed by the disappearance of the pressor response to common carotid occlusion. The aortic nerves were identified at their junction with the superior laryngeal nerves, isolated from the cervical vagus trunks, and bilaterally severed. Of the deafferented cats, four were also studied after administration of methylatropine, 1 mg/kg, to block cardioinhibitory vagal influences, and two were subjected to bilateral stelllectomy and later to administration of methylatropine as well.

Stelllectomy was carried out through an extrapleural approach, in one cat at the time sinoaortic deafferentation was performed, and in the second cat 15 days after deafferentation and after several recording sessions with cardiac sympathetic innervation intact.

Six to ten days before the sleep studies, the cats were anesthetized with sodium pentobarbital, and screw electrodes were implanted in the skull and in the floor of both frontal sinuses, and needle electrodes in the paravertebral cervical musculature, in order to obtain electroencephalographic, electrooculographic, and electromyographic evidence of the various stages throughout the wakefulness-sleep cycle.

At the same time, the thorax was opened with sterile precautions through the third intercostal space, and an electromagnetic flow transducer of the hinged type (Statham, K-type, 6 to 8 mm inner diameter according to the size of the cat) was implanted around the root of the aorta. The thorax was then closed, the pleural cavity decompressed, and the cables from the flow transducer were passed subcutaneously to a leather packet sewn to the cat's back. On the subsequent 2 to 3 days the animals were treated with penicillin and streptomycin; they recovered within 7 to 10 days.

For calibration and recording, the aortic flow transducer was connected to an M-4001 module of an M-4000 A Statham electromagnetic flowmeter the output of which was fed into a channel of a Grass P7 polygraph. Calibration tests were carried out with the transducer immersed in a saline bath while saline or blood from a reservoir was made to flow at various constant rates. Calibration was performed both before implantation (with the transducer placed around a Dacron tube of suitable diameter) and soon after killing the animal at the end of the experiment (with the transducer around the aorta removed from the animal). The values obtained were closely corresponding in both conditions. The signals showed linearity within the flow ranges usually observed in our experiments. In the infrequent cases of very low flows some lack of linearity was corrected by factors calculated on calibration curves. At the time of recording from the implanted transducer the instantaneous flow curve was displayed on a channel of the Grass polygraph. End-diastolic flow was used as the zero-flow line, since preliminary trials in which short-lasting cardiac arrest was induced by injecting minute amounts of acetylcholine intravenously showed excellent correspondence of aortic end-diastolic flow to zero flow. Stability of the end-diastolic baseline throughout the recording session was continuously checked on a 502A Tektronix dual-beam, cathode-ray oscillograph, and found very
constant both during periods of strong bradycardia and of tachycardia. The area under the instantaneous flow curve was integrated by means of an operational amplifier (Grass 7P10), automatically reset to zero at each diastolic interval. The output of the integrator, displayed on another channel of the polygraph, was a measure of the stroke volume less coronary flow. Calibration of the integrating amplifier was performed by integration of pulses of various amplitude and duration (Tektronix 161 generator and voltage step divider) displayed on the polygraph channel calibrated for flow. The instantaneous aortic flow signal was also used to trigger a cardiotachometer and to measure heart rate. Cardiac output (less coronary flow) was calculated by multiplying stroke volume by heart rate.

Arterial pressure was measured by a Statham strain-gauge transducer connected to a polyethylene catheter of 1.5 mm inner diameter, implanted in a femoral artery below the origin of its cranial branch. Implantation was performed under brief ether anesthesia the day preceding the first recording session; patency of tubing and artery could be maintained throughout several days by injection of 25 mg heparin twice a day. Total peripheral resistance was calculated in arbitrary units by dividing mean arterial pressure (mm Hg) by cardiac output (liters/min).

All cardiovascular and electrophysiological variables were recorded on an eight-channel Grass P7 polygraph, while the cat was in a sound-attenuated, electrically isolated cage, provided with a suitable window through which the cat's behavior could be observed. Several episodes of desynchronized sleep were recorded in each cat in each experimental condition. From the continuous record, measurement of the different variables was made during a period of steady cardiovascular functions in the 2 minutes of synchronized sleep immediately preceding onset of desynchronized sleep, this being called the control period. During desynchronized sleep, measurements were selected at six successive times: (1) onset of electroencephalographic desynchronization, or disappearance of electromyographic activity, or both; (2) onset of fall in arterial pressure; (3) more definite development of arterial hypotension; (4) later during the development of hypotension; (5) time of lowest arterial pressure; (6) just before the pressure rise at the end of the episode. Measurements were also made at the time of arousal from a desynchronized sleep episode, within 1 minute after the end of desynchronized sleep, and later on, when the animal was back in synchronized sleep as in the control period. Twenty-two episodes from cats 1, 7, 13, 16, 17, and 18 were

**FIGURE 1**

Effect of desynchronized sleep on mean blood pressure (solid circles), cardiac output (open circles), and total peripheral resistance (crosses) in cats with intact sinoaortic reflexes (A) and in cats with sinoaortic deafferentiation (B). Each symbol is the mean of 40 measurements in the 4 cats of Table 1 (A), and of 40 measurements in the 5 cats of Table 2 (B). Measurements performed at selected periods indicated on the abscissas: C, control period during synchronized sleep 2 minutes before onset of desynchronized sleep; 1, onset of desynchronized sleep; 2, beginning of hypotension; 3, increase of hypotension; 4, further increase of hypotension; 5, lowest pressure values during desynchronized sleep; 6, toward the end of desynchronized episode; A, arousal from desynchronized sleep; ADS, 1 minute after A; SS, reappearance of synchronized sleep. On the ordinates all cardiovascular measurements have been expressed as percent values of measurements taken during control period.
**RESULTS**

**CATS WITH INTACT SINOAORTIC REFLEXES**

The data obtained in four cats have been summarized in Figure 1, A, showing means of 40 episodes of desynchronized sleep analyzed at selected times, as described under Methods, and expressed as percent values of control measurements immediately preceding onset of desynchronized sleep. Means and standard errors of the mean of absolute values measured in each of these four cats are listed in Table 1, where only control measurements and those referring to point 5 (i.e., at the time of lowest arterial pressure) are reported. At point 5 and, more generally, throughout desynchronized sleep, the fall in mean arterial pressure was mainly paralleled by a decrease in calculated peripheral resistance with no or little change in cardiac output in three cats, while in one cat the arterial pressure fell parallel to a similar fall in cardiac output with little change in resistance. In three episodes of desynchronized sleep studied in a fifth cat (cat 11) the changes in cardiac output and in resistance were approximately of the same magnitude, but the data have not been included in Table 1 and Figure 1 because the number of observations that could be performed in this animal was too small. In all cats, the small increase in blood pressure also measured at very frequent intervals, by selecting alternate periods of 4-second duration throughout the entire episode. Statistical evaluation of absolute data was performed by analysis of variance with two-way classification, according to Snedecor and Cochran (6). When data from different cats were pooled, absolute were translated into percent data by using control measurements as reference. Percent data were evaluated by analysis of variance with one-way classification (6).

### Table 1

**Cardiovascular Changes during Desynchronized Sleep in Cats with Intact Sinoaortic Reflexes**

<table>
<thead>
<tr>
<th>Cat</th>
<th>n</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Cardiac output (ml/min)</th>
<th>Total peripheral resistance (mm Hg/L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>S</td>
<td>P</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>89 ± 4</td>
<td>71 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>85 ± 2</td>
<td>77 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>69 ± 2</td>
<td>61 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>69 ± 2</td>
<td>60 ± 1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Group values \((\frac{S}{C} \times 100)\) 86.4% 93.6% 92.4%

Results are expressed as means ± SEM of observations in the control period (C) and when pressure was lowest during desynchronized sleep (period 5). n = Number of sleep episodes, \(P =\) significance of changes in period 5 as compared to control.

* Observations at period 5 expressed as percent of control values; means of data from all animals.

### Table 2

**Cardiovascular Changes during Desynchronized Sleep in Cats with Sinoaortic Deafferentation**

<table>
<thead>
<tr>
<th>Cat</th>
<th>n</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Cardiac output (ml/min)</th>
<th>Total peripheral resistance (mm Hg/L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>S</td>
<td>P</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>91 ± 5</td>
<td>43 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>105 ± 3</td>
<td>71 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>99 ± 6</td>
<td>55 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>17</td>
<td>9</td>
<td>71 ± 2</td>
<td>52 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>126 ± 3</td>
<td>67 ± 2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Group values \((\frac{S}{C} \times 100)\) 60.1% 86.4% 69.6%

See footnote to Table 1.
known to occur at the very onset of desynchronized sleep (3) and the pressor rebound often observed toward or at the end of the episode were paralleled by an increase in peripheral resistance only, with no change in cardiac output.

Although Figure 1, A, effectively depicts overall cardiovascular changes during desynchronized sleep in cats with intact sinoaortic reflexes, it is a somewhat simplified representation of what really occurs from moment to moment throughout the course of a desynchronized sleep episode. As shown in the example of Figure 2, hypotension is often accompanied either by outbursts of bradycardia or by periods of tachycardia. The two periods measured in Figure 2 have been sampled to show that the hemodynamic pattern may be slightly different in the two situations: although calculated peripheral resistance is decreased when either tachycardia or bradycardia is associated with hypotension, cardiac output may be more markedly decreased when tachycardia is accompanied by reduced stroke volume than when bradycardia is partly compensated by increased stroke volume.

**CATS WITH SINOAORTIC DEAFFERENTATION**

**Usual Cardiovascular Pattern during Desynchronized Sleep.**—The results obtained in
five cats previously subjected to sinoaortic deafferentation have been summarized in Figure 1, B, and Table 2. The data in Figure 1, B, are mean values of measurements during 40 episodes of desynchronized sleep analyzed at selected times and expressed as percent values of control measurements preceding onset of desynchronized sleep. We have excluded from consideration all episodes (see below) in which hypotension was accompanied by signs of cerebral anoxia. The means and standard errors of the mean of absolute values measured in each of the five deafferented cats are listed in Table 2, where only control measurements and those referring to point 5 (i.e., at the time of lowest arterial pressure) are reported.

It is evident in Figure 1, B, and Table 2 that in cats with sinoaortic deafferentation the fall in blood pressure, as well as the pressor rises at the onset and end of desynchronized sleep, was closely paralleled by changes in calculated resistance which were identical in direction and similar in size. Decreases in mean arterial pressure and total peripheral resistance are highly significant statistically in each of the five cats studied. Cardiac output also fell significantly in each cat, but its percent decrease was much smaller than the decrease in arterial pressure and calculated resistance.

Comparison of the graphs in Figure 1, A and B, and of Tables 1 and 2 confirms that sinoaortic deafferentation considerably exaggerates the fall in blood pressure (3) and shows that a similar exaggeration of the decrease in calculated peripheral resistance occurs. Statistical comparison of the measurements performed at point 5 (lowest recorded values) in the group of animals with intact reflexes and in the group of deafferented cats indicates that mean arterial pressure decreased to a minimum average of 86.4% in intact animals and to 60.1% in deafferented cats; total peripheral resistance decreased to 92.4% of control values in intact, and to 69.6% in deafferented animals, both differences are highly significant statistically (P < 0.001). Cardiac output, which decreased slightly and inconstantly in intact cats, fell significantly in each of the deafferented animals. However, the difference between the changes in cardiac output in the two conditions, though statistically significant (P < 0.05), was quite small (cardiac output decreasing to 93.6% of control values in intact, and to 86.4% in deafferented animals).

The data obtained in the only cat (cat 18, Tables 1 and 2) studied both before and after sinoaortic deafferentation were similar to those presented for the two groups.

Figure 3 shows actual tracings recorded at the beginning and toward the end of an episode of desynchronized sleep in a cat (cat 1) with interrupted sinoaortic reflexes. There was a very marked fall in mean arterial pressure associated with a large decrease in total peripheral resistance. Cardiac output decreased to a lesser extent, though still considerably, because of a reduction in both stroke volume and heart rate. In other episodes or animals, however, cardiac output could be affected almost exclusively by a decreased heart rate, without any measurable change in stroke volume.

The episodes which were analyzed at very frequent intervals, by measuring alternate periods of 4-second duration, confirmed that our usual analysis of the records, though obviously simplified, was representative of the actual course of hemodynamic changes during desynchronized sleep. As shown by the three examples of Figure 4, our selection of points 1 to 5 faithfully sampled the transient circulatory changes at the onset of desynchronized sleep, and then the continuous decline of blood pressure, cardiac output, or resistance until the variables reached their lowest values. The final portion of the episode was less faithfully represented by point 6, but the end of the episode was carefully evaluated by the subsequent measurements (at the time of arousal from desynchronized sleep, 1 minute after the end of desynchronized sleep, and when the animal was back in synchronized sleep). The more detailed analysis of these twenty-two episodes, however, showed that the course of the cardiovascular changes...
FIGURE 3

Episode of desynchronized sleep in cat 1 with sinoaortic deafferentation. Top: beginning of episode. Bottom: end of episode. Other abbreviations as in Figure 2.
Three episodes of desynchronized sleep from three different cats (18, 16, 1), all with sinoaortic deafferentation. Each symbol is average measurement during 4 consecutive seconds; measurements at alternate 4-second periods. Mean blood pressure, solid circles; cardiac output, open circles; total peripheral resistance, crosses. On the abscissas: time in seconds. On the ordinates all cardiovascular measurements are expressed as percent values of measurements taken during control period. Arrows, letters and numbers refer to points which were selected, according to the criteria of Figure 1, for calculating average population values used in Figure 1, B.
during desynchronized sleep was not always as smooth as that schematically depicted in Figure 1. Although in most of the episodes hemodynamic changes developed in a relatively regular and progressive way, as that illustrated in Figure 4, A, (which follows rather strictly the simplified pattern of Fig. 1), in several episodes (see example of Fig. 4, B) arterial pressure and peripheral resistance showed conspicuous parallel oscillations. Figure 4, C, illustrates an episode in which hypotension occurred in two phases: the first one was largely due to a parallel fall in resistance (points 3 and 4), while the subsequent dip (point 5) resulted from superposition of a considerable fall in cardiac output upon a rather steady background of reduced resistance.

Role of Cardiac Innervation.—To study to what extent the various cardiovascular changes occurring during desynchronized sleep may be mediated through neural influences on the heart, 1 mg/kg methylatropine was administered intravenously to four deafferented cats, and two cats were subjected to bilateral stellectomy and to methylatropine. We have presented evidence elsewhere (5) that sleep bradycardia is largely abolished in the cat when vagal cardioinhibitory fibers are blocked by methylatropine, especially when bilateral stellectomy is also added.

All six cats gave results in the same direction. Figure 5 shows the means of measurements during ten episodes in cat 13, after bilateral stellectomy and administration of methylatropine. In confirmation of our previous observations (5), these procedures caused heart rate to remain practically unmodified throughout desynchronized sleep, while mean arterial pressure still fell considerably. Also total peripheral resistance largely decreased. Although there was no bradycardia, cardiac output still decreased. Analysis of variance with two-way classification (6) showed that arterial pressure, resistance, and cardiac output values at point 5 were all significantly (P < 0.01) lower than in the control period.

Cardiovascular Pattern in Episodes with Cerebral Anoxia.—Strikingly different cardio-

![Graph](image-url)
vascular changes were observed in those episodes of desynchronized sleep in which blood pressure falls to extremely low levels and is accompanied by electroencephalographic silence and sometimes by seizures signaling cerebral anoxia or ischemia (see electroencephalographic tracings in the example of Fig. 8). As in our previous experiments (3), these episodes were observed only in animals with sinoaortic deafferentation. Even in deafferented animals, episodes with signs of cerebral anoxia (and the associated cardiovascular pattern to be described) occurred in a minority of animals and episodes. In the present series of seven deafferented cats, cerebral anoxia occurred in 19 out of 24 episodes in cat 12, in 1 out of 41 episodes in cat 16, in 4 out of 15 episodes in cat 18, and not at all in cats 1, 7, 13, and 17.

Judging from blood pressure only, these episodes could be interpreted as a mere, though striking, exaggeration of the usual cardiovascular changes during desynchronized sleep. However, some of the hemodynamic effects are quite different from those observed when hypotension is not accompanied by signs of cerebral anoxia. Means of percent changes during ten such episodes from cats 12 and 18 are reproduced in Figure 6; means and standard errors of the mean of absolute data for control period and points 3 and 5 are summarized in Table 3 together with results of analysis of variance with two-way classification. The episodes started according to the usual pattern: at point 3, mean arterial pressure and peripheral resistance had significantly decreased in each of the two cats, while cardiac output had shown a much smaller decrease, which was not significant in either of the two cats. However, at a given moment, usually at least 1 minute from onset of desynchronized sleep, progressive hypotension began to be associated with a sudden and progressive fall in cardiac output. When overt signs of cerebral anoxia occurred, cardiac output was extremely low, down to an average of 13.2% of control values in the two cats at point 5. This striking fall in cardiac output resulted from a decrease of both stroke volume and heart rate. Marked bradycardia generally followed and outlasted the large fall in stroke volume with the time sequence.
HEMODYNAMICS OF SLEEP

Discussion

What we think is the most interesting result of our experiment is that different hemodynamic factors may underlie hypotension during desynchronized sleep and that these factors are variously affected by sinoaortic reflexes. In animals with intact sinoaortic reflexes, hypotension is commonly associated with decreased total peripheral resistance, though a moderate reduction of cardiac output may also significantly contribute. In the great majority of the episodes recorded after sinoaortic deafferentation, the hemodynamic pattern is similar to that observed in intact animals, though with remarkable quantitative differences. The fall in cardiac output is only slightly greater, or more constant, in the deafferented than in the intact animals.
Effect of methylatropine on cardiovascular patterns in desynchronized sleep with cerebral anoxia. Each symbol is the mean of measurements during six episodes before (solid circles) and after (open circles) methylatropine, 1 mg/kg iv in cat 12. Abscissas as in Figure 1. Ordinates: absolute values for each variable.

However, the fall in peripheral resistance is much greater in the deafferented cats, and this change is thus largely responsible for the exaggerated fall in mean arterial pressure in the deafferented group. However, a greater decrease in peripheral resistance is not the only and invariable effect of abolition of sinoaortic reflexes: in the few episodes associated with signs of brain anoxia, the extreme hypotension appears to be exclusively due to a dramatic fall in cardiac output; calculated peripheral resistance seems paradoxically to increase.

The fall in peripheral resistance which is typical of most episodes of desynchronized sleep indicates that a dilatation of resistance
illustrated in Figure 6, lower part. Because of the proportionally greater change in cardiac output than in arterial pressure, at this time peripheral resistance, as we calculated it, was more than doubled as compared to control values.

A big fall in cardiac output was still observed during episodes with signs of cerebral anoxia when bradycardia was completely or almost completely blocked by methylatropine, 1 mg/kg iv. Figure 7 compares data from six episodes with signs of brain anoxia recorded in cat 12 before methylatropine with an equal number of similar episodes after the drug was given. The effectiveness of cholinergic blockade of the heart is demonstrated by the almost complete disappearance of the extreme bradycardia previously occurring during desynchronized sleep. In spite of vagal blockade, stroke volume still decreased to very low levels and consequently cardiac output also fell strikingly though not to the dramatically low values observed before vagal blockade. Mean blood pressure decreased to almost exactly the same degree before and after methylatropine. Continuous tracings during an episode of desynchronized sleep leading to cerebral ischemia recorded in cat 12 after methylatropine are reproduced in Figure 8.

**Discussion**

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The fall in peripheral resistance which is typical of most episodes of desynchronized sleep indicates that a dilatation of resistance...
vessels occurred. It is true that in calculating resistance we have not taken into account possible changes in central venous pressure, which we did not measure. However, if central venous pressure increased (though an unlikely event in our experimental conditions), calculated peripheral resistance would be even less during sleep.

It is reasonable to suppose that dilatation of resistance vessels during desynchronized sleep may be induced by a decrease in tonic sympathetic activity. This hypothesis is strongly supported by recent electrophysiological experiments (7, 8) showing that hypotension during desynchronized sleep in the cat is accompanied by a marked reduction of electrical activity recorded from the renal nerves. A significant contribution of active vasodilatation through cholinergic sympathetic fibers (9) is disproved by persistence of a very large fall in resistance after administration of methylatropine. The large doses (1 mg/kg) we employed in order to abolish vagal cardioinhibitory effects were such as to block the cholinergic vasodilator sympathetic outflow also (9 and personal observations).

Resistance changes during the few episodes with brain anoxia are more difficult to assess. In these circumstances arterial pressure and cardiac output fell so low as to make coronary underperfusion, heart failure, and a considerable increase in central venous pressure possible events. The increase in resistance we have calculated during these episodes may therefore be a factitious one. Unfortunately, even when driving pressure is more correctly measured by taking into account central venous pressure, calculation of peripheral resistance is very often misleading at low flows because of the non-Newtonian properties of...
blood (10), and correct measurements require knowledge of pressure-flow relationships in the circuit. Therefore, the actual change in resistance during sleep episodes with brain anoxia is uncertain, and the hemodynamic pattern occurring in these conditions is more aptly described, at present, as one characterized by large falls in both arterial pressure and cardiac output.

Further important questions concern the physiological mechanisms of cardiac output changes during desynchronized sleep. One may wonder why in some episodes cardiac output falls so dramatically, while in most episodes it does so very slightly or only barely decreases; and whether a common mechanism is responsible for both large and slight falls. We have shown that these falls persist after stellectomy and vagal blockade, and that they are unlikely, therefore, to result from direct neural influences upon the heart. Changes in cardiac output might be due to the concomitant arterial hypotension resulting in coronary underperfusion. This mechanism, however, seems unlikely to occur in most episodes, as falls in cardiac output are only slightly affected by deafferentation in spite of a considerable exaggeration of the drop in blood pressure. Coronary underperfusion is a more likely factor to account for the very large falls in cardiac output during the few episodes with cerebral ischemia. Arterial hypoxia and hypercapnia may also develop during sleep, especially after sinoaortic deafferentation (11); these changes may play some role especially in causing the very marked decrease during the episodes with cerebral ischemia. Finally, both small and large falls in cardiac output might result, at least in part, from reduced venous or pulmonary return.

Several hypotheses may be advanced in order to give a comprehensive interpretation of the mechanisms controlling circulation during desynchronized sleep. According to one of these hypotheses, the neural mechanisms of desynchronized sleep (2) would induce a decrease in the tonic activity of vasoconstrictor sympathetic fibers (7, 8) similar to the parallel depression induced in spinal somatic activities (12). Usually, depressed sympathetic activity would result in a dilatation of resistance vessels and in a much smaller effect on capacitance vessels and venous return. Hence, the usual pattern in both intact and deafferented animals consists in predominant reduction in peripheral resistance and slight reduction in cardiac output. Exaggeration of the fall in resistance after sinoaortic deafferentation would result from the background of higher resistance caused by interruption of baroreceptive reflexes (13), as well as from a greater depression of sympathetic vasoconstrictor activity during sleep due to the abolition of chemoceptive reflexes (4), whose action on vascular resistance is well described at least in the dog (14). Only in a few episodes of desynchronized sleep would removal of this sinoaortic buffer action let sympathetic deactivation proceed further, to a point at which capacitance vessels would also become largely dilated with a consequent dramatic fall in venous return and cardiac output. A similar succession of dilatation of resistance vessels followed by decreased venous return and cardiac output fall has been recently described by Folkow et al. (15) during stimulation of the medullary depressor area, a region from which widespread suppression of sympathetic activity is induced.

It is clear, however, from discussion of our data that no crucial evidence is so far available on the actual importance of a reduced sympathetic tone in causing each and all of the various cardiovascular manifestations of sleep, and that other hypotheses may be advanced to supplement that outlined above. The problem of the mechanisms controlling circulation during sleep is still incompletely clarified.

References


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