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Vasomotor regulation during sleep in the cat

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MANCIA, GIUSEPPE, GIORGIO BACCELLI, DAVID B. ADAMS, AND ALBERTO ZANCHETTI. *Vasomotor regulation during sleep in the cat.* Am. J. Physiol. 220(4): 1086–1093. 1971.—Synchronized and desynchronized sleep are accompanied by cardiovascular changes, which differ not only in magnitude but also sometimes in direction. Blood pressure, heart rate, and cardiac output show a progressive decrease from quiet wakefulness to synchronized and then to desynchronized sleep. Changes in total peripheral conductance sometimes indicate slight vasoconstriction throughout synchronized sleep always followed by a marked vasodilatation during the desynchronized stage. The mesenteric and renal beds are variously affected during synchronized sleep, but an important vasodilatation supervenes in all animals during desynchronized sleep. A slight iliac vasoconstriction is often observed at the beginning of synchronized sleep, followed by an equally slight vasodilatation toward the end of the synchronized period. In all cats a marked vasoconstriction occurs throughout the desynchronized stage (reinforced by further vasoconstriction when rapid eye movement and hindlimb twitches occur). Vasomotor regulation during sleep, and particularly during desynchronized sleep, does not consist of a simple unidirectional readjustment, and vasoconstriction coexists with the predominant vasodilatation.

mesenteric blood flow; renal blood flow; iliac blood flow; muscle circulation; sympathetic system; blood pressure; heart rate; desynchronized sleep

CURRENT INFORMATION on circulation regulation during sleep in the cat suffers from several limitations. Indeed, the most detailed hemodynamic data concern desynchronized (or REM) sleep only, information on synchronized sleep simply consisting in the description of a very slight decrease in blood pressure and heart rate (6, 10, 12). Also our knowledge on circulation regulation in desynchronized sleep, though much broader because of the more easily definable time course of this stage and the more marked circulatory changes, is far from being complete. We know that *1*) the fall in arterial pressure is significantly greater in desynchronized than in synchronized sleep (6, 10, 12); *2*) it is accompanied by a vagally induced bradycardia (9) and a very moderate reduction in cardiac output so that the blood pressure fall largely depends on a dilatation of resistance vessels (14) buffered by sinoaortic chemoceptors (8); and finally, *3*) this vasodilatation results from a decrease in sympathetic vasoconstrictive activity, as it is largely prevented by total sympathectomy (3). However, it is still unknown whether this vasodilatation is diffuse and equal in all vascular beds or whether some beds are more markedly involved in the dilatation while others remain unmodified or are even vasoconstricted. This evidence can only be obtained by recording local blood flow in several vascular beds simultaneously with systemic arterial pressure. Furthermore, it would be interesting to learn whether regional beds show the association of long-lasting (called "tonic") and short-lasting (called "phasic") changes which have been described for blood pressure and heart rate during desynchronized sleep (7, 10, 14, 15). Phasic phenomena might have different magnitudes and peculiarities in the different vascular beds, and in some regions they might more faithfully reflect and account for the marked phasic changes in blood pressure.

The experiments to be summarized here have been aimed at answering these questions by comparing one or two visceral beds with a muscular one, and comparing each bed with the overall circulatory reaction, all cardiovascular variables being continuously monitored by appropriate devices throughout quiet wakefulness, synchronized, and desynchronized sleep. It will be seen that the synchronized stage is accompanied by circulatory changes which are not necessarily in the same direction as those occurring in the desynchronized episodes; that vasodilatation in desynchronized sleep is not a general phenomenon, vasodilatation in visceral beds coexisting with muscular vasoconstriction; and finally, that tonic and phasic changes occur with distinct peculiarities in local vascular beds also.

METHODS

The observations reported here were made in seven cats (*G*, *R*, *O*, *M*, *B*, *P*, and *U*), which were completely intact except for the surgical procedures required for implantation of recording and measuring devices.

At least 1 week before the sleep studies the cats were anesthetized with sodium pentobarbital, and screw electrodes were implanted in the skull and the floor of both frontal sinuses, and needle electrodes were implanted in the paravertebral cervical musculature, in order to obtain electroencephalographic, electrooculographic, and electromyographic evidence of the various stages throughout the wakefulness-sleep cycle. Two electromyographic electrodes were also positioned on dorsal and ventral muscles of the left thigh in order to monitor muscle activity of the leg, the blood flow of which was recorded.

At the same time electrodes were positioned, three electromagnetic flow probes were implanted in each cat. *Cats G*, *R*, *O*, *M*, and *B* had probes around the initial portion of

the ascending aorta (for measuring cardiac output less coronary flow), the superior mesenteric artery (as an example of an artery supplying a visceral bed), and the left external iliac artery. *Cats P* and *U* had flow probes around two visceral arteries, the left renal and the superior mesenteric arteries, as well as around the left external iliac artery. Care was always taken to avoid injury to the nerve plexuses around the renal, mesenteric, and iliac arteries in order not to impair vasomotor reactions in the bed supplied by these arteries.

Statham electromagnetic probes were used (K probe of the hinged type, 6–7 mm id, for the aorta; and Q probes of the slot type, 1.5–2 mm id, for the peripheral arteries) connected to three Statham M-4001 modules and power supply. Sensitivity of the flow probes and the level of zero flow were repeatedly checked, before and after implantation, according to methods previously described (1). The flow probes were aseptically positioned and their cables were passed through the paravertebral muscles and the overlying skin and were protected in a leather packet sewn to the skin of the back. After completion of surgery the cats were kept in a thermostatic cage for a few days, during which they were treated with penicillin and streptomycin. They usually recovered within 1 week.

One or 2 days before the recording session, under transient ether anesthesia, a polyethylene tubing was inserted into the right femoral artery (i.e., contralaterally to the iliac flow probe), and its free end was also passed into the back packet. From this time on, the animal was heparinized.

The day of recording the cat, which had been kept fasting for at least 3 hr, was placed in a large, sound-attenuated, electrically isolated cage provided with a suitable window through which the cat's behavior could be observed. Stages throughout the wakefulness-sleep cycle were scored both by polygraphic and behavioral criteria. As quiet wakefulness (QW) we defined a state during which the animal quietly lay in a curled position, with the eyes half closed and the head slightly elevated from the floor, as signalled by a moderate activity in the neck electromyogram; the electrooculogram periodically showed some slow movement of the eyes, and the electroencephalogram alternated runs of desynchronized activity with a few bursts of spindles and rare slow waves. Synchronized sleep (SS) was scored whenever the cat, always in a curled position, was more fully relaxed on the cage floor, the head was lying on the floor (lesser activity in the neck electromyogram) and the eyes completely closed (no electrooculographic activity). The electroencephalogram showed continuous high amplitude, slow waves. Intermediate periods, which were difficult to classify either as quiet wakefulness or synchronized sleep, were considered as transition stages and were not selected for study. Desynchronized sleep was quite easy to identify: the cat looked completely relaxed, generally lying on one side, the neck electromyogram showed no or little tonic activity, there were bursts of rapid eye movements (prominently recorded in the electrooculogram) and of body twitches (also recorded in the neck and hindlimb electromyograms), the electroencephalogram was showing low voltage, fast activity.

During sleep studies the following variables were continuously monitored in a 12-channel Grass P-7 polygraph: two electroencephalographic tracings (from right and left hemispheres, respectively), the electrooculogram, an electromyogram either from the neck or the left hindlimb, femoral arterial pressure (through a Statham P 23 Db pressure transducer), and the instantaneous flow curves from the three implanted flow probes. The respective blood flows were continuously computed from the instantaneous flow curves by integrating amplifiers (Grass 7 P 10) automatically reset at 2-sec intervals and were displayed on three other channels of the polygraph. Heart rate appeared on a further channel calculated beat by beat by a cardiotachograph triggered by one of the instantaneous flow curves. Mean arterial pressure was calculated for each 2-sec interval as systolic plus twice diastolic pressure divided by three. Total peripheral, superior mesenteric, renal, and iliac conductances were computed for the same interval by dividing flow by mean pressure. Reasons for preferring conductance to its inverse, resistance, as an index of vascular diameter changes have been reported in a previous paper (1).

When iliac blood flow had to be recorded after blocking blood flow to the ipsilateral paw, the paw was placed into a rubber sleeve of a suitable diameter, closed on the distal end, and the proximal end was sealed with tape to the skin of the leg above the ankle. The sleeve was connected through a tube to an air pump which could produce an air pressure greater than the systolic blood pressure simultaneously recorded from the contralateral femoral artery of the cat. Air pressure inside this occlusion cuff was directly measured by a second Statham pressure transducer and also recorded on the polygraph. Occlusion of the hindpaw circulation was performed for at least 60 sec at the very first signs of desynchronized sleep onset. Sometimes occlusion aroused the cat, but in several instances desynchronized sleep could initiate and develop normally.

Recording sessions lasted in each cat for the time required to observe at least six complete behavioral cycles from quiet wakefulness to synchronized and then desynchronized sleep. Tracings of 2 min duration were selected for analysis *1*) from each quiet wakefulness period (QW), *2*) from periods of synchronized sleep not too far away from those selected as representative of quiet wakefulness (average 4-min interval; early synchronized sleep, subsequently referred to as SS_1), *3*) from periods of synchronized sleep immediately preceding onset of the desynchronized phase (late synchronized sleep, subsequently referred as SS_2), and *4*) from the initial part of the desynchronized phase (DS). Periods of 1 min were also analyzed both before and after arousal from each desynchronized episode. In each length of selected tracings values from four consecutive seconds out of every 12 were taken and averaged, and means and standard errors of the mean were calculated of these averages for each of the four stages in the wakefulness-sleep cycle (QW, SS_1, SS_2, DS). These data were evaluated by analysis of variance with two-way classification according to Snedecor and Cochran (18), by comparing the means in either SS_1 or SS_2 with control values in QW and the means in DS with values in SS_2. In order to have a more detailed assessment of size and time course of the changes occurring on transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep, the values from six episodes were averaged in each cat point by point, and the points were

TABLE 1. *Cardiovascular changes from quiet wakefulness to synchronized sleep and to desynchronized sleep*

Cat	QW	SS_1	SS_2	DS
	Mean blood pressure, mm Hg			
G	104 ± 1	104 ± 2	105 ± 1	92 ± 3†
R	86 ± 2	86 ± 1	85 ± 2	74 ± 2†
O	91 ± 15	88 ± 6	85 ± 5*	66 ± 1†
M	106 ± 1	108 ± 1	106 ± 1	100 ± 1
B	90 ± 1	87 ± 1*	83 ± 1†	73 ± 1*
P	86 ± 2	83 ± 1	78 ± 1†	65 ± 1†
U	119 ± 3	119 ± 2	117 ± 3	105 ± 4†
	Cardiac output, ml/min			
G	648 ± 17	638 ± 15	620 ± 23*	576 ± 17*
R	581 ± 13	559 ± 10*	557 ± 7*	540 ± 10
O	508 ± 30	489 ± 23	487 ± 21	477 ± 17
M	350 ± 6	337 ± 6†	324 ± 2†	306 ± 2
B	330 ± 2	311 ± 2†	306 ± 1†	293 ± 3*
	Heart rate, beats/min			
G	216 ± 3	216 ± 2	215 ± 2	204 ± 1†
R	195 ± 4	186 ± 2	184 ± 2*	183 ± 2
O	247 ± 6	238 ± 7*	239 ± 6	221 ± 4†
M	230 ± 1	226 ± 2	225 ± 4	209 ± 3†
B	220 ± 1	216 ± 1*	208 ± 1†	206 ± 2
P	227 ± 5	224 ± 5	219 ± 5	210 ± 4
U	186 ± 3	183 ± 4	174 ± 3*	171 ± 2
	Total peripheral conductance, ml/min per mm Hg			
G	6.25 ± 0.17	6.14 ± 0.14	5.91 ± 0.02	6.68 ± 0.02†
R	6.77 ± 0.08	6.50 ± 0.01	6.52 ± 0.01	7.30 ± 0.02†
O	5.55 ± 0.28	5.55 ± 0.04	5.75 ± 0.02*	6.73 ± 0.02*
M	3.28 ± 0.03	3.12 ± 0.01†	3.05 ± 0.01†	3.03 ± 0.03
B	3.67 ± 0.03	3.57 ± 0.01*	3.69 ± 0.04	3.99 ± 0.04*
	Mesenteric conductance, ml/min per mm Hg			
G	0.59 ± 0.02	0.58 ± 0.02	0.57 ± 0.01	0.73 ± 0.01*
R	0.44 ± 0.01	0.43 ± 0.01	0.46 ± 0.02	0.53 ± 0.01*
O	0.29 ± 0.02	0.32 ± 0.02	0.33 ± 0.01	0.43 ± 0.01†
M	0.30 ± 0.01	0.29 ± 0.01	0.27 ± 0.01	0.32 ± 0.01†
B	0.45 ± 0.01	0.47 ± 0.01*	0.53 ± 0.02*	0.63 ± 0.01†
P	0.64 ± 0.02	0.68 ± 0.01	0.74 ± 0.01*	0.93 ± 0.01†
U	0.34 ± 0.01	0.35 ± 0.01	0.34 ± 0.01	0.38 ± 0.02
	Iliac conductance, ml/min per mm Hg			
G	0.37 ± 0.02	0.37 ± 0.02	0.38 ± 0.02	0.28 ± 0.02†
R	0.37 ± 0.02	0.37 ± 0.02	0.39 ± 0.01	0.36 ± 0.01†
O	0.52 ± 0.04	0.49 ± 0.03	0.54 ± 0.02	0.52 ± 0.01
M	0.17 ± 0.02	0.15 ± 0.01*	0.18 ± 0.01	0.14 ± 0.01†
B	0.23 ± 0.01	0.23 ± 0.01	0.26 ± 0.01†	0.21 ± 0.01*
P	0.33 ± 0.01	0.34 ± 0.01	0.34 ± 0.01	0.32 ± 0.02
	Renal conductance, ml/min per mm Hg			
P	0.42 ± 0.01	0.46 ± 0.01	0.47 ± 0.01*	0.55 ± 0.01†
U	0.21 ± 0.01	0.21 ± 0.01	0.21 ± 0.01	0.24 ± 0.01†

Means and standard errors of the means of measurements performed during six periods of quiet wakefulness (QW), beginning of synchronized sleep (SS_1), end of synchronized sleep (SS_2), and desynchronized sleep (DS) in each cat. Significance values refer to comparison of data obtained during SS_1 or SS_2 with data in QW and of data obtained during DS with data in SS_2. * $P < 0.05$. † $P < 0.01$.

plotted in order to draw average graphs representing the progressive change of a given cardiovascular variable during desynchronized sleep in each cat. All data for analysis were fed into an electronic desk-top computer, Olivetti Programma 101.

RESULTS

Cardiovascular changes during synchronized sleep. Means and standard errors of the mean of the cardiovascular variables we have measured throughout the wakefulness-sleep cycle are reported as absolute values in Table 1 and are also summarized in Fig. 1 as percent changes of values recorded in quiet wakefulness.

Circulation was only modestly and often uncertainly influenced by synchronized sleep, both in periods closer in time to waking (SS_1) and in periods immediately preceding the desynchronized phase (SS_2). Mean blood pressure was significantly, though modestly, reduced in only three out of seven cats, the decrease being constantly greater in SS_2. Also heart rate was significantly reduced in three cats only, the extent of the bradycardia being very slight even in SS_2. A small fall in cardiac output was measured in four of five cats. Total peripheral conductance was variously affected in different cats; there was a slight significant increase in one cat and a slight significant decrease in two animals. In five cats there was an increase in mesenteric conductance indicating local vasodilatation, which was marked and statistically significant in only two animals, however. The remaining two cats showed some mesenteric vasoconstriction, which did not reach the level of statistical significance. Iliac blood flow and conductance were also affected modestly by synchronized sleep, but the direction of changes seemed on the whole to be opposite in the early and in the late portion of the synchronized sleep periods (SS_1 and SS_2). However, vasoconstriction during SS_1 was significant in one cat only, and likewise vasodilatation during SS_2 attained statistical significance in only one animal. Renal blood flow was measured in two cats, one of which showed a clear, significant local vasodilatation.

Cardiovascular changes during desynchronized sleep. Average values of cardiovascular variables during the first 2 min from the beginning of desynchronized sleep episodes are reported in the fourth column of Table 1 and plotted at the right end of the curves of Fig. 1 (DS) as percent values of measurements performed during quiet wakefulness. Statistical significance of cardiovascular changes occurring during desynchronized sleep as compared to values immediately preceding its onset (i.e., during SS_2) is also reported in Table 1. The development of these changes during the 2 min preceding and the 2 min following appearance of the desynchronized phase as well as during 1 min preceding and 1 min following its end is illustrated in Figs. 2–6, each curve being the mean of six episodes in the same cat.

Mean blood pressure (Figs. 1 and 2) showed a distinct reduction at the very beginning of desynchronized sleep attaining a minimum during the 2nd min. The change occurred in all cats and was highly significant in all of them except in *cat M*. It was also significant at the $P < 0.01$ level for the total sample of seven cats. During the last minute of desynchronized sleep blood pressure was still at about the same values as reported above, thus showing that the hypotensive effect was sufficiently enduring throughout this sleep stage. Mean blood pressure promptly returned to, or slightly above, SS_2 levels within 1 min from arousal from desynchronized sleep. Also heart rate (Figs. 1 and 2) further decreased during desynchronized sleep beyond the already slightly

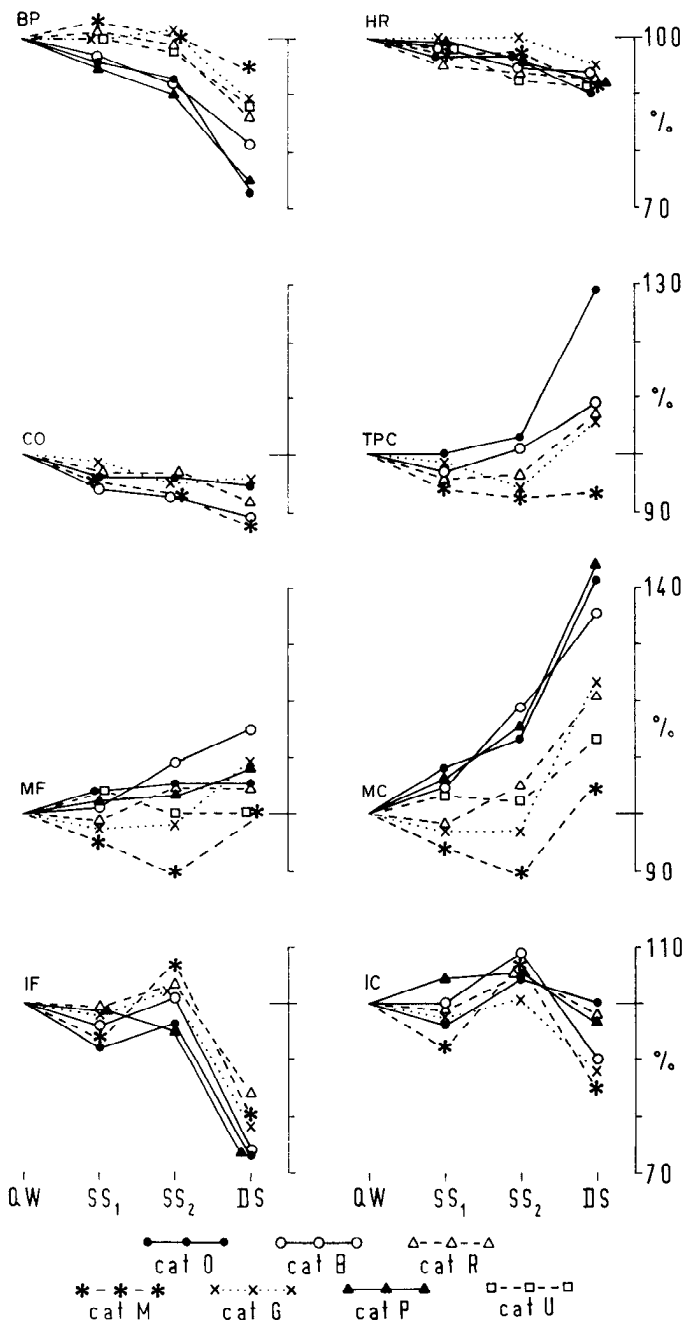

FIG. 1. Percent changes of cardiovascular variables throughout wakefulness-sleep cycle, referred to base lines in quiet wakefulness. QW: quiet wakefulness, SS_1 : early period of synchronized sleep, SS_2 : later period of synchronized sleep, DS: desynchronized sleep, BP: mean blood pressure, HR: heart rate, CO: cardiac output, TPC: total peripheral conductance, MF and MC: superior mesenteric flow and conductance, IF and IC: left external iliac flow and conductance. Different symbols refer to 7 cats studied identified at bottom of figure. Each symbol is mean of 60 measurements performed in 6 wakefulness-sleep cycles (see more details under METHODS).

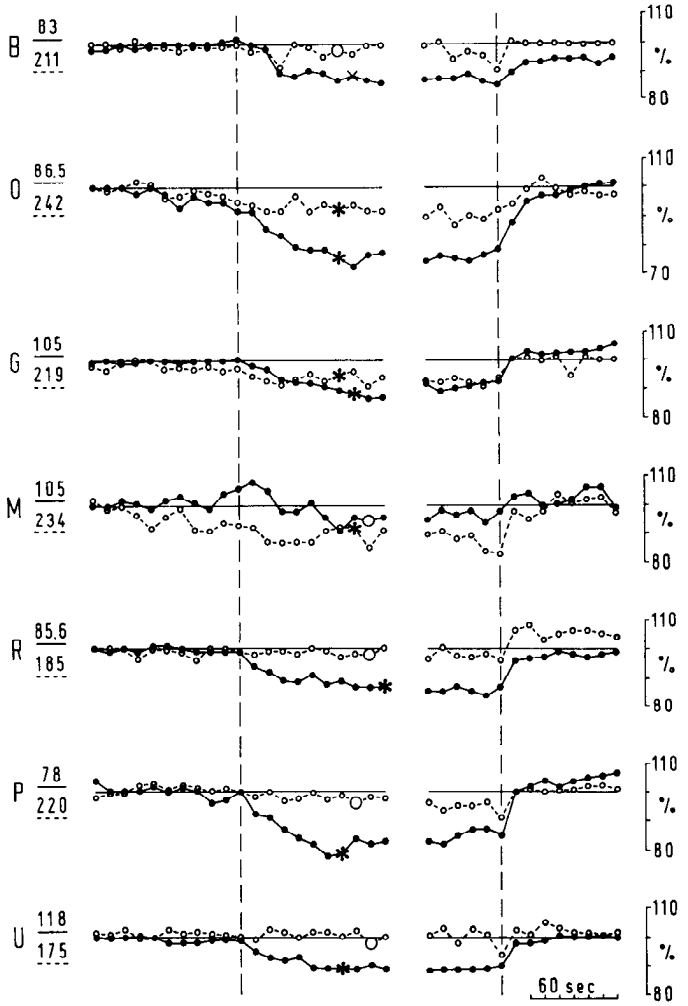

FIG. 2. Percent changes in mean blood pressure (●, continuous lines) and heart rate (○, dashed lines) during transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep. In this figure, as well as in Figs. 3–6, each symbol represents mean of 4-sec measurements selected out of 12 consecutive seconds performed during 6 episodes of desynchronized sleep in several cats (identified by letters on left). Two vertical lines indicate beginning and end of desynchronized sleep. Data are expressed as percent changes with reference to base-line values measured during final period of synchronized sleep. Means of absolute base-line values (=100%) are given for each cat at left in millimeters Hg for blood pressure (underlined by continuous lines) and in beats per minute for heart rate (underlined by interrupted lines). Results of statistical analysis, when performed, are indicated by ✳ ($P < 0.01$), × ($P < 0.05$), and ○ ($P > 0.05$).

reduced values of SS_2. The change, however, was quite moderate and statistically significant in only three of seven cats. Nonetheless, the decrease was significant at the $P < 0.05$ level for the total sample of seven cats. At the moment of arousal from desynchronized sleep, heart rate returned to or slightly above SS_2. Like blood pressure and heart rate, cardiac output (Figs. 1 and 3) continued to decrease during desynchronized sleep, but this decrease was very small and significant in only two cats. In spite of this the change was significant at the $P < 0.05$ level for the total sample of five cats. Total peripheral conductance (Figs. 1 and 3), which had been variously influenced by synchronized sleep, was markedly and significantly increased throughout the desynchronized stage in four out of five cats, the remaining one showing no change. The increase in the total sample of five cats was significant at the $P < 0.05$ level.

Mesenteric flow (Figs. 1 and 4) was unchanged during desynchronized sleep in three cats while it was increased in the remaining four. However, because of the decrease in mean blood pressure, mesenteric conductance appeared to

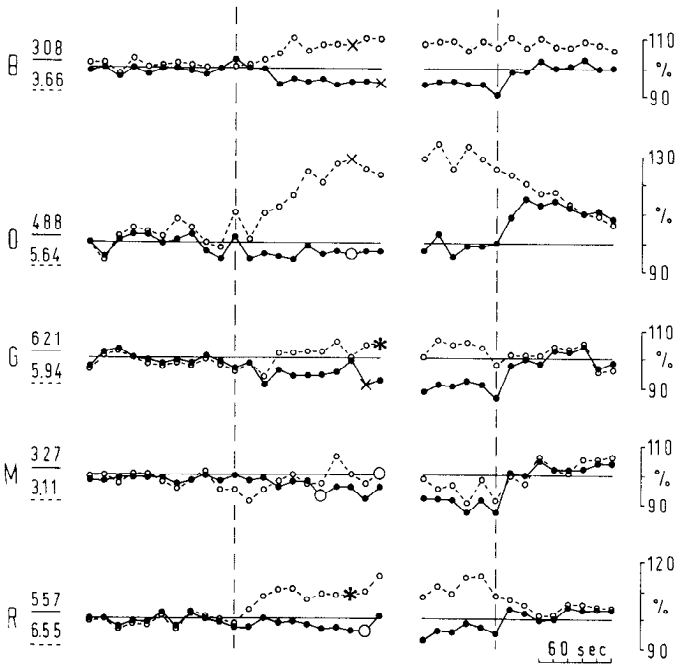

FIG. 3. Percent changes in cardiac output (●, continuous lines) and in total peripheral conductance (○, dashed lines) during transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep. Means of absolute base-line values are given at left in milliliters per minute for cardiac output (continuous lines) and in milliliters per minute per millimeter Hg for total peripheral conductance (interrupted lines). Other explanations as in Fig. 2.

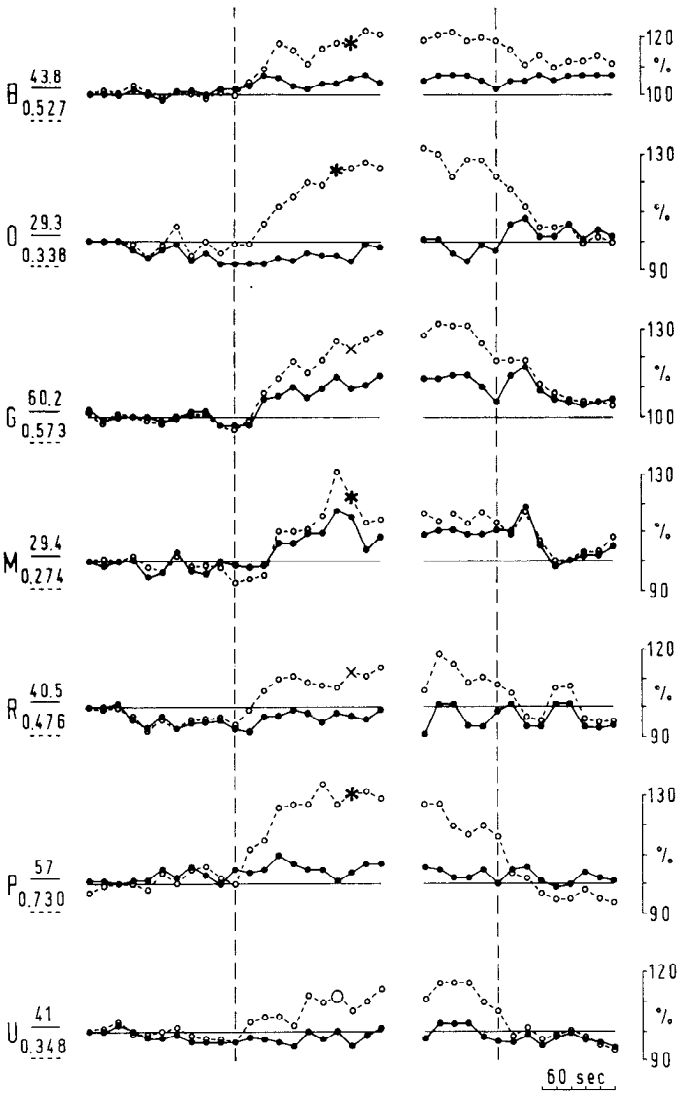

FIG. 4. Percent changes in superior mesenteric blood flow (● continuous lines) and conductance (○, dashed lines) during transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep. Means of absolute base-line values are given at left in milliliters per minute for mesenteric flow (continuous lines) and in milliliters per minute per millimeters Hg for mesenteric conductance. Other explanations as in Fig. 2.

be markedly increased in all seven cats, though in one of them just short of statistical significance. In the total sample mesenteric vasodilatation was statistically significant at the $P < 0.01$ level. During the last minute of desynchronized sleep episodes the mesenteric bed was still dilated to about the same extent as during the initial period: upon arousal mesenteric conductance promptly returned to or toward SS_2 values. Renal blood flow (Fig. 5) remained remarkably constant on transition from synchronized sleep and throughout these episodes, but the decrease in mean blood pressure caused renal conductance to increase significantly in both cats. Iliac blood flow (Figs. 1 and 6) invariably and markedly decreased at the beginning of desynchronized sleep and remained reduced throughout. In all six cats flow decreased to a greater extent than mean blood pressure so that iliac conductance constantly decreased. Iliac vasoconstriction was significant in four cats and was also significant at the $P < 0.05$ level for the total sample of six animals. This is a reverse change than that often occurring during SS_2, which consisted in a slight vasodilatation. Consequently, when compared to quiet wakefulness levels the iliac vasoconstriction induced by desynchronized sleep appeared somewhat smaller (see Fig. 1). In two cats several episodes of desynchronized sleep were studied while the paw circulation was temporarily excluded: a decrease in iliac flow and conductance was regularly observed even in these conditions. Since it is well known that the paw receives the major part of the neurally regulated cutaneous flow of the hindlimb (20), it was concluded that these diminutions of flow and conductance represent at least predominantly a vasoconstriction in the muscle components of the external iliac bed.

Tonic and phasic manifestations of desynchronized sleep. Also in our cats, cardiovascular changes of sudden development and short duration could often be observed during desynchronized sleep, superimposed upon slower ones which lasted throughout the duration of each desynchronized sleep episode. It was easily evident from our records that phasic changes not only concerned blood pressure and heart rate, as was known from previous work of Pompeiano's (7, 15) and our group (10, 14), but that the mesenteric and iliac beds could also be involved. As shown in Fig. 7 the phasic changes in iliac blood flow were sometimes very great; they consisted of sudden reductions of flow (even to half the previous level), occurring toward the end or shortly after a prolonged burst of rapid eye movements. As we also recorded the motor activity of the hindlimb, the blood flow of

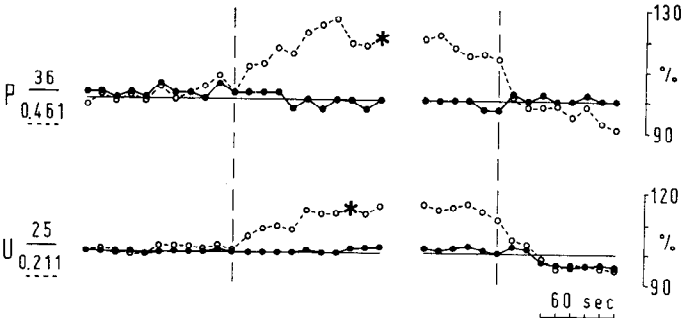

FIG. 5. Percent changes in left renal blood flow (●, continuous lines) and conductance (○, dashed lines) during transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep. Means of absolute base-line values are given in same units as in Fig. 4. Other explanations as in Fig. 2.

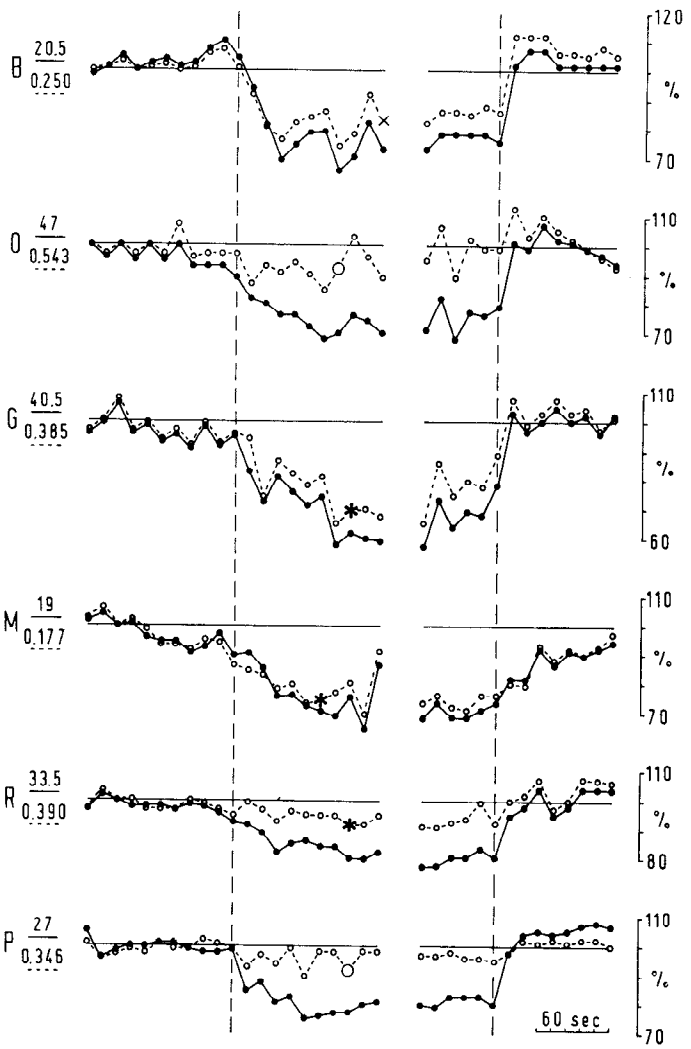

FIG. 6. Percent changes in left external iliac blood flow (●, continuous lines) and conductance (○, dashed lines) during transition from synchronized to desynchronized sleep and upon arousal from desynchronized sleep. Means of absolute base-line values are given in same units as in Fig. 4. Other explanations as in Fig. 2.

which was being measured, it became apparent that twitches occurred in the hindlimb immediately before the decrease in flow. However, as in one of the three consecutive instances illustrated in Fig. 7, phasic reductions in iliac flow could be observed in absence of electromyographic evidence of local motor activity. Figure 7 also shows the relation of phasic iliac changes with other phasic cardiovascular manifestations. The short bursts of reduced iliac flow were generally simultaneous to brief rises in arterial pressure (thus representing true, marked vasoconstriction), although they could outlast the phasic pressor changes, being occasionally followed by a brief wave of vasodilatation. Likewise, iliac vasoconstriction often started during the phasic increase in heart rate and extended well into the subsequent period of bradycardia. Mesenteric blood flow also showed phasic variations, but as apparent in Fig. 7 it was more difficult to correlate them with the other phasic cardiovascular manifestations of desynchronized sleep as well as with muscle twitches and rapid eye movements.

The occurrence of marked phasic circulatory changes should not suggest that, at least in some vascular beds, they might represent the only manifestations of desynchronized sleep, and that the rather regular, tonic development of circulatory changes apparent in Figs. 2–6 might simply represent the artificial result of averaging phasic variations with different timing. That this is not the case and that long-lasting tonic manifestations did occur and were most often the dominant phenomena is shown by several considerations. First, the standard errors of the mean of cardiovascular changes listed in Table 1 were small, those calculated for desynchronized sleep being of the same magnitude as standard errors calculated for the other periods of the wakefulness-sleep cycle in which phasic changes are absent. Second, there were several episodes of desynchronized sleep in which phasic changes were very inconspicuous, and the decrease in blood pressure and particularly in iliac flow were very regularly developing.

DISCUSSION

The data reported above provide the first quantitative evidence of the hemodynamic changes accompanying the development of synchronized sleep. On the whole these changes are small, sometimes inconsistent from cat to cat, and seldom statistically significant. Our observations confirm that blood pressure and heart rate, the only variables previously studied (6, 10, 12), change very little. It is to be noticed that in the present data, obtained by averaging prolonged periods of synchronized sleep, arterial pressure seems to decrease even less than in a previous study of our group (10) in which only the lowest pressure values were taken into consideration. It is interesting, however, that the small decrease in blood pressure during synchronized sleep was associated with a reduced cardiac output and that calculated total peripheral conductance was either unmodified or could even indicate a slight overall vasoconstriction. This contrasts with the considerable overall vasodilatation produced by desynchronized sleep. A contrast between the synchronized and the desynchronized stage was also evident in the mesenteric bed, at least in those cats which showed no vasodilatation, and sometimes a slight vasoconstriction was evident during synchronized sleep, while vasodilatation was marked whenever desynchronized episodes occurred. The iliac blood flow, on the other hand, seemed peculiar insofar as it could show opposite changes

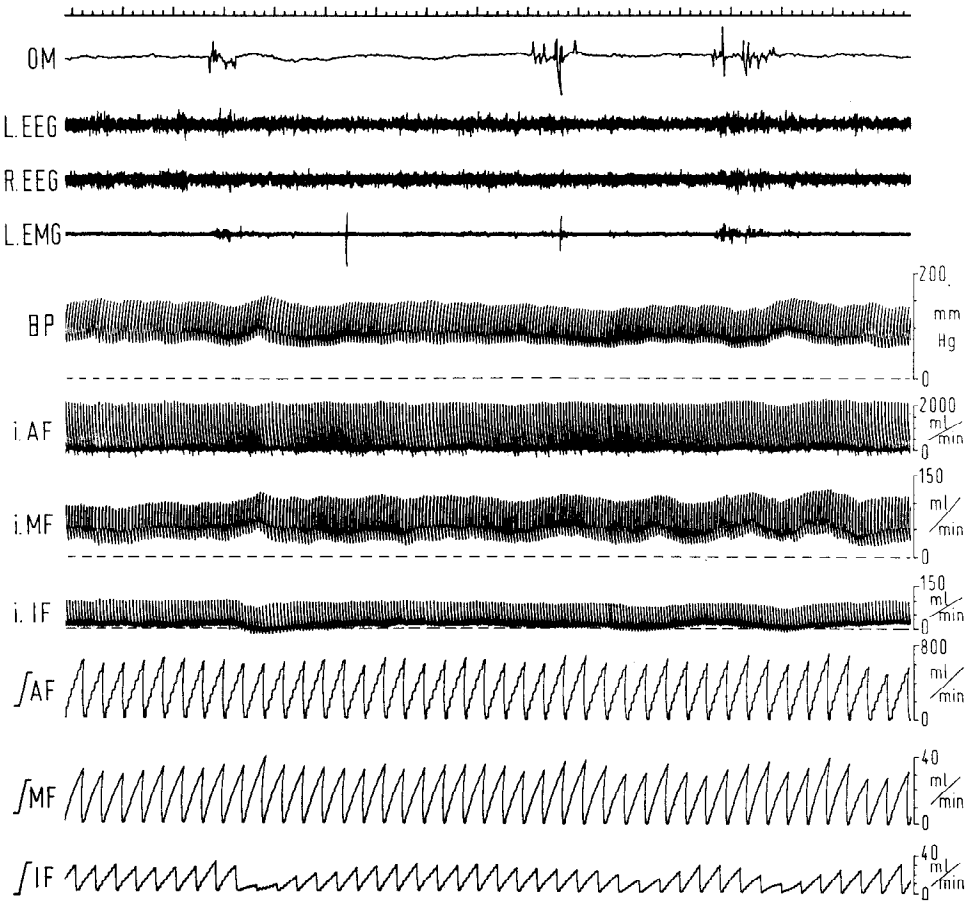

FIG. 7. Original tracings from a desynchronized sleep episode in *cat G*, showing several phasic manifestations. In this figure, from above downward: time (1 and 5 sec); OM: ocular movements; L.EEG and R.EEG: electroencephalograms from left and right hemispheres; L.EMG: electromyogram from left hindlimb; BP: arterial blood pressure; i.AF: instantaneous flow through ascending aorta; i.MF: instantaneous flow through superior mesenteric artery; i.IF: instantaneous flow through left external iliac artery; ∫ AF, ∫MF, ∫ IF: 2-sec integrations of above flows. Calibrations on right.

during early (SS_1) and late periods (SS_2) of synchronized sleep. In a few cats a small early vasoconstriction was later replaced by a slight vasodilation, which then gave way to a new wave of vasoconstriction during the desynchronized stage.

Changes during desynchronized sleep were much more marked than those observed during the synchronized period, were very consistent from cat to cat, and were always statistically significant. Some of them do not need much comment, as our new observations simply confirm what we had already described in an earlier series of animals (14): the decrease in blood pressure is greater than the reduction in cardiac output, which indicates an overall vasodilatation. The present experiments, however, show that the increase in total peripheral conductance, though generally conspicuous over SS_2 levels, is often more moderate if compared to the quiet wakefulness base line because of the slight vasoconstriction occurring during synchronized sleep.

Probably the most interesting among the new data here reported is the observation that dilatation is not diffuse in all vascular beds and that it coexists with simultaneous vasoconstriction. Vasodilatation was conspicuous in both visceral beds we have investigated: the superior mesenteric and the renal beds. Vasodilatation was somewhat greater in the mesenteric than in the renal territory, as the mesenteric blood flow could actually increase despite the decreased pressure head while the renal flow remained practically unmodified. Because cardiac output generally, though moderately, decreased during desynchronized sleep, the fractional flow perfusing the mesenteric and, probably, the renal beds increased.

If one compares the magnitude of increase in mesenteric and total peripheral conductance of each cat in Figs. 1, 3, and 4, it is easily realized that mesenteric vasodilatation is proportionally greater than overall vasodilatation. This is because of the simultaneous vasoconstriction occurring in muscles. Indeed it is apparent from Figs. 1, 3, 4, and 6 that the greater the proportional excess of visceral above overall vasodilatation, the greater the vasoconstriction measured in the muscles of the external iliac bed. In *cat M* the two opposite vascular reactions are so well balanced that practically no change in total peripheral conductance is apparent and blood pressure falls very slightly proportionally to the slight decrease in cardiac output. This case emphasizes that absence of systemic changes in arterial pressure and cardiac output cannot be taken to mean absence of vasomotor phenomena as well. This consideration might apply to the cardiovascular reactions of man during desynchronized sleep. The very small changes in arterial pressure and cardiac output recorded in man (5, 13, 19) might result from a more precise balancing of visceral vasodilatation with muscular vasoconstriction than generally occurs in cats.

A decreased fractional flow to muscles during desynchronized sleep has also been reported by Reis et al. (16, 17). Our experiments, by simultaneously recording iliac blood flow, cardiac output, and arterial pressure, demonstrate that the decrease in fractional flow actually represents an absolute reduction in local blood flow and an iliac vaso-

constriction. Our continuous method of recording cardiovascular variables also shows that this muscle vasoconstriction is a long-lasting, tonic phenomenon throughout desynchronized sleep, not merely a short-lasting, phasic change, as could be the case until evidence was limited to occasional sampling in a single desynchronized sleep episode. Since Reis et al. (16, 17) have shown that fractional flow is reduced in red muscles only, it is likely that vasoconstriction is limited to, or dominant in, this type of muscle only.

We have no evidence on the mechanisms mediating the muscular vasoconstriction of desynchronized sleep. If it were due to sympathetic vasoconstrictive discharges, this would amount to the demonstration that the sympathetic system can be acted upon in an extremely selective way during behavior, as desynchronized sleep is known to suppress the sympathetic firing to renal vessels (4, 11) and sleep vasodilatation is abolished by sympathectomy (3). This extremely selective repatterning of sympathetic discharges is a very exciting suggestion indeed (17). Alternative explanations are available, however. Muscle vasoconstriction might be induced by a decreased production of vasodilating metabolites due to the sudden fall in muscle tone characterizing desynchronized sleep. This metabolic factor might be large enough to mask the opposite effect of a diffusely decreased vasoconstrictive tone. This hypothesis might take into account the strange triphasic change in muscle circulation evident, at least in a few cats, throughout the wakefulness-sleep cycle. The initial vasoconstriction observed in SS_1 might depend from the initial fall in muscle tone upon transition from quiet wakefulness to synchronized sleep; later vasodilatation in SS_2 might result from reduced sympathetic vasoconstrictive activity unassociated with, and therefore unimpeded by, further muscle hypotonia. The sudden final fall in muscle tone at the beginning of the desynchronized phase might then account for the last marked vasoconstriction. Other less likely hypotheses can be advanced, as, e.g., the existence of a tonic vasodilating reflex effect induced by muscle proprioceptors and abolished by atonia. Of course, the stronger vasoconstrictions occurring as phasic phenomena during or shortly after local contractions cannot be explained by metabolic factors related to atonia, but phasic and tonic vasoconstrictions might well have different mechanisms. The observation that phasic vasoconstrictions clearly overlast motor twitches makes it unlikely that they simply result from the mechanical consequences of muscle contractions (1, 2) and supports the hypothesis that at least the phasic vasoconstriction represents the effect of sympathetic discharges.

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