

RESPIRATORY AND CIRCULATORY CONTROL DURING SLEEP

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SUMMARY

A survey of the literature on a large number of vertebrate animals shows that sleep is associated with profound cardiovascular and respiratory adjustments which are very similar in each species. A hypothesis is advanced that these adjustments are 'goal directed' by neural structures in the brainstem, to ensure an adequate O_2 and CO_2 transport to and from the brain whilst at the same time reducing energy cost. During synchronised sleep there is a vagal bradycardia leading to reduced cardiac output and a fall in blood pressure; despite this cerebral blood flow increases. During desynchronised sleep there is a tonic fall in blood pressure and heart rate resulting from a unique repatterning of sympathetic discharge, that to heart, kidney, splanchnic and pelvic vascular beds decreasing whilst that to skeletal muscle increasing; cerebral blood flow shows a further increase. This differential pattern is probably initiated by neurones located in the caudal raphe nucleus obscurus. Phasic increases in blood pressure and heart rate also occur during desynchronised sleep mainly as a consequence of increases in sympathetic activity. Ventilation decreases during synchronised sleep accompanied by an increase in partial pressure of arterial CO_2 , which vasodilates cerebral blood vessels, indicating that the influence of CO_2 on the level of ventilation has changed. During desynchronised sleep ventilation increases and becomes very irregular but the partial pressure of O_2 and CO_2 in arterial blood is little changed from wakefulness. Control of respiration is shifted to a central generator which apparently is different to the automatic/metabolic one which is normally dominant during wakefulness. Reflex control of the circulation and respiration is mainly governed by peripheral chemoreceptors, the threshold of most other afferent inputs being significantly raised during sleep.

INTRODUCTION

Rhythmic variations in levels of arousal and activity are a universal characteristic of higher organisms. The extreme condition is seen in man and most vertebrates each 24 h, when they exhibit periods in which they alternately are aware of environmental changes, and respond more or less purposefully to them in a state called wakefulness, or are out of touch with the external world and lie relaxed and relatively motionless in a state called sleep. Pronounced alterations in central neural activity underly these contrasting conditions. Sampling the neural activity in mammals (particularly man) using electroencephalography has revealed that alert wakefulness is associated with

low-voltage, fast electrical activity of the cerebral cortex and sub-cortical structures. Drowsiness and sleep on the other hand, are associated with high-voltage, slow electrical activity (synchronized or slow wave sleep): at times interrupted by periods of low voltage, fast discharge associated with a deeper stage of sleep when the arousal threshold is higher (desynchronized or paradoxical sleep). This latter stage of sleep is accompanied by a generalized muscle atonia and occasional rapid movements of the eyes, which has given rise to the name rapid eye movement (REM) sleep (Dement & Kleitman, 1957; Kleitman, 1963; Jouvet, 1967; Ellingson, 1972; Moruzzi, 1972; Serman, 1972).

All mammals (43 species) apart from *Tachyglossus* (*Echidna*), a monotreme, and birds (5 species) for which there is adequate data exhibit these two types of sleep (Kleitman, 1963; Hassenberg, 1965; Tauber, 1974; Zepelin & Rechtschaffen, 1974). The reptiles do not exhibit the typical mammalian electroencephalographic correlates of behavioural sleep, but this does not necessarily mean that it is not analogous to that of mammals and birds. It is important to realize that the mammalian sleep electroencephalogram serves only as a phenomenological and not a functional definition of sleep. Despite this drawback sleep studies on reptiles of the three major orders, Squamata, Chelonia and Crocodylia, have shown the unambiguous presence of behavioural sleep but an absence of desynchronized sleep (Flanigan, Wilcox & Rechtschaffen, 1973; Tauber, 1974). Therefore in the present account I have included descriptions of autonomic changes in these three major classes of vertebrates. I have omitted all reference to amphibians and fishes since the existence of behavioural sleep has yet to be rigorously demonstrated in these animals and there is no data on autonomic events during quiescent periods.

Accompanying sleep are profound cardiovascular and respiratory events. Our most detailed knowledge of these has been gained from studies on the cat, dog and man. These studies have been the subject of a number of recent excellent and extensive reviews (Mancia & Zanchetti, 1980; Phillipson, 1978; Sullivan, 1980). In this chapter I have aimed to summarize the data that have been gathered from a wide variety of species illustrating the remarkable similarity of the cardiovascular and respiratory changes during sleep in all animals. Some attempt is made to evaluate the mechanisms responsible for the changes focussing attention on areas to which my own research has recently contributed.

A hypothesis

The biological function of sleep is still a mystery despite numerous attempts to formulate tenable hypotheses (Zepelin & Rechtschaffen, 1974; Walker & Berger, 1980; Oswald, 1980; Drucker-Colin, Schkurovich & Serman, 1979; Moruzzi, 1972). Nonetheless it is very evident that sleep is associated with a reduced energy cost (Zepelin & Rechtschaffen, 1974) and a restoration of the brain to a state that was present at the beginning of a previous period of wakefulness. To this end the immediate and principal function of the cardiovascular and respiratory system is to ensure an adequate oxygen and carbon dioxide transport to and from the brain whilst at the same time ensuring that the work of these two systems is reduced to a minimum compatible with normal resting organ function in the rest of the body. We shall see

that these requirements are fulfilled by respiratory and circulatory adaptations that are not just epiphenomena of sleep but result from the activity of central nervous pattern generators that initiate goal directed activity of these systems which ensures that the main task of sleep is achieved.

Cardiovascular changes during sleep

Since the earliest studies on sleeping animals there have been reports of alterations in blood pressure and heart rate (Pieron, 1913; Kleitman, 1963). However, it was not until comparatively recent times that comprehensive analytical studies of the circulation have been conducted during sleep. As pointed out by Dement (1980) in his forward to a recent review on sleep physiology (Orem & Barnes, 1980) until the 1960s it was as though no one realized that control mechanisms would differ markedly during sleep compared to the waking state. As far as the cardiovascular system is concerned this attitude has been changed particularly because of the very thorough and extensive studies of Zanchetti and his group over the last twenty years.

For those of us concerned with understanding how the nervous system controls the heart and circulation, sleep (a behavioural state which can be precisely defined), represents a valuable condition for investigating this control under repeatable and natural circumstances. In the following sections, written from the point of view of a neurophysiologist, I have been analytical in my approach: first, dealing with the simple description of the phenomena associated with sleep, then examining the underlying events contributing to the changes and finally analysing the neural mechanisms that may be responsible.

Blood pressure

Reliable data on blood pressure levels during sleep have so far been documented on seven species, including man. In the domestic cat, a small reduction of mean blood pressure (~ 10 mmHg) occurs during synchronised sleep. A further more marked fall (> 14 mmHg) occurs during the tonic stage of desynchronized sleep, and is irregularly interspersed by substantive phasic increases in blood pressure (> 20 mmHg; Candia *et al.* 1962; Kanzow, Krause & Kuhnel, 1962; Gassel *et al.* 1964; Guazzi & Zanchetti, 1965; Iwamura, Uchino & Kidokoro, 1968; Mancina *et al.* 1971). Similar changes have been reported for the rhesus monkey (Stoyva, Forsyth & Kamiya, 1968), the dog (Tarchanoff, 1894; Heymans & Bouckaert, 1934; Kernodle, Hill & Grimson, 1944, 1946; Bonamini *et al.* 1962; Ferrario, McCubbin & Page, 1969; Seal & Zbrozyna, 1977), the opossum (*Didelphis marsupialis*; Van Twyver & Allison, 1970) and the rabbit (Dufour & Court, 1977; Franzini & Cianci 1979; Parmeggiani, 1980). In the rat there is apparently little difference between the mean blood pressure during waking and during synchronized sleep. Surprisingly, during desynchronized sleep there is a small (~ 4 mmHg) tonic increase (Junquiera & Krieger, 1976; Iwamura *et al.* 1979). In man a small reduction of mean blood pressure (15–20 mmHg) is often described during synchronized sleep (Brush & Fayerweather, 1901; Brooks & Carol, 1912; MacWilliams, 1923; Grimson, Kernodle & Hill, 1944; Snyder *et al.* 1964; Richardson *et al.* 1964; Grazi *et al.* 1967; Coccagna *et al.* 1971; Khatri & Freis, 1967; Bristow *et al.* 1969; Smyth, Sleight & Pickering, 1969). During

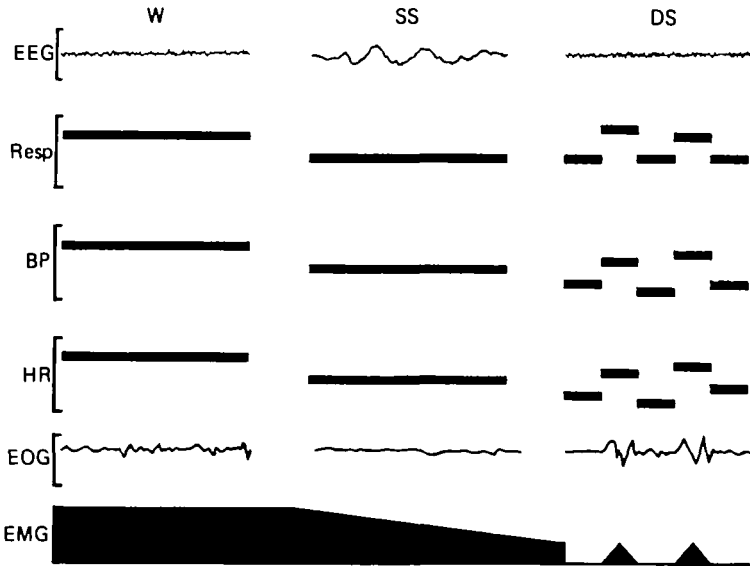


Fig. 1. Diagram illustrating schematically, for most animals so far studied, the mean ventilation (Resp), mean blood pressure (BP) and mean heart rate (HR) during alert wakefulness (W), synchronised sleep [SS, when neck muscles electromyogram, EMG, shows activity decreasing], and during desynchronised sleep [DS, when EMG is silent, tonic period in some animals] interspersed by bursts of activity (phasic period), generally associated with eye movements [indicated by activity in the electrooculogram, EOG]. EEG, shows a typical sample of the parietal cortex electroencephalogram during each of the periods W, SS, DS.

desynchronised sleep the blood pressure undergoes frequent marked oscillations, sometimes falling below the levels measured during synchronised sleep and at other times rising to levels above waking values (Snyder *et al.* 1964; Coccagna *et al.* 1971). Because of these marked swings in arterial blood pressure during desynchronised sleep a true representation of the behaviour of blood pressure cannot be obtained by calculating mean levels. This has, however, been done in most papers on human sleep, so that some workers report an increase in mean blood pressure (Khatri & Freis, 1967; Snyder *et al.* 1964) whilst others report a decrease (Bristow *et al.* 1969) during desynchronised sleep. Careful examination of the records in these papers indicate that during desynchronised sleep blood pressure reaches the lowest levels of the circadian cycle, in adults and infants.

In conclusion, it is apparent that apart from the rat a similar behaviour of blood pressure during sleep can be recognized in species as different as the opossum and man [Fig. 1]. In all seven species the difference in the blood pressure responses, particularly during desynchronised sleep, is probably a consequence of the relative amounts of tonic and phasic periods that occur.

As well as these basic rhythms in blood pressure levels associated with the different stages of sleep in the human there is the much slower rhythm superimposed on them in which blood pressure slowly falls throughout the first 2–4 h of sleep where it stabilises before beginning to rise towards awake levels (Richardson *et al.* 1964; Littler *et al.* 1972; Littler *et al.* 1975; Littler, 1979; Miller-Craig, Bishop & Rafferty, 1978; Mann *et al.* 1978).

Cardiac effects

Descriptions of changes in blood pressure give no information on the underlying cardiovascular adjustments that occur. In this section I will consider changes in cardiac performance during sleep which are reflected in studies measuring heart rate, stroke volume and cardiac output.

(a) *Heart rate.* No doubt because of the relative ease of measurement, heart rate has been recorded in 26 species of mammals, 2 species of birds and 4 different reptiles during sleep. In all these animals, apart from the mole and hedgehog, heart rate decreases on entry into sleep. In mammals and birds during desynchronized sleep heart rate becomes very variable (Table 1), but a pattern is clearly recognizable in that during the tonic stage a further bradycardia occurs which is interrupted by phasic swings to tachycardia which may be considerable (Fig. 1). In the human there are frequent marked swings in heart rate during desynchronized sleep resulting in the lowest levels during this stage as well as the highest sleeping ones. It is obvious that calculating mean values for heart rate during this latter stage can give no clue to its actual behaviour and this no doubt has led to the contradictory statements in the literature: an increase being reported by Khatri & Freis (1967) and Snyder *et al.* (1964) and a decrease by Bristow *et al.* (1969). Most of the literature on the human infant may be similarly misleading. An examination of the records from the recent study of Junge (1979) on the human new-born infant reveals that heart rate during desynchronized sleep showed marked fluctuations – reaching its lowest levels of 100 beats per min/(bpm) during periods of muscle atonia and increasing to 150 bpm during periods in which body movements occurred. These heart rates were compared with 130 bpm for quiet sleeping and 200 bpm during waking and crying. The cat and dog show fewer phasic phenomena during desynchronized sleep and therefore the tonic bradycardia is more obvious in these animals.

The changes of heart rate in children during sleep were supposed by Sutherland (1929) to be due to activity in the vagal innervation of the heart since the usual fall in heart rate during sleep disappeared after application of atropine to block the cholinergic mediated effects of this activity. In a more extensive study in the dog Saaman (1934) concluded that besides an increase in vagal activity to the heart there was also a decrease in cardiac sympathetic excitatory drive since a bradycardia of some 30 beats could be observed during sleep in vagotomized animals (as compared to 84 beats in intact animals) and sympathectomy alone in a further group of dogs produced some reduction in the heart rate decrease to sleeping. It was only combined vagal blockade and sympathectomy that markedly attenuated the heart rate change during sleep. However neither Sutherland nor Saaman were aware in 1929 or 1934 of synchronized and desynchronized sleep so they would not have differentiated between them. The problem was tackled again by Iwamura *et al.* (1968) who observed that the marked swings in heart rate during desynchronized sleep still persisted in vagotomized cats, suggesting that sympathetic activity to the heart was mainly responsible, and that this tonically decreased and phasically increased during desynchronized sleep. The picture was further clarified by a very comprehensive study of Baust & Bohnert (1969). These authors showed that in the cat the tonic fall in heart rate during a shift from wakefulness to synchronized sleep is preponderantly caused by an increase in vagal

Table 1. Mean values of heart rate (HR) in beats per minute (bpm) during quiet waking (QW) synchronized sleep (SS) and desynchronized sleep (DS) for different species of reptiles, birds and mammals

(Lowest values in brackets. In some instances mean value \pm s.e.m. is given)

Species	QW (HR, bpm)	SS (HR, bpm)	DS (HR, bpm)	References
Box turtle (<i>Terrapene carolina</i>)	25.1	19.4	—	Flanigan <i>et al.</i> 1974
Red footed tortoise (<i>Geochelone carbonaria</i>)	27.1	20.4	—	Flanigan, 1974
Tortoise (<i>Testudo denticulata</i>)	20-30	10-20	—	Walker & Berger, 1973
Iguanid lizards (<i>Ctenosaura pectinata</i>)	72	53.0	—	Flanigan, 1973
(Iguana iguana)	69	39.0	—	Flanigan, 1973
Chicken	264	216	216, variable	Klein <i>et al.</i> 1964
Pigeon (<i>Columba livia</i>)	162.8	92.4	100, variable	Van Twyver & Allison, 1972
Echidna (<i>Tachyglossus aculeatus</i>)	56.4	51.0	DS not present	Allison <i>et al.</i> 1972
Armadillo (<i>Dasybus novemcinctus</i>)	144 \pm 4.0	124 \pm 6.2	116 \pm 7.6 variable	Van Twyver & Allison, 1974
Opossum (<i>Didelphis marsupialis</i>)	180 \pm 12.4	155 \pm 12.2	158 + 19 (130), variable	Van Twyver & Allison, 1974
Hedgehog (<i>Erinaceus europeanus</i>)	217 \pm 12.5	224 \pm 5.9	204 \pm 8.6, variable	Toutain & Ruckebusch, 1975
Mole (<i>Scalopus aquaticus</i>)	231	252 \pm 2.2	245 \pm 2.0, variable	Allison & Van Twyver, 1970
Squirrel (<i>Citellus beecheyi</i>)	260	110	Not measured	Strumvasser, 1959
Ground squirrel (<i>Citellus tridecemlineatus</i>)	200-250	50	Not measured	Landau & Dawe, 1958
Rat (SHR) (<i>Okomoto strain</i>)	480	420	360	Iwamura <i>et al.</i> 1979
Rabbit	Not given	210	165 (150), variable	Dufour & Court, 1977
Woodchuck	80-90	60-70	Not measured	Lyman, 1958
Marmot (<i>Marmota flaviventris</i>)	144	96	72	Florant <i>et al.</i> 1978
Fox (<i>Vulpes</i> sp.)	77.2 \pm 0.06	77.7 \pm 1	92 \pm 1.7 (60), variable	Dallaine & Ruckebusch, 1974
Arctic fox	90	55	Not measured	Folk, 1964
Wolverine	155	125	Not measured	Folk, 1964
Wolf	56	40	Not measured	Folk, 1964
Dog	110	74	—	Saaman, 1934
Cat	217 \pm 3	209 \pm 3	200 \pm 2, variable	Orem <i>et al.</i> 1977
Sheep	85	75	55	Ruckebusch, 1972
Goat	100	85	70	Ruckebusch, 1962
Cow	50	48	35	Ruckebusch, 1972
Pig	130	122	120	Ruckebusch, 1972
Horse	41	38	39, variable	Ruckebusch, 1972
Monkey (<i>Macaca mulatta</i>)	—	150	163, variable	Stoyva <i>et al.</i> 1968
Man Infant	200	130	100-150, variable	Junge, 1979
Adult	70	48-50	42-60, variable	Snyder <i>et al.</i> 1964

tone. Further decrease in heart rate during desynchronised sleep is, however, mainly brought about by a reduced cardiac sympathetic activity superimposed on the increased vagal tone. Phasic increases in heart rate during desynchronized sleep were probably caused by reciprocal changes in cardiac sympathetic and vagal activity. There is one report (Guazzi *et al.* 1968) which is at variance with this conclusion in so far as it attributes the heart rate change entirely to alterations in vagal tone in all stages of sleep. No explanation can be offered for this finding but it does seem to me less likely to be the general case since Baust & Bohnert's (1969) results to some extent confirm those of Iwamura *et al.* (1968) and Saaman (1934) and we have recently obtained some similar results on the decerebrate cat which displays desynchronized sleep-like periods (Futuro-Neto, 1981).

(b) *Stroke volume.* There have been few studies in which stroke volume has been determined. However experiments on cat and man indicate that there are no consistent changes in this parameter during sleep (Kumazawa *et al.* 1969; Khatri & Freis, 1967; Mancina *et al.* 1971).

(c) *Cardiac output.* Measurement of cardiac output during the wakefulness sleep cycle has been performed in cats using electromagnetic flow probes placed around the ascending aorta (Mancina *et al.* 1971; Kumazawa *et al.* 1969) and in man using a dye dilution technique (Khatri & Freis, 1967). Both studies showed a reduction in cardiac output during sleep (falling from 483 ml/min during quiet waking to 438 ml/min during desynchronized sleep in cat, and in man decreasing by around 745 ml/min in synchronized sleep from a mean cardiac output of 7639 ml/min. No figures were given for desynchronized sleep. In contrast Bristow *et al.* (1969), also using dye dilution methods (but in only two subjects), could find no evidence of a change in cardiac output during synchronized sleep. They state that this may have been because of more variable data on a limited sample. This would have made their analysis less sensitive than that of Khatri & Freis (1967), although the cardiac output reported in the latter study seems remarkably high.

Regional circulation

(a) *Peripheral resistance.* In the cat Kumazawa *et al.* (1969) and Mancina *et al.* (1971) calculated total peripheral conductance from aortic flow and pressure measurements. They concluded that it was little changed or slightly reduced during synchronized sleep. However, during desynchronized sleep peripheral conductance showed an increase of 9%, indicating there was a decrease in total peripheral resistance and hence vasodilatation in some vascular beds. Similar results for synchronized sleep have been reported in man (Khatri & Freis, 1967).

We can conclude therefore that the fall in blood pressure during synchronized sleep is almost entirely a consequence of a reduction in cardiac output whereas the changes in blood pressure during desynchronized sleep are dependent on changes in total peripheral resistance as well as in cardiac output.

(b) *Cutaneous vascular bed.* In the cat, rabbit, rhesus monkey and man (species for which there are reliable data) the cutaneous circulation, or more precisely ear skin temperature or volume of the hand or digits, shows little change from waking values during synchronized sleep. There is, however, a definite increase in skin temperature

and hand volume, indicating that a vasodilatation occurs during the tonic stage of desynchronized sleep (Watson, 1962; Hayward & Baker, 1969; Parmeggiani *et al.* 1977; Franzini & Cianci, 1979). These changes can be influenced by the prevailing ambient temperature (Parmeggiani *et al.* 1977; Parmeggiani, 1980) and this may be the reason why Hayward & Baker (1969) reported a somewhat different pattern in the rabbit, cat, dog and sheep. Phasic vasoconstriction in the digits may occur in man associated with eye movements during desynchronized sleep (Khatri & Freis, 1967).

(c) *Mesenteric vascular bed.* Mesenteric blood flow, measured with an electromagnetic flow probe placed around the superior mesenteric artery of the cat, shows little change during synchronised sleep. Calculations of conductance during this stage of sleep show a small increase, suggesting a small vasodilatation. On the other hand, during desynchronized sleep mesenteric blood flow increases whilst the blood pressure shows a further fall, indicating a marked increase in conductance (28%) or vasodilatation of this vascular bed (Mancia *et al.* 1971).

(d) *Renal vascular bed.* Kidney blood flow during sleep has been measured in the cat and the dog with electromagnetic flow probes placed around the renal artery. In the cat, Mancia, Baccelli & Zanchetti (1974) found that from quiet wakefulness through synchronized sleep renal blood flow remained constant and systemic arterial blood pressure decreased slightly so that renal conductance was slightly augmented. During desynchronized sleep, renal blood flow continued unchanged despite marked decreases in blood pressure, indicating a marked increase in conductance (20%) had occurred. In the dog a 30% increase in renal blood flow was reported on entry into sleep (Seal & Zbrozna, 1977). These effects are due to two factors: local autoregulation and decreases in sympathetic nerve activity (Mancia *et al.* 1974; see p. 231).

There have been no measurements of renal blood flow in man, but plasma renin activity has been measured throughout the sleep-wake cycle. These changes are of interest since the release of renin can be affected by changes in renal blood flow and renal sympathetic nerve activity. A recent report shows quite clear decreases in plasma renin activity during desynchronized sleep (Mullen *et al.* 1980).

(e) *Muscle vascular bed.* Three studies have examined the changes in the muscle vascular bed during sleep, two on the cat and the other on the dog. In the study of Mancia *et al.* (1971) an electromagnetic flow probe was placed around an iliac artery and conductance was calculated from flow and systemic blood pressure measurements. During synchronized sleep there was little alteration in iliac conductance, but during desynchronized sleep there was a pronounced reduction in conductance (17%) indicating a vasoconstriction. The authors showed that this vasoconstriction occurred in the muscle vascular bed, since it was unaltered by tying a tight ligature around the paw to eliminate the cutaneous circulation. Similar results have been obtained by Seal & Zbrozyna (1977). In another study from a different laboratory Reis, Moorhead & Wooten (1969), using an isotope dilution method (Sapirstein, 1958) obtained basically similar results although they additionally indicated that the vasoconstriction was confined to red muscle (tonic or slow muscle). Such an effect has not been confirmed and it is somewhat suspect because of the insensitivity of the dilution technique employed.

The muscle vascular bed evidently plays an important role in the phasic increases in

blood pressure occurring during the rapid eye movement and muscle twitching stage of desynchronized sleep. During these phasic periods total peripheral conductance decreases and this apparently is largely a consequence of a further vasoconstriction in skeletal muscle (Mancia *et al.* 1971).

(f) *Cerebral vascular bed.* From the point of view of the function of sleep this perhaps is the most important vascular bed we have considered up to now. There have been numerous studies on cerebral blood flow during sleep (see review by Greenberg, 1980) providing data on three species: man, cat and sheep. A variety of techniques have been employed because the brain is a difficult organ from which to obtain precise measurements of flow or conductance particularly in intact unanaesthetized animals. However, the results are more or less in agreement and can best be summarized by referring to the quantitative study of Reivach *et al.* (1968) which used a ^{14}C antipyrine - autoradiographic technique in the cat. Cerebral blood flow increased by 30–70% during synchronized sleep compared to awake state, there also being quite a marked difference between perfusion of different brain regions. During desynchronized sleep there were further large increases in blood flow to most parts of the brain. The largest increases were to brain stem structures (> 175%) including hypothalamus (> 115%) whereas the lowest were to white matter (60%) and cerebral cortex (~ 60–90%). These values are compared to those of the awake state (see also, Brooks & Carol, 1912; Landis, 1925; Mangold *et al.* 1955; Bridges, Clark & Yahr, 1958; Kanzow *et al.* 1962; Birzia & Tachibana, 1964; Baust, 1967; Hulme & Cooper, 1968; Reis *et al.* 1968; Risberg, Gustavsson & Ingmar, 1969; Risberg, Ancrì & Ingvar, 1969; Meyer & Toyoda, 1971; Townsend, Prinz & Obrist, 1973; Mann, Duchin & Weiss, 1974). I shall not attempt to discuss the relevance of these changes to cerebral function except to point out that they take place against the background of a fall in blood pressure.

In summary, therefore, both cardiac changes and peripheral vascular changes take place during natural sleep with clear cut differences between synchronized and desynchronized sleep. During synchronized sleep there is a slight reduction in cardiac output, with little change in total peripheral resistance, resulting in a modest fall in blood pressure despite an increase in blood flow to the brain. During the tonic stage of desynchronized sleep there is a more pronounced reduction in cardiac output. This is now associated with a clear cut decrease in total peripheral resistance (hence blood pressure falls) but, even so, cerebral blood flow shows a further increase. During this latter stage a striking pattern of changes occur in the peripheral vascular beds, skin, mesenteric and renal vascular beds vasodilate whereas the skeletal muscle vascular bed vasoconstricts. These effects are dependent on an intact vagal and sympathetic innervation of the heart and blood vessels (Baccelli *et al.* 1969; Baust & Bohnert, 1969). The changes during the phasic periods of desynchronized sleep have been less clearly described but would certainly be worthy of investigation.

Sympathetic nerve activity

Sympathetic tone measured directly in the renal nerves of the cat during synchronized sleep does not differ significantly from that during quiet wakefulness, but it shows a marked tonic decrease during desynchronized sleep (Baust, Weldinger &

Kirchner, 1968). The changes in renal vascular conductance during sleep may thus be partly a consequence of a change in sympathetic nerve activity. The question of whether the changes in conductance described in other vascular beds (Mancia *et al.* 1971; Reis *et al.* 1968) are similarly dependent on changes in sympathetic nerve activity supplying the beds was examined in recent experiments in my laboratory. Because of the difficulty in recording from sympathetic nerves, other than renal ones, in the unanaesthetized unrestrained animal the experiments were performed on unanaesthetized cats which had been decerebrated at the intercollicular level. These preparations spontaneously display cyclic periods of decreased extensor rigidity, rapid eye movements, pontogeniculo-occipital waves and cardiovascular changes. These are probably caused by the same central nervous structures responsible for desynchronized sleep in the intact animal (Jouvet, 1967). These changes are accompanied by decreases in renal sympathetic nerve activity and are more pronounced after cutting the carotid sinus and aortic nerves (Iwamura *et al.* 1969). Similar changes can be induced by intravenous administration of the anticholinesterase drug, physostigmine sulphate (Matsuzaki, Okada & Shuto, 1963). In such preparations, we found that desynchronized sleep-like periods were accompanied by inhibition of activity in cardiac sympathetic nerves (23%), renal sympathetic nerves (42%), splanchnic sympathetic nerve (23%), and lumbar sympathetic nerves (26%) but, simultaneously, by a facilitation of activity in vasoconstrictor fibres to skeletal muscle (24%), (Coote & Futuro-Neto, 1980; Futuro-Neto & Coote, 1982*a*). There is therefore direct evidence for a differential pattern of sympathetic activity to heart and blood vessels during natural sleep. Contrary to the indication gained from the indirect experiments of Baccelli *et al.* (1978) the differential pattern of sympathetic activity is present in the sino-aortic denervated cat (albeit decerebrate). This is not dependent on a reflex from skeletal muscle since it occurs in the paralysed preparation. It is, however, dependent on pathways in the central nervous system, since it can be markedly attenuated by small lesions restricted to the dorsolateral part of the lateral funiculus of the cervical spinal cord. In subsequent experiments the possibility was examined whether particular neurones in the brainstem are responsible for elaborating the differential pattern of sympathetic activity similar to that observed during sleep. Following exploration with stimulating electrodes of numerous sites throughout the brainstem a discrete region corresponding to the caudal part of nucleus raphe obscurus was discovered from which a desynchronized sleep-like pattern of sympathetic activity could be obtained (Coote & Futuro-Neto, 1981; Futuro-Neto & Coote, 1982*b*).

The implications of these findings are twofold. First, there is now no need to speculate on some peculiar and, to my mind, highly unlikely interaction of sino-aortic and muscle reflexes to explain a differential repatterning of sympathetic activity (see Baccelli *et al.* 1974, 1978 and later section). Secondly, it leads to the conclusion that the pattern of vascular change during sleep (so well documented by Mancia *et al.* 1971) is the result of the activity of a central nervous sympathetic pattern generator activated during desynchronized sleep. Further experiments are needed to establish this point. However, it seems that the presence in the brain of a region able to elaborate a significant pattern of sympathetic discharge, and hence cardiovascular

changes similar to those observed during sleep, argues that these changes may have a unique significance to the functions of sleep.

Phasic increases in sympathetic activity also occur during desynchronized sleep (Baust *et al.* 1968). These increases can be observed in cardiac, renal, splanchnic, lumbar sympathetic nerves as well as in muscle vasoconstrictor fibres in desynchronized sleep-like periods in the decerebrate cat (Futuro-Neto, 1981). These phasic changes occurring during desynchronized sleep give the superficial appearance of arousal. Yet the pattern of sympathetic activity is unlike that occurring in arousal responses of the awake animal, in which inhibition of vasoconstrictor activity to muscle is thought to play a part (Coote, Hilton & Zbrozyna, 1973).

Reflex regulation of circulation

In an early study Saaman (1934) showed in the dog that a bradycardia associated with sleep was much increased following sino-aortic denervation. Since that time there has been only one series of experiments that have comprehensively examined the role of sino-aortic reflexes during sleep (Guazzi & Zanchetti, 1965; Kumazawa *et al.* 1969; Baccelli *et al.* 1978). These studies showed that in cats in which the carotid sinus and aortic nerves were cut, blood pressure values during wakefulness (mean 97 mmHg) were only slightly above those before nerve section (mean 84 mmHg). During synchronized sleep there was a fall in blood pressure of 17 mmHg which was now greater than that before denervation (9 mmHg). During desynchronized sleep the blood pressure fall was profoundly increased after sino-aortic denervation, the change before being 16 mmHg and after nerve section being 35 mmHg.

Guazzi *et al.* (1968) provided evidence, by selectively denervating the carotid chemoreceptors, that these receptors are important in cats in preventing too great a fall in blood pressure and heart rate during sleep. Such procedures in aortic denervated animals produced the same enhancement of the fall in heart rate and blood pressure normally seen following sino-aortic denervation and associated with desynchronized sleep. Selective denervation of the carotid baroreceptors in otherwise similar experiments was without effect.

This finding is an important one, but hardly surprising, since it is obvious that the simple removal of a tonic inhibitory influence on cardiovascular neurones, that are already powerfully inhibited by a central pattern generator (Coote & Futuro-Neto, 1981; Futuro-Neto & Coote, 1982*b*) during desynchronized sleep, cannot explain a fall in blood pressure to lower levels than the ones observed before deafferentation.

The blood pressure changes during sleep have been studied after sino-aortic denervation in the rat (Junquiera & Krieger, 1976). The rat is unusual in that blood pressure shows a small tonic increase during desynchronized sleep (Junquiera & Krieger, 1976; Iwamura *et al.* 1979). However, following sino-aortic denervation blood pressure falls dramatically during this sleep stage.

The baroreceptor reflex. The marked tonic inhibition of cardiac and vasomotor sympathetic activity (with the exception of that to skeletal muscle) during desynchronized sleep-like periods, could result from changes in the inhibitory effect of the arterial baroreceptors. This has been shown for the cat and man. Baccelli *et al.* (1976) demonstrated that the pressor effect of bilateral carotid occlusion (mainly a

consequence of withdrawal of baroreceptor activity) causes smaller rises in blood pressure during desynchronized sleep than during waking. Seemingly at variance with this was the finding in man that baroreflex control of heart rate was more sensitive during sleep than in waking (Smyth *et al.* 1969; Bristow *et al.* 1969). These two contrasting sets of results on cat and man are reconcilable. If we assume that the central sympathetic pattern generator in the lower brainstem, demonstrated by Coote & Futuro-Neto (1981) and Futuro-Neto & Coote (1982*b*), is active during natural desynchronized sleep (and this needs experimental proof), then in the cat experiments of Baccelli *et al.* (1976) the increased central excitatory drive resulting from the removal of carotid baroreceptor activity will be acting on cardiovascular neurones, if these are already tonically inhibited then the reflex pressor effect during desynchronized sleep is bound to be less than during waking. On the other hand in the experiments on man (where the baroreceptors are activated by drug induced rises in blood pressure) the resultant increase in reflex tonic inhibition of cardiovascular neurones, or excitation of vagal cardio inhibitory neurones, would sum with similar, centrally-produced, effects of the sleep-pattern generator. Hence during desynchronized sleep larger effects than during waking could be produced by a similar input. On this basis there is no need to postulate a central inhibition of the baroreceptor reflex (Mancia & Zanchetti, 1980), a mechanism which does not accommodate all of the experimental data or account for a central facilitation of the baroreceptor reflex (Bristow *et al.* 1969).

A summary of the cardiovascular events during sleep and their functional significance

On passing from the waking state to sleep there is a fall in blood pressure and heart rate which has been observed in virtually all species of mammals, birds and reptiles so far studied. There are further falls in heart rate and blood pressure on passing into the tonic stage of desynchronized sleep. Underlying these changes is a unique pattern of blood flow to different vascular beds. The conductance of the vascular bed in brain, skin, kidney and splanchnic region increase whilst that of the vascular bed in skeletal muscle decreases. The pattern is dependent on sympathetic nerves and is generated by the central nervous system probably from a discrete region in the lower brainstem. It appears that the events observed are directed to increasing blood flow to the brain but with minimum energy cost. To this end there is a movement of blood away from the muscles and heart rate decreases. The peripheral chemoreceptors are active during desynchronized sleep and may be considered to protect the brain blood flow since they prevent blood pressure decreasing by too great an extent.

Respiratory changes during sleep

Ventilation during sleep has been documented in a large number of species, at least in purely descriptive terms (Table 2). The most common variable measured has been respiratory rate, no doubt because of its ease of registration in field studies. Therefore, although it is lacking as an indicator of the full extent of the changes in ventilation, it serves as a useful response for comparison across a wide range of species and with animals on which more extensive studies have been conducted.

(a) *Synchronised sleep.* In all animals, respiratory rate decreases on entry into synchronized sleep from quiet waking, becoming very regular but with definite

Table 2. Mean values of respiratory frequency (Resp) in breaths per minute (bpm) during quiet waking (QW), synchronized sleep (SS) and desynchronized sleep (DS) for different species of reptiles, birds and mammals

(In some instances, mean value \pm S.E.M. is given)

Species	QW Resp. bpm.	SS Resp. bpm.	DS Resp. bpm.	References
Box turtle (<i>Terrapene carolina</i>)	1.2	1.0	apnoea up to 14 mins. no DS	Flanigan <i>et al.</i> 1974
Red footed tortoise (<i>Geochelone carbonaria</i>)	8-13	5.2	apnoea up to 5 mins. no DS	Flanigan, 1974
Crocodile (<i>Caiman sclerops</i>)	3.5	0.2-0.4	shallow apnoea up to 3 mins. no DS.	Flanigan <i>et al.</i> 1973
Pigeon (<i>Columba livia</i>)	28.4	15.8	21.8, irregular	van Twyver & Allison, 1972
Echidna (<i>Tachyglossus aculeatus</i>)	11.6	7.8	6.4	Allison & van Twyver, 1972
Armadillo (<i>Dasyurus novemcinctus</i>)	58 \pm 8.9	51 \pm 5.3	48 \pm 8.4	van Twyver & Allison, 1974
Opossum (<i>Didelphis marsupialis</i>)	38 \pm 8.8	21.8 \pm 2.3	21.5 \pm 3.8, irregular	van Twyver & Allison, 1970
Hedgehog (<i>Erinaceus europaeus</i>)	55.5 \pm 12.8	36 \pm 2.3	27 \pm 2.7, irregular	Toutain & Ruckebusch, 1975
Mole (<i>Scalopus aquaticus</i>)	102	71 \pm 0.7	77.3 \pm 1.7, shallow irregular	Allison & van Twyver, 1970
Squirrel (<i>Citellus tridecemlineatus</i>)	100-125	30	No figures	Landau & Dawe, 1978
Fox	25.8 \pm 0.7	19.8 \pm 0.4	21 \pm 0.5, irregular	Dallaire & Ruckebusch, 0000
Dog	20	11	Fast irregular	Phillipson <i>et al.</i> 1978
Cat	37.5 \pm 1.5	25.5 \pm 0.4	41.8 \pm 1.9, irregular	Orem <i>et al.</i> 1977
Sheep	37	35	33	Ruckebusch, 1972
Cow	14	12	5	Ruckebusch, 1972
Pig	32	25	25	Ruckebusch, 1972
Horse	12.5 \pm 2.8	9.8 \pm 1.7	10 \pm 2.6, irregular	Ruckebusch <i>et al.</i> 1970
Monkey (<i>Macaca mulatta</i>)	36-38	28-36	40-48, irregular	David <i>et al.</i> 1972
Man	16	14-18	10-24, irregular	Snyder <i>et al.</i> 1964

expiratory pauses appearing. In man, cat and dog where more extensive respiratory measurements have been made there is in addition a small increase in tidal volume but even so the decrease in frequency is sufficiently large to decrease minute ventilation (Bulow & Ingvar, 1961; Bülow, 1963; Orem, Netick & Dement, 1977; Phillipson, 1978a; Lugaesi *et al.* 1978). It seems reasonable to assume that this is occurring in all the species listed in Table 2. Accompanying the decreases in frequency there is also a reduction in oxygen uptake and in carbon dioxide production amounting to 10-20%, so indicating a decrease in metabolic rate during synchronized sleep (Magnusson, 1944; Robin *et al.* 1958; Bülow, 1963; Brebbi & Altshuler, 1965; Phillipson, Murphy & Kozar, 1976).

Periodic fluctuations in the depth of breathing superimposed on the decreased rate

have been described in the dog, man and in the new-born infant (Magnusson, 1944; Bülow & Ingvar, 1961; Bülow, 1963; Phillipson *et al.* 1978*a*). These changes occur during the early stages of synchronized sleep. They consist of successive reductions in the tidal volume with each inspiration and end in an expiratory apnoea which is terminated by a large inspiration and the cycle repeats itself. Thus it is rather similar to the classical Cheyne-Stokes pattern of respiration.

Alveolar ventilation decreases during synchronized sleep, by between 15–30%. This is indicated by the increased alveolar partial pressure of CO₂ (PACO₂), of 1.3 to 3.8 mmHg, in man, cat and dog (Bülow & Ingvar, 1961; Bülow, 1963; O'Flaherty, 1967; Phillipson *et al.* 1976), and by the finding that arterial partial pressure of CO₂ (PaCO₂) in man (Birchfield, Sieker & Heyman, 1958, 1959) and dog (Guazzi & Freis, 1969) is increased by 4.1 to 6.5 mmHg. Coincident with these changes during synchronized sleep, are small decreases in PaO₂ and PaO₃, ranging from 3.5 to 9.4 mmHg (Robin *et al.* 1958; Guazzi & Freis, 1969), and small decreases in arterial pH (Birchfield *et al.* 1958; Robin *et al.* 1958; Guazzi & Freis, 1969).

(*b*) *Desynchronized sleep.* Breathing during desynchronized sleep is characteristically more rapid than during synchronized sleep and is often highly irregular in all animal species so far studied (Table 2). Periods of hyperventilation are interspersed with periods of more regular respiration and apnoeas of varying length. The degree to which these changes occur obviously varies from one animal species to another. At one extreme there is the cow which reduces its respiratory rate to less than half that during synchronized sleep (Ruckebusch, 1972). Unfortunately, no other data are available which allow us to determine what happens to minute ventilation in this animal. In man, dog and cat minute ventilation increases to approach that during the awake state (Bülow, 1963; Bolton & Herman, 1974; Hathorn, 1974; Purcell, 1976; Fagenholtz, Connel & Shannon, 1976; Finer, Abroms & Taeusch, 1976; Phillipson *et al.* 1976; Orem, Netick & Dement, 1977). There is some evidence suggesting that the hyperventilation is related to the degree of muscular activity and eye movements during the phasic periods of desynchronized sleep (Wurz & O'Flaherty, 1967; Guazzi & Freis, 1969; Phillipson, 1978*a, b*; Orem, 1980).

Arterial gas measurements have shown that PaCO₂ decreases to approach awake values, whereas PaO₂ is unchanged or slightly increased over the course of a desynchronized sleep cycle (Bülow, 1963; Snyder *et al.* 1964; Snyder, 1967; Guazzi & Freis, 1969; Phillipson, 1978*a, b*).

Respiratory control during sleep

The increased PaCO₂ found during synchronized sleep together with the decrease in ventilation suggests that the sensitivity of the respiratory control system has changed. This has been directly demonstrated. In studies on sleeping man Bülow (1963) plotted the ventilatory response to various PACO₂. He found that the slope of the relationship decreased progressively from 1.25 l min⁻¹ m⁻² mmHg⁻¹, in waking, to 0.5 l min⁻¹ m⁻² mmHg⁻¹ in later stages of synchronized sleep. This confirmed earlier studies under steady-state conditions, in which subjects breathed CO₂ in air while awake and asleep (Magnusson, 1944; Ostergaard, 1944). We can conclude that the response of ventilation to changes in CO₂ is moderately reduced during synchronized sleep compared to waking (Phillipson *et al.* 1977).

There have been few studies of the ventilatory responsiveness to changes in CO_2 in desynchronized sleep. This is possibly because of the difficulty of studying responses during the irregular pattern of breathing. However, in the dog, Phillipson *et al.* (1977), using a re-breathing method, have shown that there is a marked decrease in the response of ventilation, tidal volume and respiratory frequency to changes in CO_2 in desynchronized sleep compared to synchronized sleep. In addition, the highly irregular pattern of breathing persisted during hypercapnia, suggesting that the respiratory control system was little influenced by the CO_2 stimulus. In fact, the irregular respiratory pattern during desynchronized sleep is remarkably insensitive to changes in any afferent input: it is unchanged by metabolic alkalosis (Sullivan *et al.* 1978), hypoxia (Phillipson *et al.* 1978), hyperoxia (Sullivan *et al.* 1978), lung inflation (Phillipson *et al.* 1976), vagal blockade (Phillipson *et al.* 1976; Remmers, Bartlett & Putnam, 1976; Sullivan *et al.* 1978), and denervation of the carotid and aortic chemoreceptors (Sullivan *et al.* 1978).

Despite these characteristics of the irregular pattern of respiration during desynchronized sleep there is still a relatively normal response of ventilation to hypoxia. Thus, the increase in minute ventilation is similar to those in the awake and the synchronized sleep states (Reed & Kellogg, 1960; Bolton & Herman, 1974; Fagenholz *et al.* 1976; Phillipson *et al.* 1978). An interesting observation was made by Phillipson *et al.* (1978). In their study on the dog they showed that, unlike ventilation, the arousal threshold of the animals to hypoxia was greatly elevated during desynchronized sleep. This is in keeping with elevated arousal thresholds to other stimuli such as increases on PACO_2 , activity in somatic afferent fibres and auditory stimuli (Dement, 1958; Benoit & Bloch, 1960; Jouvet, 1965; Iwamura *et al.* 1969; Baust, Bohmke & Blossfeld, 1971 *a, b*; Phillipson *et al.* 1977), during this sleep stage. The threshold of respiratory and autonomic responses to the latter series of stimuli is also raised. Therefore, the sino-aortic chemoreceptors are more or less unique during sleep, in that they continue to provide an important excitatory drive to both respiratory and cardiovascular neurones in the central nervous system.

Respiratory reflexes. The threshold of pulmonary inflation and deflation reflexes in opossum, dog and human infant is increased considerably during desynchronized sleep (Farber & Marlow, 1976; Phillipson *et al.* 1976; Finer *et al.* 1976).

Respiratory muscles. Studies in adult humans (Duron, Tassinari & Gastaut, 1966; Duron, 1972; Tusiewicz *et al.* 1977), in sheep (Henderson-Smart & Reed, 1976) and in cat (Parmeggiani & Sabbatini, 1972; Duron & Marlot, 1980) have demonstrated that during desynchronized sleep there is a reduction in both tonic (postural) and phasic (inspiratory related) electromyogram activity of the intercostal muscles. According to Duron & Marlot (1980) there is a complete inhibition of the intercostal postural muscle tone throughout a desynchronized sleep period. They point out, as have others (see Phillipson, 1978), that such an effect will modify chest wall compliance, and hence functional residual capacity, to reduce the effective tidal volume.

Integrative mechanisms during sleep

Evidence suggests that during sleep breathing is controlled by two quite separate systems: an automatic, or metabolic system, dependent on afferent input, and a brain-

by Mitchell & Berger, 1975). The automatic respiratory system controls the pattern of breathing during synchronized sleep (Phillipson, 1978; Sullivan, 1980). In this stage studies on dogs have shown that removal of the major respiratory afferent stimuli produces marked slowing of respiration and an apnoea, but had little effect during the waking state (Phillipson *et al.* 1970; Phillipson *et al.* 1976; Phillipson, 1977; Sullivan *et al.* 1978). The latter finding also shows that waking (arousal) stimulates respiration. This was previously nicely demonstrated by Fink (1961) in a normal human subject. Following a period of alveolar hyperventilation (i.e. removal of the CO₂ respiratory drive), rhythmic breathing only continued if the subject remained awake, but apnoea developed during synchronized sleep. Other evidence which supports this concept of wakefulness drive to breathing comes from reports of human patients with defective chemoreceptors or damaged ventrolateral spinal tracts who fail to breathe only during sleep ('Ondine's curse'; Mellins *et al.* 1970; Krieger & Rosomoff, 1974*a, b*; Shannon, *et al.* 1976). In this connexion recent studies by Hilton and collaborators are interesting, in that they show that regions of the ventral medulla, previously thought of as central chemoreceptor areas (Loeschke, 1974; Schlafke, 1981), may be involved in arousal and defence behaviour in the cat (Guertzenstein *et al.* 1978).

In summary, current thinking is that the automatic respiratory control system determines the normal breathing pattern during synchronized sleep as well as during waking (Phillipson, 1978; Sullivan, 1980).

During desynchronized sleep breathing behaves as though it is virtually independent of an automatic control system, apart from the peripheral arterial chemoreceptors. Some evidence for this has already been reviewed, but it is further supported by the report of Shannon *et al.* (1976) on two human infants with demonstrable defects of central chemoreceptors. These hypoventilated in synchronized sleep, but not in wakefulness and resumed breathing at adequate levels during desynchronized sleep. Presumably in the latter stage the peripheral arterial chemoreceptors were interacting centrally with a respiratory pattern generator which differs from that operating during synchronized sleep. Sullivan (1980) suggested that this generator could be the 'behavioural' system of respiratory neurones (Mitchell & Berger, 1975) through which cortical influences operate in the awake state. The responsible respiratory neurones must be located in the *pons* and *medulla* and the irregular respiratory rhythm must be generated at this level of the central nervous system. The rhythm is virtually independent of afferent input since it can be observed in decerebrate and sino-aortic denervated cats during spontaneous desynchronized sleep-like periods (Jouvet, 1967; Futuro-Neto, 1981).

Recent studies, in which recordings from respiratory neurones in the brainstem have been carried out (in unanaesthetized cats during wakefulness and different stages of sleep), are beginning to provide direct evidence for some of the above suggestions. A majority of the respiratory neurones (located in the medullary 'centres' and in the *pontine* pneumotaxic region) declined in activity during desynchronized sleep (Lydic & Orem, 1979). Respiratory neurones were also located in the medulla whose activity was related to the tonic and phasic components of desynchronized sleep (Orem, 1980).

Significance of the changes in breathing to the functions of sleep

Having surveyed the data on changes in respiration during sleep and commented on the mechanisms that are involved it is now appropriate to return to the question of the functional significance of these changes to the state of sleep. It was my primary purpose to demonstrate that the responses are not simply epiphenomena of sleep but are goal-directed, at least in part. On this theme some simple statements can be made about ventilation during sleep. First, ventilation is adequate to provide oxygen requirements of the body tissues during all stages of sleep, since PaO_2 is little changed, at least not sufficiently to alter significantly the saturation of haemoglobin. This occurs despite the marked changes in breathing pattern, changes that are remarkably similar across a wide range of animal species. Secondly, during the earlier stages of sleep (synchronized sleep) there is a lowering of ventilation (so reducing energy cost), yet PaCO_2 increases. Thus at a time when the blood pressure is reduced the blood vessels of the brain will be dilated by the increased PaCO_2 (Kety & Schmidt, 1948) so ensuring that cerebral blood flow increases. Thirdly, during desynchronized sleep it is apparently important for the brain to isolate itself from most afferent input or to prevent response to afferent input. This being the case respiratory control switches away from the automatic-metabolic mechanism towards a perhaps more primitive behavioural one that can operate in isolation. Therefore the irregular respiratory pattern of desynchronized sleep, which still provides an adequate ventilation, is the price that is paid to ensure that the functions of sleep are fulfilled.

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