Brain (1991), **114**, 1281–1295

SYMPATHETIC MUSCLE NERVE ACTIVITY DURING SLEEP IN MAN

by MAGDOLNA HORNYAK, MICHAEL CEJNAR,[1] MIKAEL ELAM, MILOS MATOUSEK *and* B. GUNNAR WALLIN

(*From the Department of Clinical Neurophysiology, Sahlgrenska Sjukhuset, Gothenburg, Sweden*)

SUMMARY

Muscle sympathetic activity (MSA) was recorded in the peroneal nerve during sleep in 14 sleep-deprived healthy subjects. Continuous noninvasive recordings of finger blood pressure were obtained in 7 subjects. In light sleep (stage 2 sleep) the number of sympathetic bursts/min decreased to 90 ± 8% (mean ± SEM) and total MSA (= burst/min × mean burst area) to 89 ± 5% of the awake value ($P < 0.05$, n = 14). In deep sleep (stage 3–4) total MSA decreased further, to 71 ± 8% of the awake value (n = 5). There was no close correlation between variations of depth of sleep and variations of sympathetic activity but during continuously deepening sleep MSA decreased progressively with time. In stage 2 sleep, high amplitude K complexes were accompanied by short-lasting increases of sympathetic activity. Since these increases of MSA were not preceded by decreases of diastolic blood pressure, which is known to evoke increased sympathetic nerve traffic in muscle nerves, we suggest that K complex related increases of MSA are signs of arousal which elicit both cortical EEG phenomena and activation of cerebral sympathetic centres. During desynchronized (REM) sleep, total MSA increased to 124 ± 12% of the value in awake state (n = 5). The increases occurred mainly in short irregular periods, often related to rapid eye movements and there was an inverse relationship between the duration of the desynchronized sleep and the increase of total MSA. Our findings are similar to the data obtained in animal experiments and may partly explain changes of blood pressure during synchronized and desynchronized sleep reported previously in man.

INTRODUCTION

Sleep is accompanied by changes of cardiovascular functions. During synchronized (non-REM) sleep, blood pressure, cardiac output, total peripheral resistance and heart rate have been found to decrease in many species (for references *see* Mancia and Zanchetti, 1980; Coote, 1982). During desynchronized sleep a further (tonic) fall of blood pressure was reported in the majority of investigated species (although a slight increase was found in the rat) but often interrupted by irregular short-lasting (phasic) blood pressure increases. In mammals, heart rate also became variable during desynchronized sleep with bradycardia interrupted by considerable tachycardic swings (*see*, e.g., Gassel *et al.*, 1964; Guazzi and Zanchetti, 1965; Mancia *et al.*, 1971). In man, heart rate and blood pressure increased slightly during desynchronized (REM) sleep (Khatri and Freis, 1967) and displayed large variations (Snyder *et al.*, 1964; Coccagna *et al.*, 1971).

Several attempts have been made to clarify the mechanisms underlying cardiovascular changes during sleep. Since variations of blood pressure are influenced by sympathetic nerves supplying resistance vessels, sympathetic activity to different vascular beds has

Correspondence to: Dr M. Hornyak, Neurologische Klinik und Poliklinik der Universität, Hansastrasse 9, D-7800 Freiburg, Germany.

[1] Present address: Royal North Shore Hospital, St Leonards, Australia.

been recorded in animals. During synchronized sleep, renal sympathetic nerve traffic decreased in the cat (Baust *et al.*, 1968). In desynchronized (REM) sleep, mean activity decreased in renal and splanchnic sympathetic fibres but increased in muscle sympathetic fibres. During this sleep stage the variability of sympathetic activity in all nerves was much higher because of short-lasting marked increases of sympathetic traffic (Coote and Futuro Neto, 1981; Coote, 1982).

In man, sympathetic activity has not been recorded during sleep. In the awake state the microneurographic technique has been used extensively for measurements of sympathetic outflow to skeletal muscles. Such recordings have shown that muscle sympathetic activity (MSA) is involved in blood pressure homeostasis. The sympathetic muscle nerve traffic is composed of bursts of vasoconstrictor impulses synchronous with the heart beat (Delius *et al.*, 1972; Wallin and Fagius, 1988). The bursts occur predominantly during transient reductions of blood pressure and are normally not influenced by arousal or short-lasting emotional stimuli.

The present study deals with human MSA during spontaneous sleep. The aim was to investigate whether the cardiovascular changes mentioned above have a counterpart in sympathetic outflow to muscles. To this end we recorded MSA (and in some experiments arterial blood pressure) during different sleep stages in healthy volunteers.

METHODS

Experiments were performed on 21 healthy subjects, 4 males and 17 females aged 23–53 (mean 34) yrs who had not slept for more than 2–3 h during the night before the experiment. The study was approved by the local Ethics Committee and the subjects gave their informed consent. Experiments in which subjects only reached stage 1 sleep (4 cases) or just a few minutes of stage 2 sleep (3 cases) were excluded from the analysis. The 14 experiments included in the analysis were conducted mostly in the afternoon (11 subjects), in 2 cases in the morning and in 1 case in the evening.

The following parameters were recorded: 13 bipolar EEG derivations from the frontotemporal, temporocentral, temporotemporal, temporo-occipital, centroparietal, parieto-occipital and the Fz-Cz regions; a submental electromyogram (EMG); an electro-oculogram (EOG) by electrodes at the outer canthi; electrocardiogram (ECG) by precordial surface electrodes; respiratory movements by a strain gauge attached around the chest with a rubber strap; muscle sympathetic nerve activity (*see below*) and blood pressure (*see below*). Analogue signals of all parameters were stored on a 16-channel tape-recorder (V-Store, Racal, Southampton, UK) and, in addition, all signals were displayed on a 21-channel ink jet recorder (Siemens-Elema, Solna, Sweden) mostly with a paper speed of 15 $mm \cdot s^{-1}$.

Recording of sympathetic nerve activity

Intraneural recordings of multiunit sympathetic activity were made in the peroneal nerve at the fibular head with tungsten microelectrodes having uninsulated tips of a few μm. The signals were amplified with a total gain of 50 000 and passed through a bandpass filter (bandwidth 0.7–2 kHz) and an amplitude discriminator to improve the signal-to-noise ratio. An RC-integrating network (time constant 0.1 s) was used to obtain a mean voltage neurogram. Muscle nerve sympathetic activity (MSA) was identified according to the following criteria: (1) weak electrical stimulation through the recording electrode evoked muscle twitches without concomitant skin paraesthesiae; (2) tapping on the muscle belly or passive stretching of the muscle gave rise to afferent mechanoreceptive activity; and (3) light skin touches did not evoke afferent activity. Evidence that MSA is composed of sympathetic vasoconstrictor impulses and details of the recording technique have been described previously (Delius *et al.*, 1972; Sundlöf and Wallin, 1977).

Measurement of blood pressure

Blood pressure was measured continuously on a finger by a device based on the volume-clamp principle (Yamakoshi *et al.*, 1988). The instrument clamps the volume of the finger, measured by infrared

plethysmography, at a value where arteries experience zero transmural pressure. This is done by a servoloop-controlled hydraulic finger constriction cuff which, as a consequence, develops a pressure which closely follows the intra-arterial pressure and which may be used as a continuous indirect measure of blood pressure (Cejnar *et al.*, 1988). Unfortunately, a periodic cuff readjustment procedure (every 100–500 heart beats) necessary for accurate blood pressure measurement tended to arouse the subjects and therefore blood pressure was measured only in the first 7 experiments (*see* Table).

Experimental procedure

Subjects were lying in a comfortable supine position at a room temperature of 22–25° C. After placing the EEG, EMG, EOG and ECG electrodes and the strain gauge around the chest, the recording electrode was inserted in the peroneal nerve. When a suitable recording site was found, resting awake MSA was recorded for 10 min and then subjects were encouraged to go to sleep. If the nerve recording site deteriorated within the first 45–60 min, small adjustments were made and after a 5 min awake period subjects were allowed to go to sleep again. Experiments were terminated after 90–120 min of sleep or when the recording site was lost.

In 2 experiments the intraneural position of the recording electrode changed during sleep due to leg movements; in both cases REM sleep occurred after the change. In these 2 experiments only the recording after the change of the position of the electrode was analysed, the awake or stage 1 periods following the movements were taken as 'awake' values. In 2 other experiments limb movements made the nerve recording unreliable during the second part of the experiments; in these cases we included only the initial part of the experiment (before movement artefacts) in the analysis.

Analysis

Sleep stages were scored by 2 investigators throughout the whole record in 1 min epochs according to the criteria of Rechtschaffen and Kales (1968). Spectral EEG analysis was made with a computer-aided method using the parieto-occipital EEG derivations (Matousek and Petersén, 1983). For statistical analysis the relative power (in %) within the frequency bands of 1.5–7.5 Hz (delta and theta waves) and 7.5–12.5 Hz (alpha waves) were calculated.

Muscle sympathetic activity was analysed using a computer program (M. Cejnar, F. Goethe, M. Hornyak, B. G. Wallin, unpublished). The program emulates the manual analysis by detecting each MSA burst in the mean voltage neurogram and calculating its area. In this procedure mean voltage neurogram, ECG and time code were digitized off-line at 200 Hz using a DataTranslation (DT-2851) analogue-to-digital interface card. A sympathetic burst was identified on the basis of a monotonic rise and fall with a local maximum occurring in a smoothed MSA signal within 1000–1800 ms from the preceding R wave in the ECG signal. Most of the parameters defining a burst could be changed manually, for example, the tolerance limits of the skewness of the rising or falling parts, the latency of the peak of the burst from the R wave and the minimum height of bursts, respectively. Artefacts were rejected on the basis of having short rise time and/or duration (less than 0.17 s). The area of a burst was calculated on a relative baseline (mean value of background activity between bursts). The digitized mean voltage neurogram and the identified bursts were displayed together on an ink jet recorder via two digital-to-analogue converters and if the automatically detected bursts did not agree with the visually defined ones, parameters were changed and the automatic burst detection was restarted. Artefacts falsely identified as bursts occurred seldomly and were eliminated by manual editing of the burst record. Values of nerve activity, R-R interval, sympathetic reflex latency and systolic, mean and diastolic blood pressures were evaluated for each heart period and stored. Sympathetic reflex latency for the inhibitory baroreflex was measured from the R wave of the ECG to the peak of the corresponding burst in the mean voltage neurogram, the peak being taken as the start of inhibition induced by the systolic pressure wave (for details, *see* Fagius and Wallin, 1980). Finally, for each minute the computer calculated the number of sympathetic bursts, total MSA (number of bursts × mean burst area) and mean values of sympathetic reflex latency, R-R interval, systolic, diastolic and mean blood pressure.

In stage 2 sleep, additional analysis of MSA was made when a K complex in the EEG recording occurred. A K complex was selected for analysis if it lasted more than 0.5 s, was extensively distributed, started with a well defined, high-amplitude (more than 10 μV) sharp-wave and was not followed by another K complex within 4–6 s (*see also* fig. 4). In all subjects MSA was compared between two 4 s periods, one immediately preceding and one immediately following the peak of the first sharp-wave of a K complex.

Furthermore, in 6 subjects in whom blood pressure was recorded in stage 2 sleep MSA, cardiac interval, and diastolic blood pressure were analysed for each cardiac cycle starting 4 cardiac cycles before and ending 8 cycles after the peak of the first sharp-wave of the K complex.

Statistical analysis

For statistical comparisons of MSA between different sleep stages, 5 min sections of stage 2 sleep, regardless of the numbers of K complexes occurring in these sections, and stage 3–4 were analysed (in the stable phase of the first occurrence of the sleep stage). The results were compared with 5 min periods of the awake state usually taken from the awake period before sleep (in 2 cases following sleep, and in another 2 cases after an arousal causing limb movements and change of the recording site) even if in some cases the EEG record already showed signs of drowsiness (stage 1). This was justified by the finding that MSA values in the awake stage and in stage 1 did not differ (*see* Results).

For statistical analysis Wilcoxon's pair-matched sign-ranked test was used. Statistical tests were performed with the SPSS-PC+ statistical package (Version 2.0; SPSS Inc., USA). Results are expressed as mean ± SEM. P values less than 0.05 were considered as significant.

RESULTS

In general, there was good agreement between the visual scoring of sleep stages and the results of the spectral analysis of the EEG (fig. 2B). The normal temporal pattern of MSA did not change during sleep (fig. 1). Thus in all sleep stages there were still irregular sequences of sympathetic bursts which occurred predominantly during temporary blood pressure reductions (*cf* Delius *et al.*, 1972). The baroreflex latencies also remained constant (awake: 1.37 s, sleep stage 2: 1.37 s, sleep stage 3–4: 1.35 s and desynchronized (REM) sleep: 1.35 s). The EEG analysis showed that already during the initial 'awake' period some subjects reached sleep stage 1 (drowsiness). When true awake periods were compared with periods of drowsiness the strength of sympathetic activity did not differ significantly (total MSA during drowsiness was 97 ± 18% of the awake value, $P = 0.46$, $n = 6$). Therefore, MSA values from the awake period were accepted even if they also contained data from stage 1.

Synchronized (non-REM) sleep

Fourteen subjects reached stage 2 sleep (light sleep) and 5 subjects stage 3–4 (deep sleep, *see* Table). With increasing depth of sleep MSA decreased successively and in stage 2 the number of bursts/min was 90 ± 8% and total MSA was 89 ± 5% of the value in the awake state ($P < 0.05$ for both). In the 5 subjects who reached deep sleep (stage 3–4), total MSA decreased to 71 ± 8% from 81 ± 8% in stage 2 (a further decrease in 4 and unchanged activity in 1 subject). Examples of MSA records in different sleep stages in one subject are shown in fig. 1 and quantitative data from all subjects are summarized in fig. 2A and the Table. There was no close correlation with variations of depth of sleep, yet when total MSA was measured during consecutive 1 min periods during continuously deepening sleep MSA decreased progressively with time ($P < 0.001$ in 4 and $P = 0.10$ in 1 subject). An example of this relationship is shown in fig. 3. In stage 3–4, changes of total MSA were fairly consistent but in stage 2 there were more variations. To exclude a bias in the selection of 5 min periods we also analysed the whole period of stage 2 sleep in all subjects. The result was similar, that is, a decrease of the number of bursts/min to 92 ± 8% and a decrease of total MSA to 79 ± 10% of the awake value. When comparing total MSA between the first and last 5 min periods of stage 2 (mean duration: 14 min, range: 5–31 min), there was no change in 9 subjects

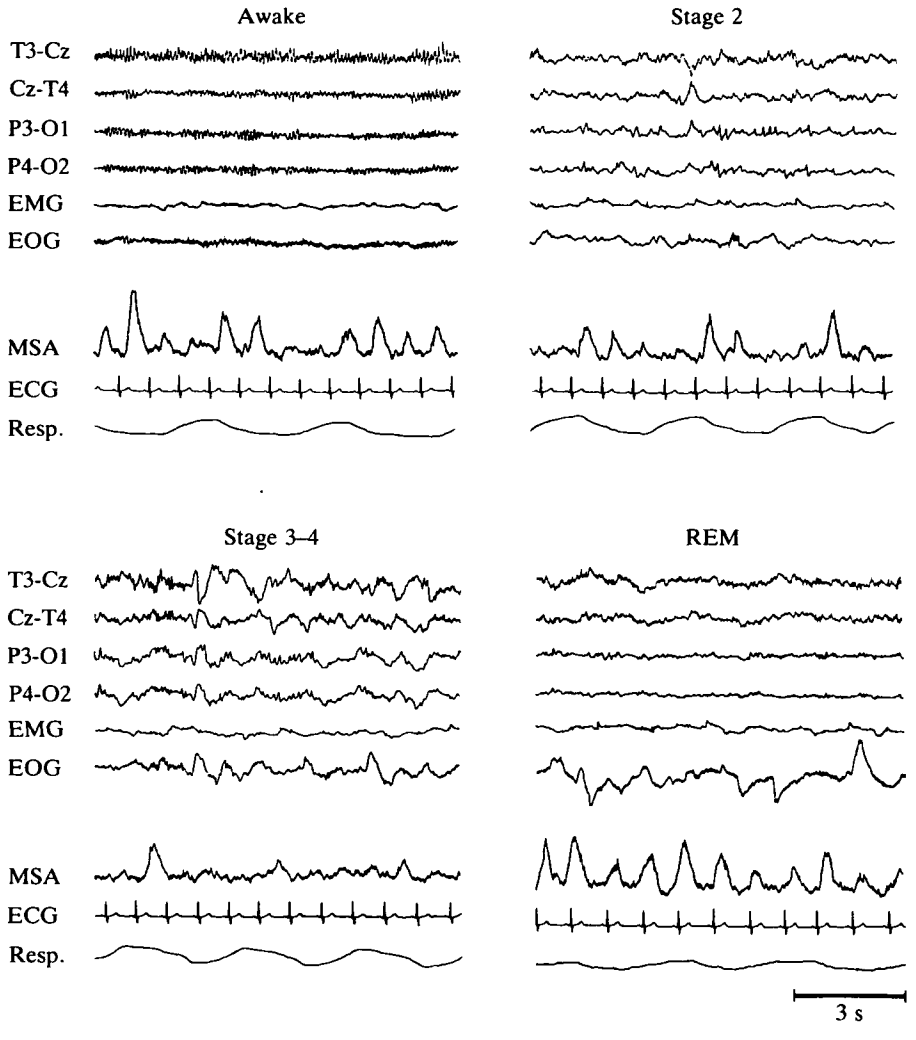

FIG. 1. Polygraphic recording in one subject (N.E.) during sleep. With increasing depth of sleep, muscle sympathetic activity (MSA) decreases. During rapid eye movements (REM) in desynchronized sleep a marked increase of MSA occurs. In stage 2 and stage 3–4 EEG artefacts appear in the EOG signal. Traces from above: EEG derivations (T3-Cz, Cz-T4, P3-O1, P4-O2), electromyogram (EMG), electro-oculogram (EOG), muscle sympathetic activity (MSA), electrocardiogram (ECG) and respiratory movements (Resp.).

but in 5 subjects total MSA was markedly lower at the end of stage 2 which accounts for the difference between the analysis of the whole stage 2 and of the selected 5 min periods.

Blood pressure did not change between the awake state and stage 2 sleep (n = 7). Heart rate was 67.2 ± 2.9 min^{-1} in the awake state, decreasing significantly to 63.4 ± 2.8 min^{-1} during stage 2 sleep (n = 14, $P = 0.02$) and to 65.1 ± 3.3 min^{-1} in stage 3–4 sleep (n = 5).

TABLE. SUMMARY OF DATA FROM ALL SUBJECTS*

		Awake			*Stage 2*				*Stage 3–4*				*Desynchronized (REM) sleep*			
Subject	*Age (yrs)*	*Bursts min^{-1}*	*BP*	*Heart rate*	*Bursts min^{-1}*	*Total MSA % of awake*	*BP*	*Heart rate*	*Bursts min^{-1}*	*Total MSA % of awake*	*BP*	*Heart rate*	*Bursts min^{-1}*	*Total MSA % of awake*	*BP*	*Heart rate*
C.M.	31	25	131/83	61	19	99	133/83	53	–	–	–	–	–	–	–	–
S.K.	25	35	147/82	96	33	118	148/76	86	–	–	–	–	–	–	–	–
B.O.	35	26	134/73	56	18	51	136/75	61	17	41	136/76	62	34	170	135/73	59
N.E.	42	58	113/72	72	55	88	114/70	68	56	88	102/63	68	59	104	108/67	68
G.P.	25	29	123/73	60	25	88	127/71	55	–	–	–	–	–	–	–	–
J.G.	32	42	–	75	39	81	–	71	–	–	–	–	–	–	–	–
R.E.	26	20	120/78	54	19	98	136/84	50	–	–	–	–	–	–	–	–
G.M.	53	42	137/75	70	40	120	131/70	69	–	–	–	–	–	–	–	–
E.U.	37	32	–	75	28	102	–	64	27	78	–	65	–	–	–	–
B.L.	31	33	–	58	33	80	–	53	32	71	–	55	41	107	–	60
B.A.	49	39	–	73	33	83	–	75	33	78	–	75	41	122	–	78
S.A.	39	38	–	65	39	103	–	62	–	–	–	–	–	–	–	–
H.K.	44	56	–	66	51	72	–	69	–	–	–	–	–	–	–	–
F.U.	24	33	–	61	25	65	–	52	–	–	–	–	33	120	–	57
Mean	35	36	129/77	67	33	89	132/76	63	33	71	119/70	65	42	124	122/70	64
SEM	2.5	2.9	4/2	2.9	3.1	5	4/2	2.8	6.4	8.0	–	3.3	4.7	12	–	3.9

* Total muscle sympathetic activity (MSA) is expressed as a percentage of the awake value. Blood pressure (BP) and heart rate values are given in mmHg and min^{-1}, respectively.

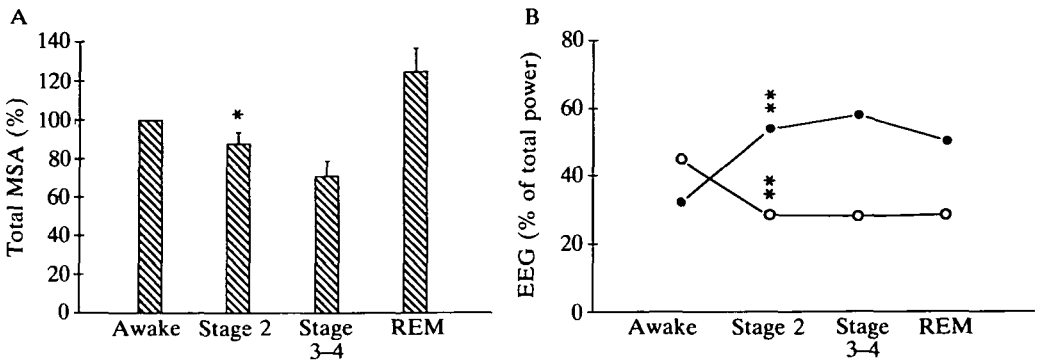

FIG. 2. Total muscle sympathetic activity (MSA) and EEG activity in 5 min periods of sleep stage 2, stage 3–4 and during the whole period of desynchronized (REM) sleep (mean duration: 7.4 min). A, MSA is expressed as a percentage of the awake value. B, percentage of total power of the frequency bands of 1.5–7.5 Hz (theta and delta waves, filled circles) and of 7.5–12.5 Hz (alpha waves, open circles) in the parieto-occipital EEG derivations. Significant differences from awake: $*P < 0.05$; $**P < 0.01$. Number of observations: n = 14 in the awake state and stage 2; n = 5 in stage 3–4 and in desynchronized (REM) sleep.

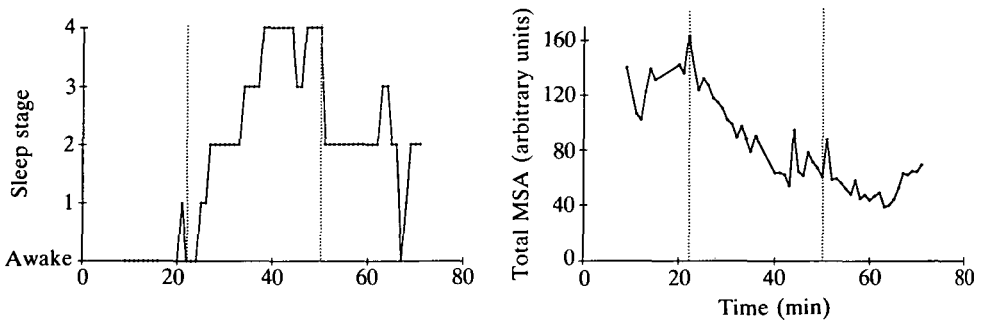

FIG. 3. Gradual fall of total muscle sympathetic activity (MSA) during sleep (subject N.E.). MSA and sleep stages were analysed in 1 min periods. During the period of continuously deepening sleep, indicated by dotted lines, MSA decreased progressively with time ($P < 0.001$).

Relation of MSA to K complexes. In stage 2 sleep, high amplitude K complexes were accompanied by short-lasting increases of MSA (*see* fig. 4 and stage 2 sleep in fig. 1). For quantitative analysis 8–25 (mean 20) spontaneously occurring K complexes from 12 experiments met the criteria described in the Methods section (2 experiments were excluded because of the small number of K complexes meeting the criteria). Total MSA measured during the first 4 s after the first sharp-wave peak of the K complexes was significantly higher than total MSA during the 4 s preceding the K complexes (52 ± 7 vs 33 ± 5, arbitrary units; $P < 0.01$, n = 12). When compared during the same 4 s periods, heart rate was also higher after the K complex (64.2 ± 2.9 min^{-1} vs 61.2 ± 2.9 min^{-1}, $P < 0.01$, n = 12).

Blood pressure was recorded in 6 of the 12 experiments. In these cases, analysis of total MSA, R-R interval and diastolic blood pressure was made for each heart beat to

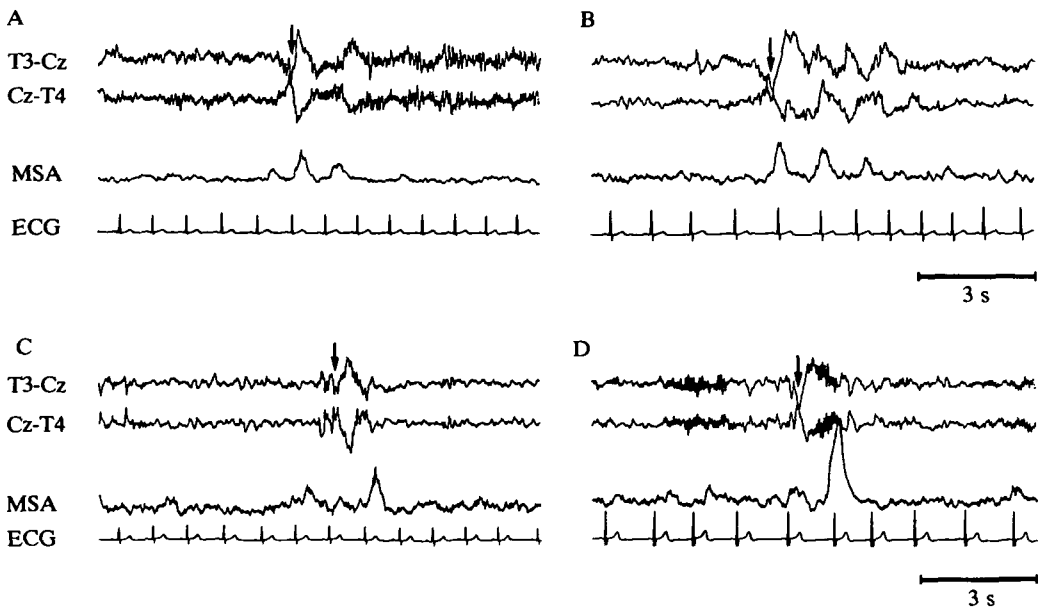

FIG. 4. Polygraphic recordings in 4 subjects (A, B, C, D) showing simultaneously appearing spontaneous K complexes and increases in muscle sympathetic activity (MSA) in stage 2 sleep. Arrows indicate the peak of the first sharp-wave of a K complex defined for the statistical analysis. For selection criteria of K complexes, *see* Methods. Abbreviations as in fig. 1.

reveal the exact time relationship between these parameters. MSA increased suddenly to a maximum during the second heart beat following the K complex (fig. 5). After the peak, MSA fell successively to values below the control level and at the sixth heart beat after the K complex, MSA was significantly less than the control, that is, the value during the cardiac cycle immediately preceding the K complex. The change of instantaneous heart rate occurred slightly later with a maximal value at the third heart beat whereas diastolic blood pressure reached its peak value 4 heart beats later than MSA (sixth heart beat from the K complex). Peak values of all 3 parameters were significantly different from the control values ($P < 0.05$).

Desynchronized (REM) sleep

Desynchronized sleep occurred in 5 subjects. Since its duration varied widely (mean 7.4, range 2–13.5 min), the whole period was analysed in all subjects. A record is shown in fig. 1.

During desynchronized sleep, total MSA increased to a mean of $124 \pm 12\%$ of the awake value (fig. 2A). The increases occurred mainly in short (10–30 s), irregular periods of high amplitude bursts. These periods of high sympathetic activity during desynchronized sleep were often but not always related to rapid eye movements (fig. 6). The increase of total MSA was inversely correlated with the duration of the desynchronized (REM) sleep (fig. 7). This may be related to the finding that the longer the period of desynchronized sleep the shorter the relative duration of rapid eye

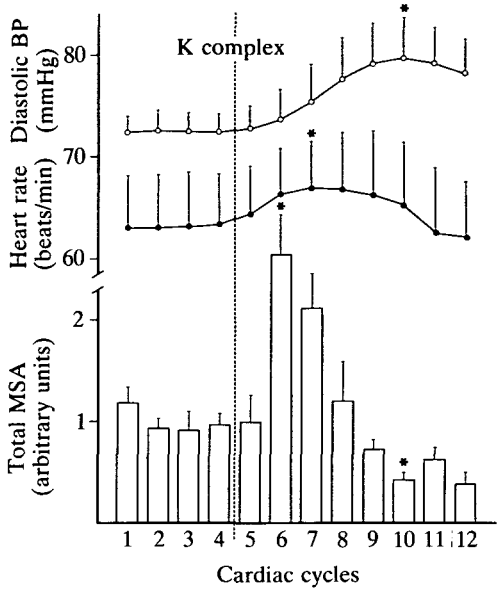

FIG. 5. Changes of total muscle sympathetic activity (MSA), heart rate and diastolic blood pressure (BP) during 4 cardiac cycles preceding and during 8 cardiac cycles following the first sharp-wave peak of the K complexes (indicated by broken line) in 6 subjects. MSA values are normalized for the mean of the values obtained in 4 heart cycles preceding a K complex. * Significant difference from the control level (the cardiac cycle immediately preceding the K complex).

movements. For example, in subject B.O. rapid eye movements comprised 22% of a 2 min period of desynchronized sleep and MSA increased to 170% of the awake value. In contrast, in subject N.E. rapid eye movements occurred during 8% of the 13.5 min period of desynchronized sleep and MSA increased to only 104% of the awake value.

DISCUSSION

We have measured sympathetic nerve activity in humans during sleep. Our main findings were: (1) muscle sympathetic nerve activity decreased during synchronized (non-REM) sleep; (2) in stage 2 there were transient increases of MSA and heart rate which were closely related to the occurrence of K complexes in the EEG recordings; (3) MSA increased during desynchronized (REM) sleep. The increase occurred mainly in short periods of high activity and was usually associated with rapid eye movements.

Decrease of MSA during synchronized (non-REM) sleep

Our finding of a decrease of MSA during non-REM sleep in humans agrees with data obtained in animal experiments. Direct recordings of sympathetic activity during synchronized sleep have been made in the renal nerve of the cat in which a decrease was observed (Baust *et al.*, 1968) but there is also evidence of vasodilatation in muscle, renal and mesenteric vascular beds in the cat (Mancia *et al.*, 1971).

The reduction of sympathetic outflow may be due to a reduced central sympathetic

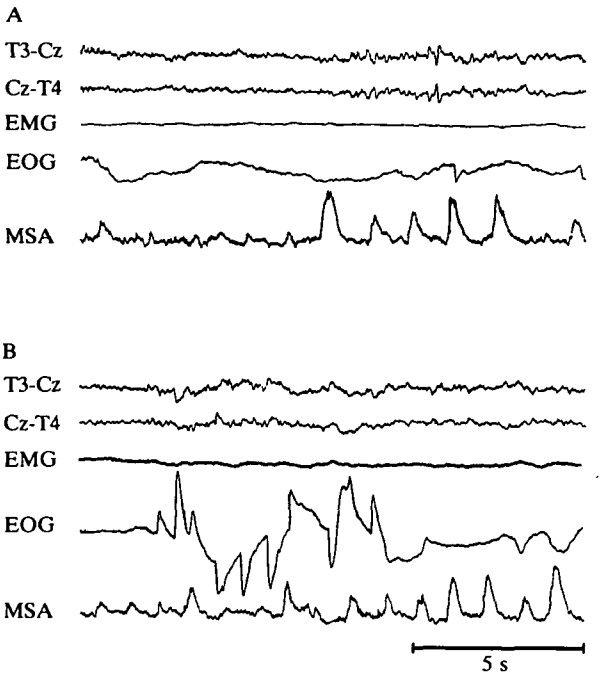

FIG. 6. Polygraphic recordings in 2 subjects (A, B). Short-lasting increases of MSA in desynchronized (REM) sleep may not (A) but usually are (B) associated with rapid eye movements. Abbreviations as in fig. 1.

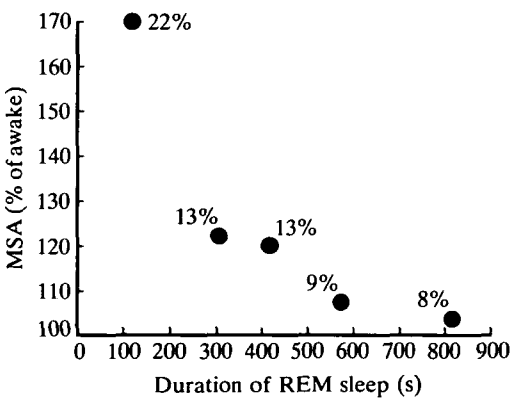

FIG. 7. Increase of total muscle sympathetic activity (MSA) during desynchronized (REM) sleep is inversely related to the duration of this sleep stage. Numbers above the dots indicate the relative duration of rapid eye movement periods during the whole desynchronized sleep.

excitability. Experimental evidence of reduced neuronal activity in the brainstem and in other regions of the brain during non-REM sleep (Siegel, 1990) supports this assumption. In man, there are several studies showing that the baroreceptor-cardiac

reflex is reset to lower blood pressure values during synchronized sleep (Bristow *et al.*, 1969; Smyth *et al.*, 1969; Conway *et al.*, 1983; Kasting *et al.*, 1987), whereas data about changes of the sensitivity of the reflex are inconsistent. No circadian variation of the sensitivity of the baroreceptor-heart rate reflex was found when subjects were investigated in the awake state or after awakening during normal sleep-waking cycles (Kasting *et al.*, 1987). However, Smyth *et al.* (1969) described an increased sensitivity during sleep which was similar in different sleep stages although, in a later study from the same group (Bristow *et al.*, 1969), no consistent change of sensitivity was found.

K complex-related increase of sympathetic activity

We found transient increases of MSA in stage 2 sleep which were related to spontaneous K complexes. What is the mechanism underlying this finding? An arterial baroreflex effect on MSA can probably be excluded since the increase of nerve traffic was not preceded by a decrease of blood pressure. The increase of blood pressure occurring about 4 s after the increase of MSA is in agreement with the result of a previous study (Wallin and Nerhed, 1982) on the time relationship between a transient increase of MSA and the succeeding blood pressure increase. Thus our interpretation is that a K complex is associated with a nonbaroreflex-mediated increase of vasoconstrictor drive to skeletal muscle vessels which contributes to a succeeding blood pressure increase. In contrast, the MSA reduction following the primary increase coincided with the blood pressure peak (fig. 5) and therefore probably was a baroreflex response.

The increase of MSA occurred approximately 1 s after the first sharp-wave peak of a K complex (fig. 5). Since there is a conduction delay for MSA from the brain to the peroneal nerve at the knee of slightly more than 1 s (Fagius and Wallin, 1980), it must be postulated that activation of sympathetic centres occurs at the same time as cortical activation, that is, in terms of time relationships both phenomena may have the same origin.

K complexes are often associated with slight movements, cessation of snoring or a sudden change of regular respiration. They may occur spontaneously or may be elicited by external stimuli and are considered as signs of abortive arousal (*see*, e.g., Roth *et al.*, 1956; Johnson and Karpan, 1968). This interpretation is supported by the finding that K complexes are often associated with signs of cutaneous vasoconstriction and sweating (Johnson and Karpan, 1968). Could the increase of MSA also be an arousal-related phenomenon? As mentioned in the Introduction, arousal stimuli do not influence MSA in awake healthy subjects. This may be due to an inhibitory influence of the baroreceptors on MSA: after temporary baroreceptor deafferentation (Fagius *et al.*, 1985) or cervical spinal cord lesions (Stjernberg *et al.*, 1986) interrupting baroreflex pathways, arousal responses in MSA do occur. Thus if baroreceptor influence on MSA were weakened, the K complex-related increases of MSA may also be arousal phenomena. Possibly the K complex is associated with a generalized sympathetic activation: besides the activation of skin sympathetic fibres causing cutaneous vasoconstriction and sweating, direct recordings in the cat showed an increase of renal sympathetic activity following arousal during synchronized sleep.

Whether there are transient K complex-related changes of baroreceptor reflex mechanisms has not been investigated systematically. However, Smyth *et al.* (1969) showed a figure in which the reflex bradycardia in response to a blood pressure increase

was suddenly interrupted when a K complex occurred and, though the pressure continued to rise, the heart rate accelerated. This observation may be an example showing that the inhibitory influence of baroreceptors in stage 2 sleep cannot override a strong central sympathetic activation.

The functional importance of a K complex is unknown. However, if the K complex-related increase of sympathetic activity is an indicator of an (internally evoked?) generalized arousal, it may be speculated that it has survival value. During deep sleep the low responsiveness to external stimuli makes the individual vulnerable to external threats. Perhaps, therefore, stage 2 sleep is a preparation for deep sleep during which the K complex-related partial awakenings allow the individual a long enough appraisal of the 'danger situation' before and between periods of deep sleep.

In the rat, parallel changes in activity of the splanchnic sympathetic nerve and of noradrenergic neurons of the nucleus locus coeruleus have been demonstrated in several physiological situations (Elam *et al.*, 1981, 1984, 1986). The locus coeruleus has a key function for alerting reactions and has a widespread terminal network innervating the entire cortex (*cf* Foote *et al.*, 1983). Hypothetically, the simultaneous cortical K complexes and peripheral MSA increases could be a correlate in humans to the concomitant activation of peripheral and central noradrenergic neurons seen in rats.

Increase of MSA during desynchronized (REM) sleep

We found a clear increase of MSA in desynchronized sleep. A similar increase of muscle nerve sympathetic activity has been found also in decerebrate cats exhibiting desynchronized sleep-like periods. During such periods sympathetic traffic to the muscle vascular bed increased but traffic in renal, splanchnic, cardiac and lumbar sympathetic nerves decreased (Coote and Futuro Neto, 1981). In addition, the tonically reduced (background) level of activity was interrupted by sudden, short-lasting increases of sympathetic activity in all nerves (Coote, 1982).

In man, previous studies of desynchronized sleep showed a marked variability of mean blood pressure values (Snyder *et al.*, 1964; Coccagna *et al.*, 1971). It seems likely, from our findings, that short periods of strong activation of MSA contribute to this variability. The fact that no or only minor increases of blood pressure have been reported during desynchronized sleep (e.g., Snyder *et al.*, 1964; Khatri and Freis, 1967; Bristow *et al.*, 1969; Coccagna *et al.*, 1971) despite the increase of MSA may indicate that in humans as well, there is a decrease of sympathetic activity to other vascular beds similar to that demonstrated in animal experiments (*see above*). This would also agree with reports of decreased total peripheral resistance during desynchronized sleep in man (Khatri and Freis, 1967; Bristow *et al.*, 1969).

The mechanism behind the increase of sympathetic outflow to muscles during desynchronized sleep is not clear. Increased sensitivity of the baroreceptor-heart rate reflex has been reported in humans (Bristow *et al.*, 1969; Smyth *et al.*, 1969), but in a recent study in the cat the sensitivity of the reflex was found to be decreased during desynchronized sleep (Knuepfer *et al.*, 1986). Similar, perhaps only transient, suppressions of the reflex in humans cannot be excluded since another sympathetic reflex, the thermoregulatory reflex, is suppressed during desynchronized sleep in man (Obál, 1984). Another mechanism was suggested by Baccelli *et al.* (1974). They hypothesized on the existence of a spinal vascular reflex originating from the muscles themselves

which would act during desynchronized sleep and would be suppressed in the awake state and during synchronized sleep.

Limitations of the study

We think that the findings in our study represent changes which occur in sleep during normal sleep-awake cycles. There are, however, two points which merit discussion. The study was made in partly sleep-deprived subjects and it is known that an acute reversal of the awake-sleep periods may alter the duration and frequency of sleep cycles (Weitzman *et al.*, 1970). Although we are not aware of any data on this point, we cannot exclude that sleep-related changes of sympathetic activity are also influenced by sleep deprivation. The existence of circadian rhythms of blood pressure (e.g., Richardson *et al.*, 1964; Snyder *et al.*, 1964)—perhaps related to circadian changes of the secretion of various hormones (e.g., corticoids, aldosterone, renin; for references, *see* Carandente, 1989)—would also affect our results. However, in a more recent study, Littler (1979) found no difference in blood pressure decrease during nocturnal and during daytime sleep. Based on his findings and on the re-evaluation of data published previously, he suggested that changes of arterial blood pressure are not specifically related to time but governed by physical activity and the state of sleep itself.

In summary, we recorded MSA in the peroneal nerve, in some experiments also blood pressure, during sleep in healthy subjects. During non-REM sleep the mean level of total MSA decreased. The decrease became apparent in stage 2 and continued in stage 3–4. In stage 2, we found transient increases of MSA which were associated with the occurrence of K complexes in the EEG. We suggest that K complex-related increases of MSA are signs of arousal and if so they may indicate a weakened inhibitory influence of baroreceptors on MSA. During desynchronized sleep MSA increased in short periods of high activity usually related to rapid eye movements.

ACKNOWLEDGEMENTS

The authors thank Tomas Karlsson for his expert technical assistance with the equipment and Ann-Britt Andrén for her help during the experiments and in the preparation of the figures. The study was supported by the Swedish Medical Research Council Grant B90-04X-03546-19C, and a postdoctoral fellowship to Dr Hornyak from the Deutsche Forschungsgemeinschaft (Grant HO 1067/1-1).

REFERENCES

BACCELLI G, ALBERTINI R, MANCIA G, ZANCHETTI A (1974) Central and reflex regulation of sympathetic vasoconstrictor activity to limb muscles during desynchronized sleep in the cat. *Circulation Research*, **35**, 625–635.

BAUST W, WEIDINGER H, KIRCHNER F (1968) Sympathetic activity during natural sleep and arousal. *Archives Italiennes de Biologie*, **106**, 379–390.

BRISTOW JD, HONOUR AJ, PICKERING TG, SLEIGHT P (1969) Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects. *Cardiovascular Research*, **3**, 476–485.

CARANDENTE O (1989) Hormones and blood pressure: clues from chronobiology. *Chronobiologia*, **16**, 45–88.

CEJNAR M, HUNYOR SN, LIGGINS GW, DAVIS RJ (1988) Description of a new continuous non-invasive blood pressure monitoring instrument. *Proceedings of the Australian Physiological and Pharmacological Society*, **19**, 90*P*.

COCCAGNA G, MANTOVANI M, BRIGNANI F, MANZINI A, LUGARESI E (1971) Arterial pressure changes during spontaneous sleep in man. *Electroencephalography and Clinical Neurophysiology*, **31**, 277–281.

CONWAY J, BOON N, JONES JV, SLEIGHT P (1983) Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypertension*, **5**, 746–748.

COOTE JH (1982) Respiratory and circulatory control during sleep. *Journal of Experimental Biology*, **100**, 223–244.

COOTE JH, FUTURO NETO HA (1981) Pattern of sympathetic activity to different vascular beds during paradoxical sleep. *Journal of Physiology, London*, **312**, 29*P*–30*P*.

DELIUS W, HAGBARTH K-E, HONGELL A, WALLIN BG (1972) General characteristics of sympathetic activity in human muscle nerves. *Acta Physiologica Scandinavica*, **84**, 65–81.

ELAM M, YAO T, THORÉN P, SVENSSON TH (1981) Hypercapnia and hypoxia: chemoreceptor-mediated control of locus coeruleus neurons and splanchnic, sympathetic nerves. *Brain Research, Amsterdam*, **222**, 373–381.

ELAM M, YAO T, SVENSSON TH, THORÉN P (1984) Regulation of locus coeruleus neurons and splanchnic, sympathetic nerves by cardiovascular afferents. *Brain Research, Amsterdam*, **290**, 281–287.

ELAM M, SVENSSON TH, THORÉN P (1986) Locus coeruleus neurons and sympathetic nerves: activation by cutaneous sensory afferents. *Brain Research, Amsterdam*, **366**, 254–261.

FAGIUS J, WALLIN BG (1980) Sympathetic reflex latencies and conduction velocities in normal man. *Journal of the Neurological Sciences*, **47**, 433–448.

FAGIUS J, WALLIN BG, SUNDLÖF G, NERHED C, ENGLESSON S (1985) Sympathetic outflow in man after anaesthesia of the glossopharyngeal and vagus nerves. *Brain*, **108**, 423–438.

FOOTE SL, BLOOM FE, ASTON-JONES G (1983) Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. *Physiological Reviews*, **63**, 844–914.

GASSEL MM, GHELARDUCCI B, MARCHIAFAVA PL, POMPEIANO O (1964) Phasic changes in blood pressure and heart rate during the rapid eye movement episodes of desynchronized sleep in unrestrained cats. *Archives Italiennes de Biologie*, **102**, 530–544.

GUAZZI M, ZANCHETTI A (1965) Blood pressure and heart rate during natural sleep of the cat and their regulation by carotid sinus and aortic reflexes. *Archives Italiennes de Biologie*, **103**, 789–817.

JOHNSON LC, KARPAN WE (1968) Autonomic correlates of the spontaneous K-complex. *Psychophysiology*, **4**, 444–452.

KASTING GA, ECKBERG DL, FRITSCH JM, BIRKETT CL (1987) Continuous resetting of the human carotid baroreceptor-cardiac reflex. *American Journal of Physiology*, **252**, R732–R736.

KHATRI IM, FREIS ED (1967) Hemodynamic changes during sleep. *Journal of Applied Physiology*, **22**, 867–873.

KNUEPFER MM, STUMPF H, STOCK G (1986) Baroreceptor sensitivity during desynchronized sleep. *Experimental Neurology*, **92**, 323–334.

LITTLER WA (1979) Sleep and blood pressure: further observations. *American Heart Journal*, **97**, 35–37.

MANCIA G, BACCELLI G, ADAMS DB, ZANCHETTI A (1971) Vasomotor regulation during sleep in the cat. *American Journal of Physiology*, **220**, 1086–1093.

MANCIA G, ZANCHETTI A (1980) Cardiovascular regulation during sleep. In: *Physiology in Sleep*. Edited by J. Orem and C. D. Barnes. New York and London: Academic Press, pp. 1–55.

MATOUSEK M, PETERSÉN I (1983) A method for assessing alertness fluctuations from EEG spectra. *Electroencephalography and Clinical Neurophysiology*, **55**, 108–113.

OBÁL F (1984) Thermoregulation and sleep. *Experimental Brain Research*, Supplement 8, 157–172.

RECHTSCHAFFEN A, KALES A (1968) *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, DC: Public Health Service, US Government Printing Office.

RICHARDSON DW, HONOUR AJ, FENTON GW, STOTT FH, PICKERING GW (1964) Variation in arterial pressure throughout the day and night. *Clinical Science*, **26**, 445–460.

ROTH M, SHAW J, GREEN J (1956) The form, voltage distribution and physiological significance of the K-complex. *Electroencephalography and Clinical Neurophysiology*, **8**, 385–402.

SIEGEL JM (1990) Mechanisms of sleep control. *Journal of Clinical Neurophysiology*, **7**, 49–65.

SMYTH HS, SLEIGHT P, PICKERING GW (1969) Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. *Circulation Research*, **24**, 109–121.

SNYDER F, HOBSON JA, MORRISON DF, GOLDFRANK F (1964) Changes in respiration, heart rate, and systolic blood pressure in human sleep. *Journal of Applied Physiology,* **19,** 417–422.

STJERNBERG L, BLUMBERG H, WALLIN BG (1986) Sympathetic activity in man after spinal cord injury: outflow to muscle below the lesion. *Brain,* **109,** 695–715.

SUNDLÖF G, WALLIN BG (1977) The variability of muscle nerve sympathetic activity in resting recumbent man. *Journal of Physiology, London,* **272,** 383–397.

WALLIN BG, NERHED C (1982) Relationship between spontaneous variations of muscle sympathetic activity and succeeding changes of blood pressure in man. *Journal of the Autonomic Nervous System,* **6,** 293–302.

WALLIN BG, FAGIUS J (1988) Peripheral sympathetic neural activity in conscious humans. *Annual Review of Physiology,* **50,** 565–576.

WEITZMAN ED, KRIPKE DF, GOLDMACHER D, MCGREGOR P, NOGEIRE C (1970) Acute reversal of the sleep-waking cycle in man: effect on sleep stage patterns. *Archives of Neurology, Chicago,* **22,** 483–489.

YAMAKOSHI K, ROLFE P, MURPHY C (1988) Current developments in non-invasive measurement of arterial blood pressure. *Journal of Biomedical Engineering,* **10,** 130–137.

(Received May 11, 1990. Revised August 16, 1990. Accepted August 22, 1990)