Central Nervous Control of Blood Pressure in Man; Preliminary Report*

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Clinicians have long recognized the importance of the mind in the moment-to-moment regulation of blood pressure in their hypertensive patients. Ayman and Goldshine (1940) long ago demonstrated that blood pressure measured by a physician in a hospital clinic was always higher than the pressure recorded by the same patient or by a member of his family in his home. Pickering's group (Richardson *et al.*, 1964), using an automatic blood pressure recorder, has recently shown that elevation in blood pressure ranging from 10 to 50 mm Hg occurred when a physician entered the patient's room merely to say a word of greeting. Figure 1 illustrates the dramatic rise in the pressure of a hypertensive subject during examination by an unfamiliar neurologist who concluded, within the patient's hearing, that brain damage was present.

To study further the relation between cerebral activity and blood pressure, we have recorded electroencephalograms and intra-arterial blood pressure in normal people during natural sleep.

Materials and Methods

The subjects of these experiments were twenty-two healthy volunteers, five women and 17 men, aged 19 to 51 years, two hypertensive patients recently recovered from heart failure, and one totally-nephrectomized man awaiting renal transplantation. Blood pressure and heart rate were recorded continuously through a soft plastic catheter inserted into a brachial or radial artery. Cerebral electrical waves and eye movements were recorded with a Grass electroencephalograph from electrodes pasted on the scalp and beside the eyes. Rate and depth of breathing were recorded with pneumographs placed around chest and abdomen. The subjects slept on their backs in a bed in a dark, quiet room. Recording equipment and observers were in an adjoining room. No sedatives were given.

The depth of sleep was assessed from the electroencephalogram by the scheme of Oswald (1962). Dreaming was recognized by the occurrence of rapid conjugate eye movements during light (stage B) sleep, as first pointed out by Dement and Kleitman (1957), who observed that subjects awakened just after a burst of rapid eye movements described dreams vividly. On the other hand, if they were allowed to sleep for 5 to 10 minutes after the eye movements stopped, and were then awakened, their recall of dreams was diminished or lacking. These eye movements signal the presence of

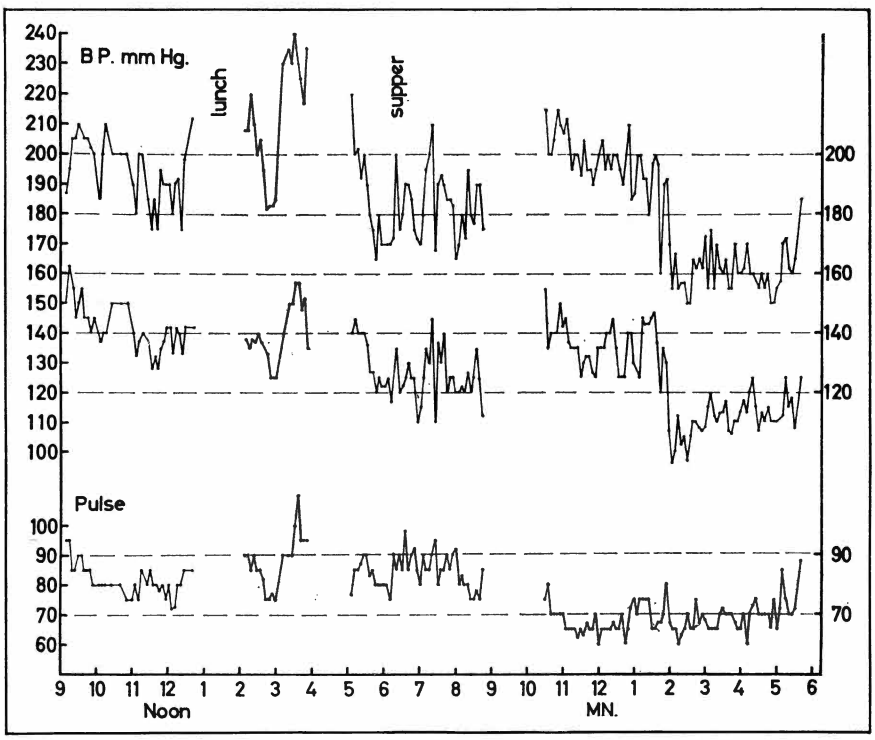

Fig. 1—Arterial pressure and pulse rate recorded indirectly at 5-minute intervals for 24 hours in a young, hypertensive man. At 2:40 p.m. he was awakened from a nap by a consultant neurologist. At about 1 a.m. he fell asleep. Reproduced by permission of the editors of *Clin. Sci.* (Richardson *et al.*, 1964). Variation in arterial pressure throughout the day and night.

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dreaming but provide no information about the content of the dream.

In three subjects, the changes in blood pressure which follow the type of paroxysmal cerebral electric activity called K complexes (fig. 3) were observed before and during blockade of β-adrenergic receptors with 5 mg of propranolol given intravenously without waking the subject (Courtesy of Dr. Alex Sahagian-Edwards of Ayerst Laboratories, 685 3rd Ave., N.Y. 17, N.Y.). Blockade of β-adrenergic receptors prevents the increase in cardiac output and heart rate induced by stimulation of sympathetic nerves, without preventing the peripheral arterial constriction which sympathetic neural discharge produces. The use of propranolol thus can yield information about the mechanism by which cerebral activity produces a rise in blood pressure. The effectiveness of β blockade was tested in each subject by intravenous infusion of 10 μg of epinephrine per min. This produced marked elevation of blood pressure and slowing of the heart when given after propranolol, instead of the usual response of tachycardia without change in mean blood pressure.

Results

1. Effect of Sleep

In four healthy subjects, systolic pressure fell more than 60 mm Hg between the highest waking pressure and the lowest sleeping pressure; in ten, systolic pressure fell more than 50 mm Hg. The average fall in systolic pressure for nineteen normal subjects was 49 mm Hg. Diastolic pressure fell less than systolic, with an average change from waking to sleeping of 29 mm Hg. About 40% of the total decrease in pressure occurred while the patient was resting prior to onset of sleep; the remaining 60% occurred after sleep began. Prompt rise in pressure occurred as soon as the subjects awoke in the morning, and during brief periods of wakefulness during the night. Subjects whose waking pressure was highest experienced the largest decreases in pressure during sleep. No clear correlation was observed between depth of sleep, judged by the electroencephalographic criteria, and level of blood pressure.

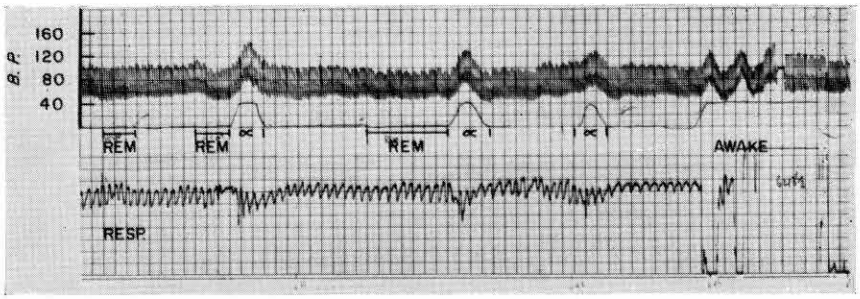

Fig. 2—Intra-arterial pressure (upper tracing) recorded continuously during the end of sleep in a healthy young man. The periods marked REM indicate rapid eye movements associated with dreaming. During the periods marked "α" there was brief arousal. Each vertical line represents 5 seconds. The entire graph represents 5½ minutes. See text.

2. Dreams

Figure 2 shows a typical example of the variable changes in blood pressure that occurred during periods of rapid eye movements which indicate dreams. The bars marked REM indicate the bursts of rapid eye movements. The periods marked "α" indicate brief wakefulness following each dream. The first dream did not alter blood pressure. During the 2nd and 3rd dream periods, blood pressure fell slightly. In other subjects, a rise of pressure as much as 45/30 mm Hg that reached levels of 180/100 mm Hg, occurred during the periods of rapid eye movement. Each subject showed considerable variability in the response of arterial tension to dreams, perhaps related to varying content of the dreams.

3. K Complexes

During sleep of moderate depth, there occur paroxysmal bursts of cerebral electrical activity called K complexes, which are characterized by one or more large (50 to 200 μv), slow (0.5 to 1 cycle per sec) waves on which are super-imposed regular, higher frequency (about 14 cycle per sec) waves called sleep spindles. The large, slow waves are recorded all over the head; the spindles are maximal in the frontal regions. The anatomic site of origin of K complexes, and their functional significance, are unknown. K complexes frequently follow within a few msec a noise or a light flash, but may occur without obvious external stimuli. Many of these K complexes are followed by a rise in blood pressure, as shown in figure 3. Heart rate speeds slightly as the pressure rises following a K complex, and slows below the resting rate at the height of the rise. The rise in arterial pressure begins two or three heart beats after the onset of the K, and lasts 10 to 20 seconds. In six healthy subjects whose records have been completely analyzed, K complexes were associated with an average rise in systolic pressure of 18 mm Hg, with maximal rises of 35 mm Hg in two subjects.

4. Blockade of β-Adrenergic Receptors

In three healthy subjects, effective blockade of β-adrenergic receptors, as indicated by reversal of the usual effects of intravenously administered epinephrine, did not modify the pressor response to K complexes. Figure 4 shows the rise in pressure occurring with a K complex after the injection of propranolol, the β-blocking drug, into the same subject shown in figure 3 prior to injection of propranolol.

Discussion

1. Circulatory Effects of Sleep

Sleep reduces blood pressure in normal and in hypertensive people (Richardson *et al.*, 1964). The neuroanatomic basis for this circulatory change is unknown in man, but ablation experiments in animals indicate that connections between the reticular formation in the midbrain and the cerebral cortex are necessary for wake-

fulness (Oswald, 1962). A current hypothesis suggests that activation of the cerebral cortex by ascending impulses from the mesencephalic, reticular, activating system produces wakefulness, and that impulses from the same area result in sympathetic discharge to the heart and blood vessels, either indirectly by activation of higher brain centers, or more directly by descending fibers to the medullary circulatory centers.

Clinical application of sleep as therapy for high blood pressure has been used by Russian workers who have induced prolonged sleep pharmacologically in the management of hypertension. The long-term efficacy of such therapy is not well evaluated.

2. *Dreams*

Snyder *et al.* (1964), using indirect (cuff sphygmomanometric) and discontinuous measurement of blood pressure have concluded that the blood pressure of twelve subjects in 30 nights of sleep averaged slightly higher during the rapid-eye-movement periods, which indicate dreaming, than at other times. This is a conclusion not borne out by our continuous blood pressure records. The same authors also found that blood pressure and heart rate vary more during dream periods, an observation which our data support. The dramatic rise in pressure occasionally seen with dreaming has obvious clinical import regarding nocturnal angina and paroxysmal nocturnal dyspnea.

3. *K Complexes*

The short interval between the onset of K complexes and the subsequent rise in blood pressure (two or three heart beats) suggests strongly that neural pathways are used exclusively to transmit the message from brain to circulation; it is unlikely that adrenal medullary (or other) hormones could be released into the circulation and reach the effector area in so brief a period. Observation of similar hypertensive responses to K complexes in a totally nephrectomized patient demonstrates that the kidneys are unnecessary for this kind of elevation in blood pressure.

Since propranolol, which blocks the

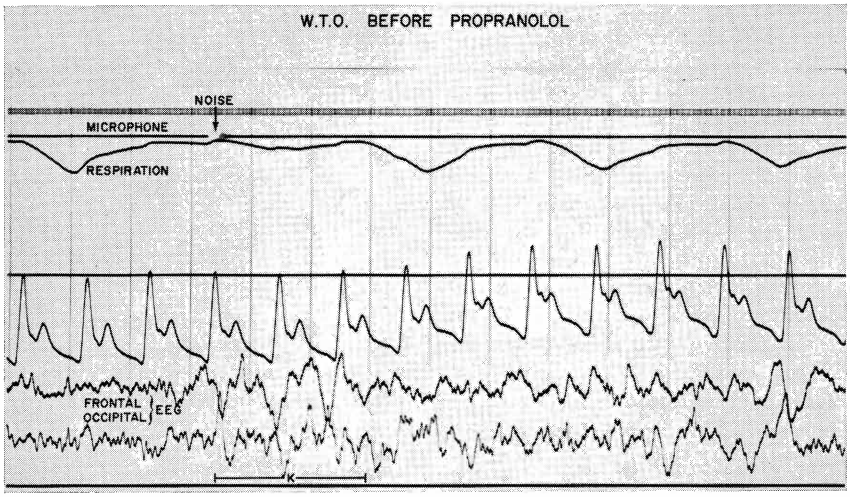

Fig. 3—Respiration, intra-arterial pressure and frontal and occipital electroencephalograms from a healthy man during sleep of moderate depth. Each vertical line represents 1 second. See text.

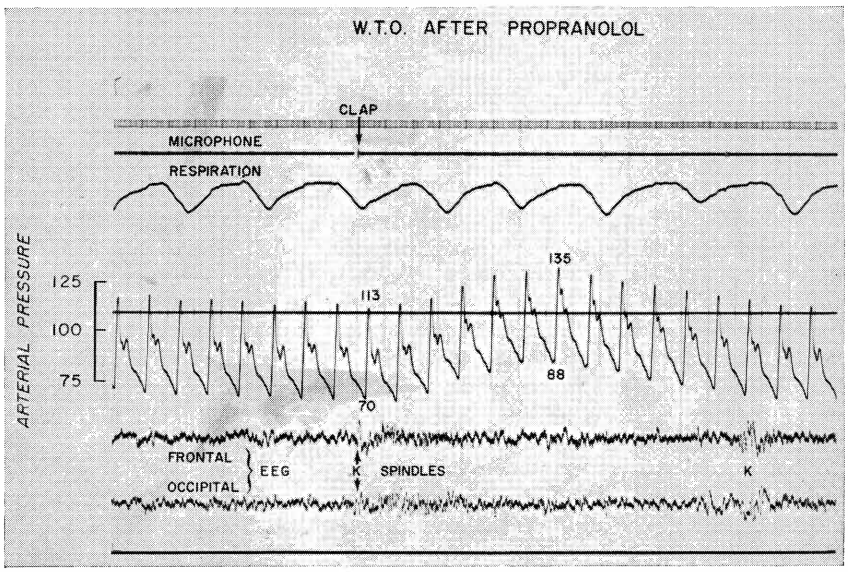

Fig. 4—Response of blood pressure to K complex during β-adrenergic blockade. See text.

cardiac excitatory effects of sympathetic nerve discharge, did not modify the hypertensive response to K complexes, we presume that the K complexes stimulate sympathetic vasoconstrictor nerves to peripheral arterioles, causing an increase in peripheral vascular resistance, and consequent elevation in blood pressure. The hypertension associated with K complexes clearly demonstrates the importance in man of cerebral activity in moment-to-moment control of blood pressure. The immediate relation between cerebral activity and elevation of blood pressure increases interest in the role of the brain in chronic (essential) hypertension, and as a contributing factor in the abnormal physiology leading to paroxysmal nocturnal dyspnea and nocturnal angina.

Summary

1. Electrical activity of the brain, eye movements, arterial pressure, heart rate, and respiratory rate and depth have been recorded continuously during a night of sleep not induced by drugs in 22 healthy subjects, two hypertensive patients, and one anephric man who was awaiting renal transplantation.

2. Sleep was associated with reduction in arterial pressure averaging 50 mm Hg systolic and 30 mm Hg diastolic.

3. Dreams, although occasionally associated with marked elevation of blood pressure, were usually accompanied by no change or a slight fall in pressure.

4. The dramatic paroxysmal electroencephalographic alterations termed K complexes, occurring spontaneously or after a noise in sleep of moderate depth, were followed within two or three heart beats by abrupt elevation in arterial pressure, as much as 35 mm Hg, lasting 10 to 20 seconds. Blockade with propranolol of β-adrenergic receptors, which mediate cardio-excitatory effects of sympathetic nerve discharge, did not modify the hypertension following K complexes.

5. Cerebral activity, transmitted by sympathetic peripheral vasoconstrictor pathways, is an important regulator of blood pressure during sleep in man.

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