All-Night Polygraphic Studies of Nocturnal Angina Pectoris

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SUMMARY

In 12 patients with nocturnal angina pectoris, all-night continuous polygraphic recordings were made, including electroencephalogram, electrooculogram, electromyogram, impedance pneumogram and electrocardiogram, and ECG was analyzed in relation to heart rate and sleep stages. Out of 58 episodes of ischemic ST,T changes which were recorded with the peak frequency between 4:00 and 6:00 a.m., 24 were REM-associated and 21 occurred in awake state. The number of attacks per hour in individual sleep stages was most prominent in REM sleep stage. In 3 cases episodes were seen only in awake period, and in 1 case in NREM sleep stages alone. The analyses of ECG and heart rate during sleep disclosed that the attacks were not likely to be induced by REM-associated increase of heart rate and, in individual episodes, heart rate increase did not precede the ST,T changes. The triggering mechanism of attacks remains to be investigated. Two representative cases were presented.

Additional Indexing Words:
Heart rate  Ischemic ST,T changes  Nocturnal angina pectoris  Sleep  REM sleep

Since the era of Heberden there have been many hypotheses on the mechanism of angina pectoris, especially of nocturnal angina. Recent advances in physiological knowledge have given us hope for a better understanding of nocturnal angina in the light of sleep physiology. The observation made by Nowlin and associates, which suggested the close relationship between anginal attack and rapid eye movement (REM) period of sleep, has encouraged us to investigate this matter in greater detail.
MATERIALS AND METHODS

Studies were carried out on 12 patients with nocturnal angina pectoris. These patients consisted of 8 males and 4 females, with their ages ranging from 27 to 70 (average 53.6). Polysomnographic recordings including electroencephalogram, electro-oculogram, electromyogram (recorded from the chin), impedance pneumogram and electrocardiogram (from the position of V5 with an indifferent electrode placed just below the mid-point of the right clavicle), were performed for 7 to 10 hours continuously through the night, with 10-channel Sani Electroencephalograph model 1A11-10. In order to get the details of sequential electrocardiographic changes and also to pinpoint the onset of ischemic ST,T changes, 3 orthogonal electrocardiograms were also taken by modified Frank’s lead system,5) using Fukuda Vectorcardiograph FVC-3 and Nihon Koden Data Recorder SDR 813, during the same period, with the tape speed of 2 cm./sec. They were displayed later on an oscilloscope for analysis with the playback speed of 50 cm./sec. When the ischemic changes were observed, the ECG was reproduced on a direct-writing 3-channel electrocardiograph.

Since ischemic ST,T changes in ECG during sleep were observed whether or not the patients were awakened by anginal pain, they were considered as significant whenever the positional changes of QRS-T due to body movement were excluded and manifest ischemic ST,T changes persisted more than 30 sec., and were analyzed in relation to heart rate and sleep stage. Sleep stages were classified as 1, 2, 3, 4, and REM, and the awake state was designated as W, according to the classification of Association for the Psychophysiological Study of Sleep.6) All the recordings were made on the earliest possible date after admission, lest the chances should be missed due to subsiding symptoms of nocturnal angina after taking a bed rest.

In 6 patients, Master’s double two step test was performed.

RESULTS

Fourteen all-night polysomnographic recordings in 12 patients showed a total of 58 episodes of ischemic ST,T changes. In 5 patients ECG revealed ST segment elevation in one or more leads of the orthogonal lead system during attacks, while in the other 7 patients, ST segment depression was the major ECG abnormalities. The frequency of episodes of ischemic ST,T changes was progressively increased in the course of nightly hours, with the peak notable between 4:00 and 6:00 a.m. (Fig. 1).

1. Relation between ischemic ST,T changes and sleep stages

The episodes occurred most frequently during REM sleep, with the least frequency in the deep stage of non-rapid eye movement (NREM) sleep (Fig. 2). Twenty-four out of 37 episodes during sleep were REM-associated, occurring in the course of or in close proximity to REM sleep period, and 39 out of all episodes throughout the recording time were observed during REM sleep and awake periods.
The number of episodes per hour in individual sleep stages was most prominent in REM sleep stage (Fig. 2).

The REM-associated episodes were seen most frequently between 4:00
and 6:00 a.m., almost parallel with the over-all incidence of the attacks (Fig. 1).

The relation of ECG changes in each REM-associated episode to the REM sleep period is shown in Fig. 3. The electrocardiographic changes of the attacks preceded the onset of REM sleep on 3 occasions, followed the end of it on 2, and on the remaining 16, occurred during the period of REM sleep.

In one patient, episodes were observed only during NREM sleep, and in 3, their episodes were always associated with the awake state.
2. Representative cases

Case 1. A 48-year-old woman, known hypertensive since 2 years ago, was admitted to Tokyo University Hospital with complaints of progressive frequency of anterior chest pain occurring both on exercise and at rest. Physical examination on admission revealed blood pressure of 170/80 mmHg with a pulse rate of 64/min., regular. Urinalysis, blood cell count and serum transaminase were all within normal limits. Slight cardiac enlargement was evident from chest X-ray films. Conventional ECG showed Q waves and slight ST elevation in III and aVF, and ST depression (less than 0.05 mV.) in I, V₅, and V₆, suggesting remote inferior myocardial infarction. All-night polygraphic recording was made twice. The first recording showed only one episode of 20 minutes' duration, while the second one performed 3 weeks later indicated 8 episodes of severe myocardial ischemia. Fig. 4 shows the progress of sleep stages and the occurrence of attacks then. It is of clinical importance that the ECG showed 2 patterns of ST,T changes, the one (A) with ST elevation in X and Y axes and ST depression in Z (Fig. 5), and the other (B) with ST elevation in X and Z

and ST depression in Y (Fig. 6). Concomitant with B pattern, ventricular premature beats or bouts of ventricular tachycardia were observed at the peak of ST,T changes. The spatial directions of ST vector in both patterns were left-
posterior-inferior and left-anterior, respectively, which indicated the presence of 2 different sites of myocardial ischemia.

Two days later after the second recording, the patient succumbed to ventricular fibrillation during conversation. Post-mortem examination disclosed more than 90% stenosis in the main stems of the right coronary artery, the left anterior descending and circumflex arteries, and diffuse fibrous process in the entire myocardium.

Case 2. The patient was a 48-year-old male who had had left anterior chest pain of 1 hour's duration a month prior to admission. The anginal attacks occurred once every 2 or 3 days thereafter, becoming more and more intense in frequency and duration until he was admitted to Tokyo University Hospital. Physical examination on admission indicated no abnormal findings. Blood pressure was 102/68 mm. Hg and pulse rate was 52 per min., regular. Blood cell count, chest X-ray films and S-GOT showed no abnormalities. ECG revealed regular sinus rhythm with negative T waves in aV_L, and slight ST segment depression in V_5 and V_4. Double two step test was negative, but the ECG taken at the time of anginal attack he had while taking bath indicated obvious ischemic changes. One of the attacks during nocturnal sleep is shown in Figs. 7 and 8. Elevated ST segment and peaked T waves are remarkable in leads X and Z. Of 9 separate episodes, 4 were associated with REM sleep (Fig. 9).

3. Relation between heart rate increase and ischemic ST,T changes

In considering the initiating mechanism of nocturnal angina pectoris, the
hemodynamic changes occurring with or preceding the ECG alterations should be taken into account. Therefore, the heart rate was also investigated along with the ischemic ST,T changes.

Fig. 10 shows the relation of heart rate increase to ST,T changes in 2 REM-associated episodes.

When the heart rate of several minutes’ period prior to the attack was taken as its own control, the onset of ST, T changes occurred simultaneously with or by a few seconds ahead of heart rate increase in 21 out of 35 episodes during sleep. In 4 episodes, heart rate increase lagged behind the onset of ST,T changes (the time lags were 25”, 40”, 3’, and 6’, respectively), and on no occasion increase in heart rate preceded the latter. In 4 episodes, there were no changes in heart rate, and in 5, body movement or respiratory movement interfered with the onset of ST,T changes, which made the record obscure (Table I).
One problem in REM-associated attacks is the increase of basic heart rate in REM sleep stage. From the comparison of heart rate made between before and during REM sleep in divided nightly hours in control 16 patients, the increase was evident in mean value with the largest difference of 10 beats per min. (Fig. 11).
Table 1. Relation between Heart Rate Increase and Ischemic ST, T Changes at the Onset of Attack

<table>
<thead>
<tr>
<th>H.R. &gt; ST, T</th>
<th>H.R. = ST, T</th>
<th>ST, T &gt; H.R.</th>
<th>No change in heart rate</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>35</td>
</tr>
</tbody>
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H.R. > ST, T signifies that the onset of heart rate increase precedes the ST, T changes. See text.

In relation to REM-associated attacks, heart rate was plotted against the course of sleeping time. As shown in Fig. 12, the increase of heart rate during REM sleep over NREM period is less than 10 beats per min. This is an increase not great enough to be an only causative factor of myocardial ischemia.

In 6 of these patients, double two step test was performed, but they gave negative responses, in spite of the marked increase of blood pressure and heart rate.
DISCUSSION

It is shown in the present study that 24 out of 58 episodes recorded through the night were REM-associated, and only 3 occurred in deep NREM sleep stage. This trend is in accordance with Nowlin et al. who first recognized the close association of nocturnal angina pectoris with REM sleep in polygraphic recordings of 4 patients.

It should also be stressed, however, that the present data have some difference from theirs in 1) episodes also occurred in the awake state during the recording period, with the frequency coming next to that in the REM stage, 2) incidence of episodes was most conspicuous between 4:00 and 6:00 a.m., 3) the onset of REM sleep did not always precede the ECG changes, and 4) there were some patients whose episodes were not associated with REM sleep.

The recent development of sleep physiology has disclosed that in REM sleep stage there are such wide variations of autonomic nervous functions as are contrasted with NREM sleep stages. In human sleep, heart rate, blood pressure and respiration rate are slightly increased with augmented variability in conjunction with periodic recurrence of REM sleep. Besides the rapid eye movement, other conspicuous findings in the same stage are miosis, erection, dreaming, etc.
From these physiological backgrounds is it necessary to take into consideration the hemodynamic events in REM sleep stage that might have initiated myocardial ischemia. However, the beat-to-beat measurement of heart rate in individual cases has shown that the increase during REM sleep is less than 10 beats per min. as compared with that in the preceding NREM sleep stages, which seems to be too small a change to induce sudden increase of myocardial oxygen consumption with this sole index.

Though recording of blood pressure has not been made so far in our study, Snyder10) has reported 4% rise of blood pressure with more distinctive fluctuations during REM sleep stage as compared with stage II, and Khatri11) et al. have noted that the mean increase of blood pressure is 6.4 mm.Hg over the preceding period (mean value 99.6 mm.Hg), accompanied by slightly increased sympathetic discharge indicated by digital plethysmogram. Admitting the augmented sympathetic tone during REM sleep stage and high frequency of episodes in the same stage, it is sure from the currently available data that the hemodynamic features in this stage do not offer a sufficient explanation for the mechanism of nocturnal angina for their seeming persuasiveness. Actually, there are observations12),13) that do not support the association of anginal attack with REM sleep, and we also have cases whose episodes are not associated with it.

Regardless of sleep stages, changes in heart rate in the course of episodes of myocardial ischemia in the present study did not precede the onset of ECG changes, but mostly coincided with or, in some cases, followed the latter. According to the studies made by Roughgarden,14) who made continuous monitoring of systemic arterial pressure in patients with spontaneous angina pectoris, the elevation of blood pressure preceded the ST segment shift in 7 out of 17 attacks, occurred simultaneously in 4, followed it in 4, and the average increase over control levels was 24% in systole and 26% in diastole at the onset of pain. Though he concludes that blood pressure rise is related to the cause of anginal pain, not the result of pain, the cause per se is not commente due to the inconsistent data as to which one of both parameters precedes the other.

It is to be noted here that the conventional ECG from body surface has its own limitations in revealing the early localized events of the myocardium and the ST,T changes recorded on ECG are produced only by the ischemic myocardial damage severe enough to be detected by chemical and hemodynamic parameters.15)

The above discussion leads us to the assumption that the ischemic episodes of nocturnal angina is precipitated by another unknown cause, rather than the secondary effects to hemodynamic changes that occur during sleep. Support
is also gained from the negative responses in our patients to exercise test which induces greater hemodynamic alterations.

Nowlin considers as significant in his particular case the reduced Pco₂ due to increased respiration during REM sleep, and Gorlin ascribes one of the possibilities to the fall in blood pressure at night, which may result in inadequate blood supply beyond the stenosed coronary artery. Guazzi et al. observed in patients with Prinzmetal's angina pectoris arterial hypotension and reduced cardiac output during attacks, and confirmed that these circulatory changes did not precede the ECG manifestations.

In unveiling the mechanism of non-exertional angina pectoris that is brought on without increased cardiac work, studies of circadian variations of hormones, like ADH, catecholamines, etc., would be an important clue for pursuing unknown triggering factors of the attack.

References