

Sleep and Ventricular Premature Beats

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SUMMARY

Sixty-nine 24-hour electrocardiographic monitoring sessions were conducted in 54 ambulatory subjects. Thirty-one had coronary heart disease (CHD); 11 had miscellaneous heart ailments; and 12 were free of any heart disease. Monitoring was accomplished with a miniaturized cassette recorder and ventricular premature beats (VPBs) were analyzed as to incidence and grade. The occurrence of VPBs during sleep hours was compared to the awake state.

In 22 patients, the incidence of VPBs was reduced by at least 50% during sleep. An additional 13 patients showed a reduction of 25 to 50%. If patients free of ectopic activity during 24-hour monitoring sessions are excluded from analysis, then in 35 of 45 patients, or in 78%, sleep was associated with a lowered occurrence of ventricular extrasystoles. During sleep the VPB grade was likewise lowered. Thus the mean grade for 45 patients changed from 2.75 while awake to 1.78 while asleep. It is of interest that in a number of these patients, trials of various antiarrhythmic drugs were less effective than sleep in reducing the incidence and grade of VPBs. It is concluded that treatment of sporadically occurring ventricular ectopic activity in some patients may require attention to the neurophysiologic trigger rather than the cardiac target.

Additional Indexing Words:

Monitoring Ventricular ectopic activity

Ventricular tachycardia Neural activity

VENTRICULAR ectopic beats are sporadic and seemingly random in occurrence. The reason for their emergence precisely at any moment in time remains obscure even in patients with significant heart disease; in most instances, no immediate provocative factor can be identified. The development of extrasystoles without apparent cause in healthy subjects suggests that there may be mediating agencies extrinsic to the heart. Physicians have long been aware that psychologic and neural factors may affect heart rhythm. Irregularities in pulse due to emotion were already appreciated by Galen in the Roman era. The passage of two millenia has provided much anecdotal information relating cardiac arrhythmia to psychologic factors, but hard clinical facts continue to be meager.

The sleep-wakefulness cycle represents a marked diurnal variation in behavioral and neural activity. Yet day-night alterations in cardiac rhythm have not been adequately studied. This is surprising, for 50 years ago the noted physiologist MacWilliam called attention to the fact that sleep was at times associated with profound cardiac alterations.¹ He emphasized that sleep represents a continuous shift between disturbed and sound phases and that "circulatory changes in disturbed sleep are sometimes so very pronounced that it is remarkable they should so long have escaped observation."

The present investigation addresses itself to one preliminary aspect, namely, the diurnal variation in the frequency and pattern of ventricular premature beats (VPBs) in patients with and without heart disease.

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Material and Methods

The Population

Sixty-nine 24-hr electrocardiographic monitoring sessions were conducted on 54 ambulatory subjects. Heart disease was present among 42 and is detailed in table 1. Of the 31 patients with coronary heart disease (CHD), 28 had sustained a previous documented myocardial infarction while three were afflicted with angina pectoris. Eleven patients, six males and five females, had diverse cardiac disease, while 12 subjects were free of organic cardiovascular problems.

The mean age for those with CHD was 55, with a range of 33 to 76 years. Eleven of these patients had sustained myocardial infarction in the preceding 12

Table 1
Types of Heart Disease Among 54 Monitored Patients

	Number	Male	Female
Coronary heart disease	31	28	3
Miscellaneous heart disease	11	6	5
Rheumatic	4		
Cardiomyopathy	2		
Ruptured chordae	1		
Atrial septal defect	1		
Hypertensive	1		
Undetermined	2		
No heart disease	12	8	4

months, five within two years, four within three years and in the remaining eight the interval exceeded three years. In 21 patients the monitoring was routine and not occasioned by the presence of known or troubling arrhythmia. In 10 patients, monitoring was instituted because of arrhythmia; in three of the 10 patients the mechanism was atrial fibrillation; in three VPBs were present; in two there was paroxysmal ventricular tachycardia; one had atrial flutter and one had experienced a single episode of ventricular fibrillation. Twelve of the patients were receiving antiarrhythmic drugs: three, procaine amide; six, quinidine sulfate; and three, propranolol. The latter drug was being administered for severe angina pectoris. None of these drugs was withheld during the study.

The 11 patients with heart disease other than CHD ranged in age from 33 to 68 with a mean of 54.2 years. Eight were monitored routinely, while three patients were monitored because of one of the following recurring disorders: frequent VPBs, ventricular tachycardia, or ventricular fibrillation.

The 12 patients without heart disease, ranging from 26 to 68 years, had a mean age of 48. All were monitored because of some symptoms such as palpitation, dizziness, weak or fainting spells, possibly ascribable to arrhythmias or the known presence of VPBs.

Monitoring Equipment

Continuous electrocardiographic recordings were obtained by means of a portable cassette tape unit.* The recorder measures $13.5 \times 10.3 \times 4.8$ cm and weighs with batteries and carrying pouch 680 g (1.5 lbs). The unit is powered by two 7-volt type TR 135 mercury batteries. It is driven by an AC synchronous motor at a tape speed of approximately 2 mm/sec. FM recording is utilized to obtain a frequency response of 0.3 to 25 Hz. Standard Phillips type C-120 cassettes permit data acquisition for a period of 24 hr on each side of the cassette.

Patients were coupled to the monitoring apparatus with standard disposable silver-silver chloride electrodes, employing a modified lead II placement. One

lead was positioned in the second right intercostal space at the sternal border and the other lead was in the fifth left intercostal space at the left anterior axillary line. The compact recorder was attached to a belt worn around the waist and did not interfere with strenuous activity or even vigorous exercise. An hourly event card was provided for checking off activities such as eating, smoking, exercise, bowel movements, the occurrence and type of symptoms and drug ingestion. The importance of recording the time of going to bed, the approximate time of falling asleep, and the precise time of waking up was emphasized to each participant in the study. The patient was advised to omit sleeping medication during the monitoring session; all but five did so. No other drugs were prescribed. Patients were instructed to proceed with their routine activities and not to avoid their usual daily stresses.

Data Reduction

Analysis of the 24-hr continuous ECG records was accomplished with a high speed playback analyzer running at 60 times real time, and a low speed paper recorder. Tapes were played back on an Auricord cassette deck and analyzed by a trained operator. Audio-visual techniques using an R wave triggered oscilloscopic display and an ECG coupled sound system enabled detection of VPBs. The technician employed a special hand counter to record cumulatively the frequency of VPBs per minute on a trend record which simultaneously charted heart rate. A slow speed display and printout permitted clarification of questionable high speed observations. When an arrhythmia was detected that portion of the tape was rerun at normal speed and recorded. The printed record of all the arrhythmias was checked by a physician. Cassettes were not erased and were replayed by two other technicians for verification of the initial data acquisition.

Frequent VPBs exceeding one per minute cannot be accurately analyzed with the high speed system. This necessitated employment of additional methods for data reduction. Various sampling techniques were developed. The cassettes were replayed twice real time, permitting 24 hr tape review in 12 hr. Tandem recycling clocks were preset to activate the paper chart printout at fixed intervals for fixed durations. These were run during the night, thus freeing the playback analyzer for daytime use.

All tapes were scanned at 60 times real time and then classified into one of three categories:

1) *Low VPB frequency*—VPBs occurring at less than one per minute during each hour of the monitoring session. In this category the initial scanning proved adequate for precise definition of frequency and grade of ectopic activity. These tapes were not processed further.

2) *High VPB frequency*—VPBs occurring with an incidence in excess of three per minute. These tapes were reviewed with the sampling technique. The sampling intervals consisted of 30 sec printout every 20 min or 15 sec printout every 10 min. This provided 36 min real time printout for a 24 hr period of monitoring or 2.5% of the available data. Both of these methods

* Developed by American Optical Company, Framingham, Massachusetts.

Table 2

Incidence of Ventricular Premature Beats (VPBs) During Sleeping Compared to Waking Hours in 54 Patients, Monitoring Sessions

Diagnosis	Alteration in incidence of VPBs								Totals	
	Substantial decrease		Marginal decrease	No change		Increase	No VPBs			
	Patients	Sessions	Patients Sessions*	Patients	Sessions	Patients/ Sessions*	Patients	Sessions	Patients	Sessions
Coronary heart disease	13	17	10	4	4	1	7	8	35†	40
Miscellaneous heart disease	5	5	1	2	4	1	2	2	11	13
No heart disease	4	7	2	2	2	0	5	5	13‡	16
Total	22	29	13	8	10	2	14	15	59	69

* When there is identity between numbers of patients and sessions, these are not separated.

† In four patients monitored two sessions each there was a difference in sleep-wake findings. Each result is presented accounting for the number exceeding the 31 CHD patients studied.

‡ One patient monitored twice showed a discrepancy of result and thus appears twice.

yielded identical results as to grade and frequency of ectopics. On the basis of these samples the VPB incidence per hour was estimated.

3) *Moderate VPB frequency*—VPBs ranging in incidence from one to three per minute and highly random in occurrence. This required more tedious processing. In such instances, scanning techniques established the time of development of VPB clusters and sampling time was then lengthened to record in real time their occurrence.

Data Analysis

For each monitoring hour the incidence and grade of VPBs were determined. The grading system has been previously described² and assigns VPBs into one of the following categories: 1) occasional VPBs, 2) frequent VPBs (greater than 30/hr or 1/min), 3) multiform VPBs, 4) repetitive VPBs, a) pairs (2 consecutive ectopics), b) runs (3 or more in sequence), 5) early VPBs (R on T).

Sleep periods were determined from the patient's activity card. The recorded trend in heart rate reduction provided supporting evidence that sleep occurred. Since there was no certainty as to the precise time of falling asleep, the hour in which the patient indicated that this occurred was excluded from the sleep-awake analysis.

The average hourly incidence during waking hours as

well as the highest VPB grade achieved was determined. A similar determination was carried out for the hours the patient slept. Sleep-awake periods were compared if there were at least 10 VPBs during one of these diurnal cycles. For a change in VPB frequency in the two periods to be regarded substantial, the average hourly incidence during waking hours had to differ by 50% or more from the average obtained during sleep hours. Changes from 25 to 50% were regarded as marginal. For a change in grade to be deemed significant, alteration by at least one grade was required, with 4a and 4b considered to be different grades. For statistical calculation 4b was assigned a numerical value of 4.5. Student's paired *t*-test was used for statistical analysis.

Results

General Findings

Of the 54 patients, 45 (83.3%) demonstrated some ventricular ectopic activity during at least one 24-hr monitoring session. VPBs were observed in 54 of the 69 sessions (78.3%). Sleep was associated with a reduction of 50% or greater in the incidence of VPBs among 22 patients during 29 monitoring sessions. A decrease between 25 and 50% was noted in 13 additional patients. Thus 35 of the 54 patients

Table 3

Change in Grade of VPBs During Sleep in 45 Patients with Ectopic Activity During 24-Hour Monitoring

Type of heart disease	Patients (number)	Sessions (number)	Mean Grade		P value
			Awake	Asleep	
Coronary heart disease	28	32	2.6	1.6	< 0.001
Miscellaneous heart disease	9	11	3.5	2.8	< 0.1
No heart disease	8	11	2.4	1.2	< 0.025

Table 4

Grade of VPBs Observed as well as Maximum Grade Reached During Each of 40, 24-Hour Monitoring Sessions, in 31 Ambulatory Patients with CHD

Grade of VPB	Grade observed	Number of sessions Maximum grade reached
0	8	6
1	17	12
2	13	0
3	15	9
4a	7	7
4b	2	2
5	4	4

(64.8%) exhibited a lessening VPB frequency during sleep (table 2). These findings become more striking if the nine patients who were free of arrhythmia throughout the 24-hr monitoring session are excluded from the analysis. Of the 45 patients who exhibited ectopic activity, 35 or 77.7% showed a decrease. In nearly half of these patients the mean hourly incidence during sleep was reduced by 50% or more as compared to those patients observed during waking hours. The tendency for sleep to be associated with a reduction in VPBs was observed in patients with far advanced heart disease and congestive failure as well as in subjects without any cardiac ailments.

In addition to the reduction in VPB incidence during sleep there was also a lessening in grade (table 3). Thus in 54 monitoring sessions among 45 patients with ectopic activity, there was a change in maximum grade from 2.74 while awake to 1.76 during sleep ($P < 0.001$). The extent of grade alterations in the three groups of patients is detailed

Table 5

Change in Maximum Grade of VPBs During Sleep as Compared to Awake Hours. Analysis Based on 22 Patients (29 Monitoring Sessions) Who Showed a 50% or Greater Reduction in Incidence of Ectopic Activity.

Diagnosis	Monitoring sessions	Number of sessions with reduction during sleep by:			
		3 grades	2 grades	1 grade	0 grade
Coronary heart disease (13)*	17	3	3	5	6
Miscellaneous heart disease (5)	5	1	2	1	1
No heart disease (4)	7	2	1	2	2
Total	29	7	6	8	8

* In () are number of patients in each group.

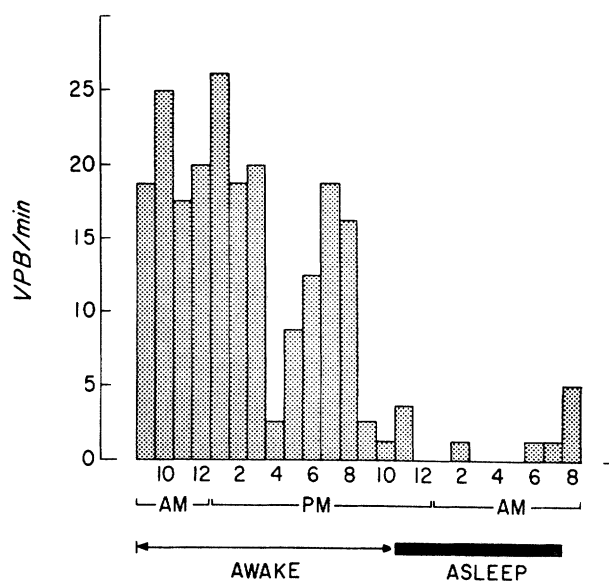
in table 3. In 12 of the 54 sessions (22%) VPBs disappeared entirely during sleep.

Coronary Heart Disease (CHD) Patients

The 31 patients with CHD were monitored 40 sessions for a total of 960 hours. The distribution of VPBs by grade as well as by maximum grade achieved during a single session is presented in table 4. Of interest is that in none was grade 2 the highest grade achieved. This is accounted for by the fact that whenever VPBs were frequent, they were invariably multiform or repetitive.

Among the 28 CHD patients with ventricular ectopic activity, 13 patients during 17 monitoring sessions showed a decreased incidence of 50% or greater during sleep (table 5). There was also reduction in highest grade observed during waking hours, 2.6, to 1.6 during sleep ($P < 0.001$). The following patient is representative of this group:

A 63-year-old man, C.E., had sustained an acute transmural myocardial infarction two years earlier. While awake he experienced frequent and multiform VPBs. He was not receiving any antiarrhythmic drugs. During 15 waking hours ectopic activity was never less than 2/min and was frequently bigeminal in pattern. During nine of these hours the frequency of VPBs exceeded 15/min. However, during five of his sleeping hours, ectopic activity was entirely absent (fig. 1). When he was

**Figure 1**

(C.E.—Patient with CHD.) During five of eight sleep hours, the incidence of VPBs was consistently less than 1/min; during all waking hours, the arrhythmia was of Grade 2 with frequent bigeminy.

remonitored three weeks later, an identical diurnal pattern in VPB distribution was observed (fig. 2). Peak ectopic activity occurred during early morning hours, reaching a level of 25/min. Thereafter VPBs decreased and during five sleep hours no ectopic activity was encountered.

In all patients progressive reduction in heart rate was observed during sleep; an example is illustrated in figure 3. The frequency of VPBs did not appear to correlate with the minute-to-minute variation in heart rate. In a number of these patients when the heart rate reached its lowest level toward late sleep, there was a resumption or increase in incidence of VPBs. Ectopic morphology frequently altered during sleep. This was observed in 10 of the 17 sessions demonstrating a greater than 50% reduction in VPB activity during sleeping as compared to waking hours (fig. 4).

In 10 patients with CHD subjected to 10 monitoring sessions, the VBP incidence nocturnally was reduced by less than 50% compared to the mean for waking hours. None of these patients experienced advanced grades of arrhythmia. Ventricular ectopic activity was at a low level, rarely exceeding 2/hr and occurred only in a fraction of the waking hours. VPBs were noted in 29% of the 16 waking hours, compared to 12% of seven sleep hours.

In four patients no change in incidence or grade of VPBs was noted during sleep. These patients had a high frequency of ectopics: in one, grade 3; in two, grade 4a; and in one, grade 4b. Only one patient showed an increase of ectopic activity during

sleep. The reason for this is not clear. All five of these patients had taken sleeping pills and were the only CHD patients to do so.

Miscellaneous Heart Disease

Thirteen monitoring sessions were conducted among this diverse group of 11 patients (tables 1 and 2). Five of these patients were receiving digitalis and diuretic drugs. Six of nine patients with arrhythmia showed a reduction in incidence of VPBs during sleep. The mean grade was altered from 3.5 while awake to 2.5 while asleep ($P = 0.05$). In three patients the reduction was by at least two grades (table 5). One of the two patients afflicted with cardiomyopathy is of particular interest.

R.B. was a 62-year-old man with a long history of heavy alcohol consumption. Congestive heart failure developed four years earlier and progressed to recurring pulmonary edema. Cardiac catheterization showed left ventricular (LV) end-diastolic pressure of 20 mm Hg, a cardiac index of 1.5 L/min, an ejection fraction of 20%, and uniformly poor ventricular wall motion. Coronary angiography revealed none of the major vessels to be narrowed by more than 50%. Frequent but asymptomatic ventricular ectopic activity was consistently observed during daytime monitoring, with a pattern of ventricular bigeminy: the highest grade of VPBs reached was 4a. He had experienced difficulty in sleeping, falling off to sleep only after 2:00 a.m. During the ensuing four hours of sleep, though the

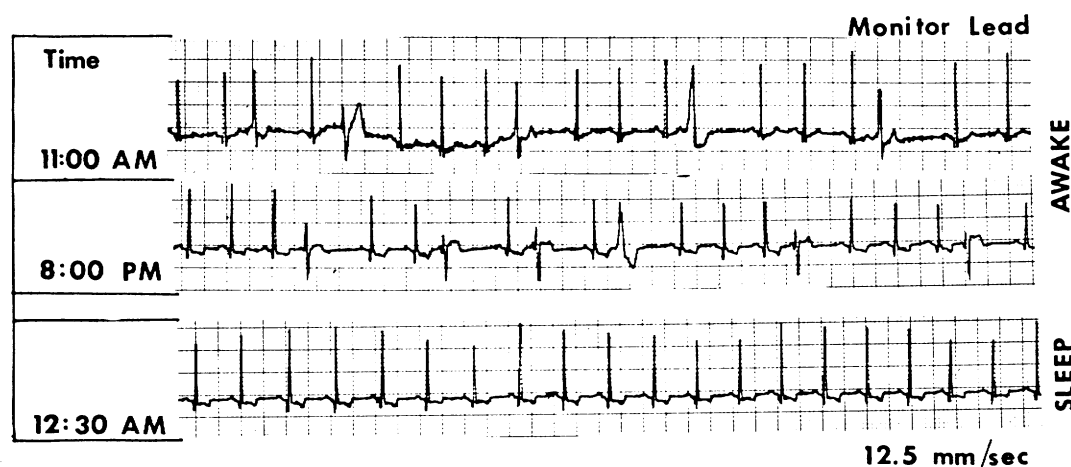


Figure 2

(C.E.—same patient as shown in fig. 1.) In the morning during second monitoring session both ventricular and atrial ectopic beats prevailed. In early evening (8:00 p.m.) the VBP's were multiform, bigeminal and quadrigeminal. During sleep extrasystoles disappeared. The sinus rate at these three times was 74, 78, and 78/min, respectively.

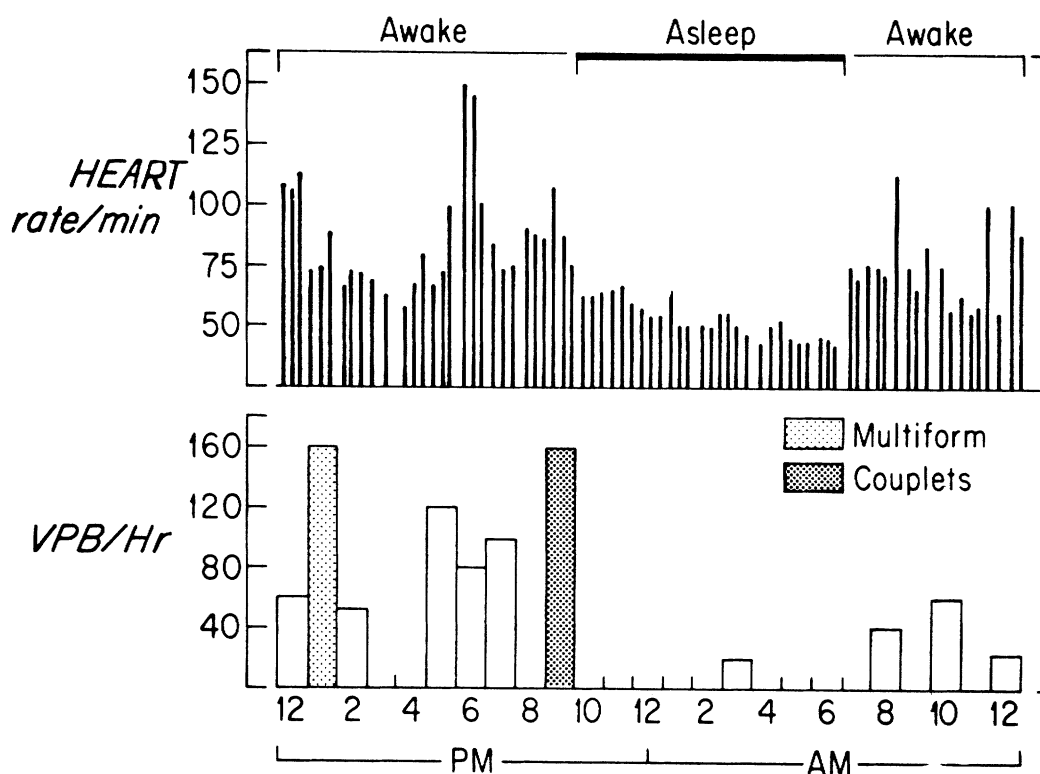


Figure 3

(J.B.—43-year-old man with old diaphragmatic transmural infarction.) With onset of sleep Grade 2 VPBs were abolished. There was a progressive slowing in heart rate during the night. Upon awaking there was a recurrence of VPBs.

heart rate continued to be rapid, VPB frequency was reduced to 35/hr and did not exceed grade 1. At 6:00 a.m., when the lowest heart rate was reached, VPBs disappeared entirely only to increase rapidly upon awaking shortly thereafter (fig. 5).

Subjects Without Heart Disease

This group included 12 subjects, all of whom were monitored because of the presence of VPBs or of symptoms suggestive of arrhythmia. Five were entirely free of ectopic activity during the 24-hr monitoring period. Four of the remaining seven patients showed a substantial decrease in VPBs during sleep. In three patients VPBs were completely absent during sleep. Of interest is the fact that in the absence of heart disease, unlike in patients with CHD, frequent VPBs were not associated with higher grades of arrhythmia. In five of 11 monitoring sessions, grade 2 was not accompanied by multiformity or repetitive firing. One patient who was monitored three times at weekly intervals deserves brief comment.

S.B., a 34-year-old asymptomatic mother of three, was observed to have transient T wave inversions

and frequent ectopic beats following a cholecystectomy one year earlier. There was no evidence of heart disease. The resting electrocardiogram, except for frequent VPBs, was normal. Maximal treadmill exercise testing was negative. She was initiated on 4.0 g of procaine amide daily resulting in a blood level of 6.0 $\mu\text{gm/ml}$ without effect on ectopic activity. An increase in procaine amide to 6.0 g daily provoked adverse reactions. Quinidine sulfate 0.4 g four times daily resulted in a blood level of 4.5 $\mu\text{gm/ml}$ and reduced the incidence of VPBs. The addition of propranolol, initially in a dose of 80 mg and then 160 mg daily (blood level 68 ng/ml), appeared to attenuate the arrhythmia further (fig. 6) but did not abolish ectopic activity. However, during each of the three monitoring sessions, VPBs were markedly reduced during sleep and were entirely absent two nights.

Reproducibility of Sleep-Wake Changes

To determine reproducibility of sleep-wake changes, 13 subjects were monitored a total of 28 sessions. The mean interval between monitoring sessions was one week. The group consisted of nine

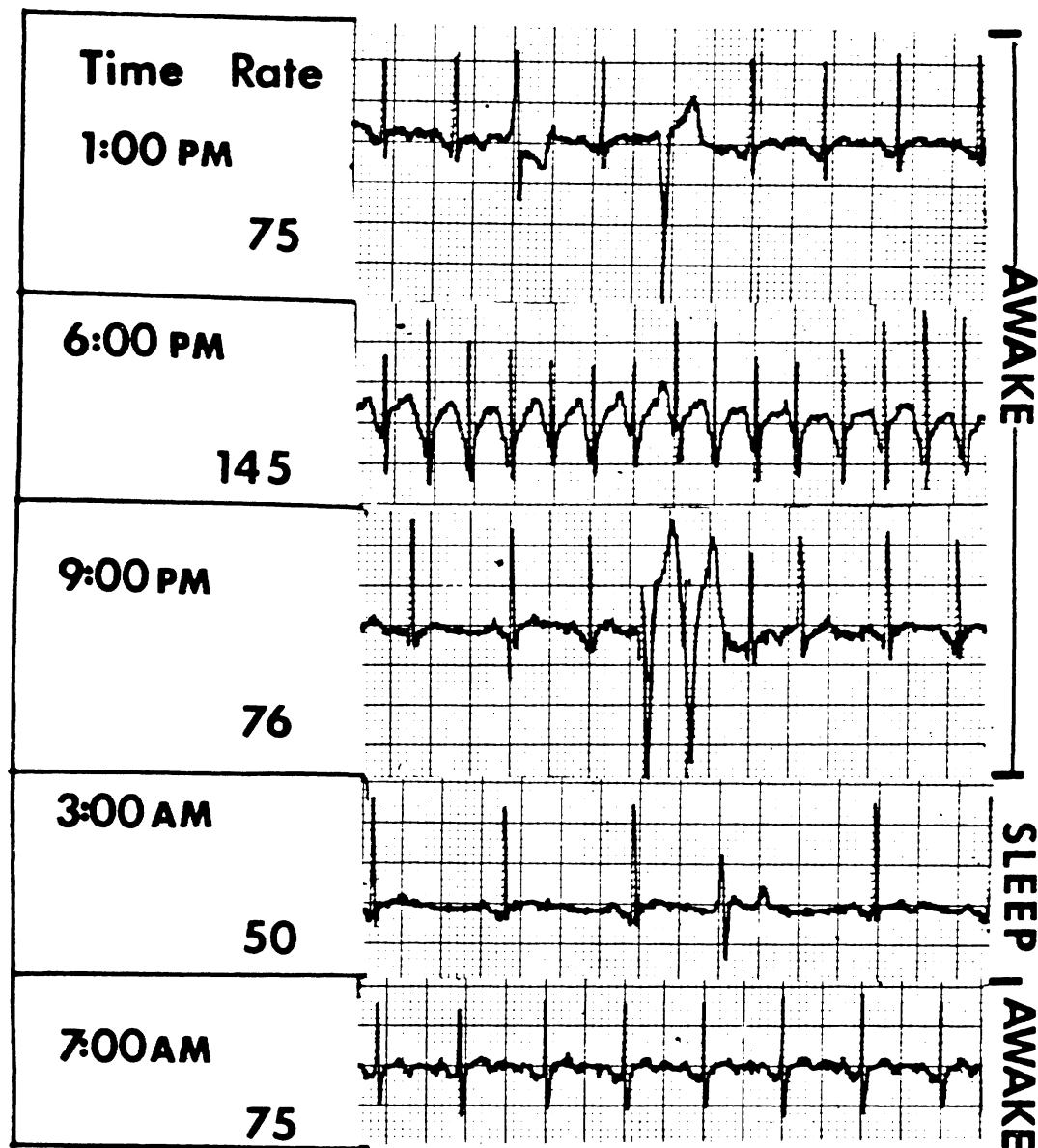


Figure 4

(J.B.—same patient as shown in fig. 3.) Frequent and multiform VPBs disappeared during vigorous game of tennis at 6:00 p.m. with heart rate acceleration to 145/min. Couplets were observed while he was resting and reading quietly at home. During sleep the heart rate decreased to 50/min, a new ectopic morphology developed—a junctional focus with aberration cannot be excluded (paper speed 12.5 mm/min).

females and four males. CHD was present in nine, one had cardiomyopathy, and three were without heart disease. One patient was free of VPBs during two 24-hr monitoring sessions. In eight of the 13 patients, or in 61.5%, the same maximum VPB grade was observed upon repeated 24-hr monitoring. A consistent decrease in VPB incidence during sleep in successive monitoring occurred in six patients (46%). No reproducibility in sleep-wake comparison was observed in five patients (38.5%). One of these

patients with grade 4a arrhythmia on two monitoring sessions while awake showed a decrease during the first night, but on the second occasion, when sleep was interrupted by gas pains, the incidence of VPBs remained unaltered.

Other Observations

While a decrease in ventricular ectopic mechanisms was evident during sleep, atrial arrhythmia appeared to increase. Atrial premature beats were

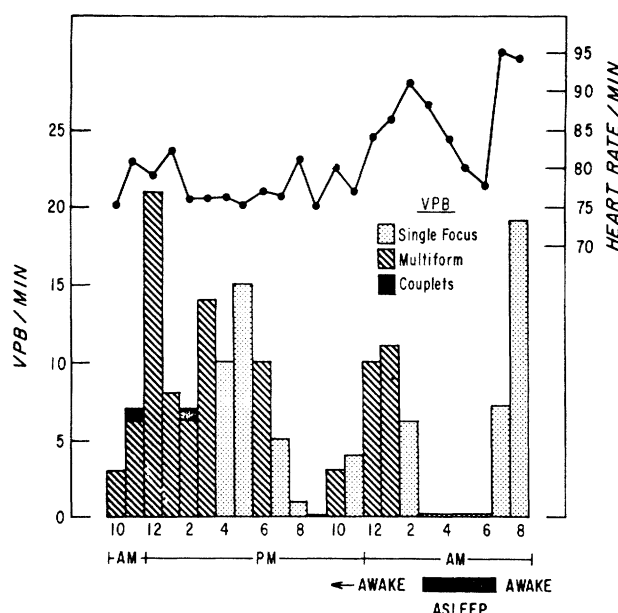


Figure 5

(R.B.—patient with cardiomyopathy.) Exhibited multiform VPBs during the majority of hours while awake. When the patient finally slept, there was a striking reduction in VPB incidence. Though the heart rate decreased during sleep, it was more rapid than during the majority of waking hours.

more numerous during sleep than during waking hours. Many patients exhibited brief paroxysms of supraventricular tachycardia, even when sleep subdued the frequency of ventricular ectopic activity. Episodes of sinus bradycardia and sinus pauses with shift to a junctional mechanism punctuated by bursts of complex atrial ectopic rhythms were common. The precise definition of these nocturnal changes awaits further technologic development in methods for reducing monitored data relating to atrial and junctional arrhythmia.

Discussion

Until a few decades ago sleep had been viewed as a unique passive resting phase of the brain, "the diastole of the cerebral beat."³ Modern sleep psychophysiology had its inception with the pioneering investigations of Asserinsky and Kleitman⁴ and Dement and Kleitman⁵ who discovered regularly recurring sleep cycles. These were distinguished by rapid eye movements (REM) and EEG patterns associated with alert wakefulness which correlated with the recall of dreams. The generalization emerging from these findings is that during sleep the brain, and the peripheral nervous system under its control, undergo continuous oscillations in activity with a periodicity approximating 90 minutes.

Sleep has been arbitrarily divided into five stages depending upon distinctive polygraphically recorded physiologic activity. While a good deal of data has been accumulated relating stages of sleep to heart rate and blood pressure changes, there is very limited information on the effects of sleep in patients with cardiac disease. Nowlin et al.⁶ correlated the occurrence of nocturnal angina with REM periods. During desynchronized REM sleep they observed significant ST-segment depressions even when the patient was not awakened by anginal discomfort. Karacan, Williams and Taylor⁷ found no such association between nocturnal angina and the REM state; they did note that patients with angina experienced fewer shifts in the stages of sleep than control subjects.

The literature on the effects of sleep on heart rhythm is noteworthy for its poverty of meaningful observations. In one limited study of 13 subjects with premature beats, ectopic activity appeared to be more frequent during REM periods and sleep stages 3 and 4. Arrhythmias also occurred while awaking from any stage.⁸ The prominence of arrhythmia during deep sleep stages was ascribed to bradycardia. In a second study, 17 patients with VPBs were monitored electroencephalographically as well as for heart rhythm for a period of 6.5 hr while in a coronary care unit.⁹ Eight patients had acute myocardial infarction, eight had diverse heart disease and one had digitalis intoxication. During the nocturnal monitoring, occurrence of ventricular and atrial extrasystoles did not vary in the different stages of sleep or in the awake as compared to asleep periods. The highest frequency of VPBs was noted during sleep-wake transitions. No consistent relation could be established between emergence of ectopics and altered heart rate. One additional notation has been published on sleep and cardiac arrhythmia involving a 48-year-old woman with psychiatric problems, factitial skin ulcers, VPBs and recurrent paroxysms of ventricular tachycardia.¹⁰ Various antiarrhythmic drugs were ineffective. It was observed repeatedly that when she slept all ectopic activity disappeared.

The focus of the present study was limited to examining the incidence and grade of VPBs during the sleep period compared to the awake state. A reduction was observed in nearly 80% of 45 patients who exhibited arrhythmia during daytime monitoring. Since onset of sleep could not be precisely and objectively defined, this conclusion is in need of critical examination. The exclusion from the analysis of the transitional hour between wake and sleep

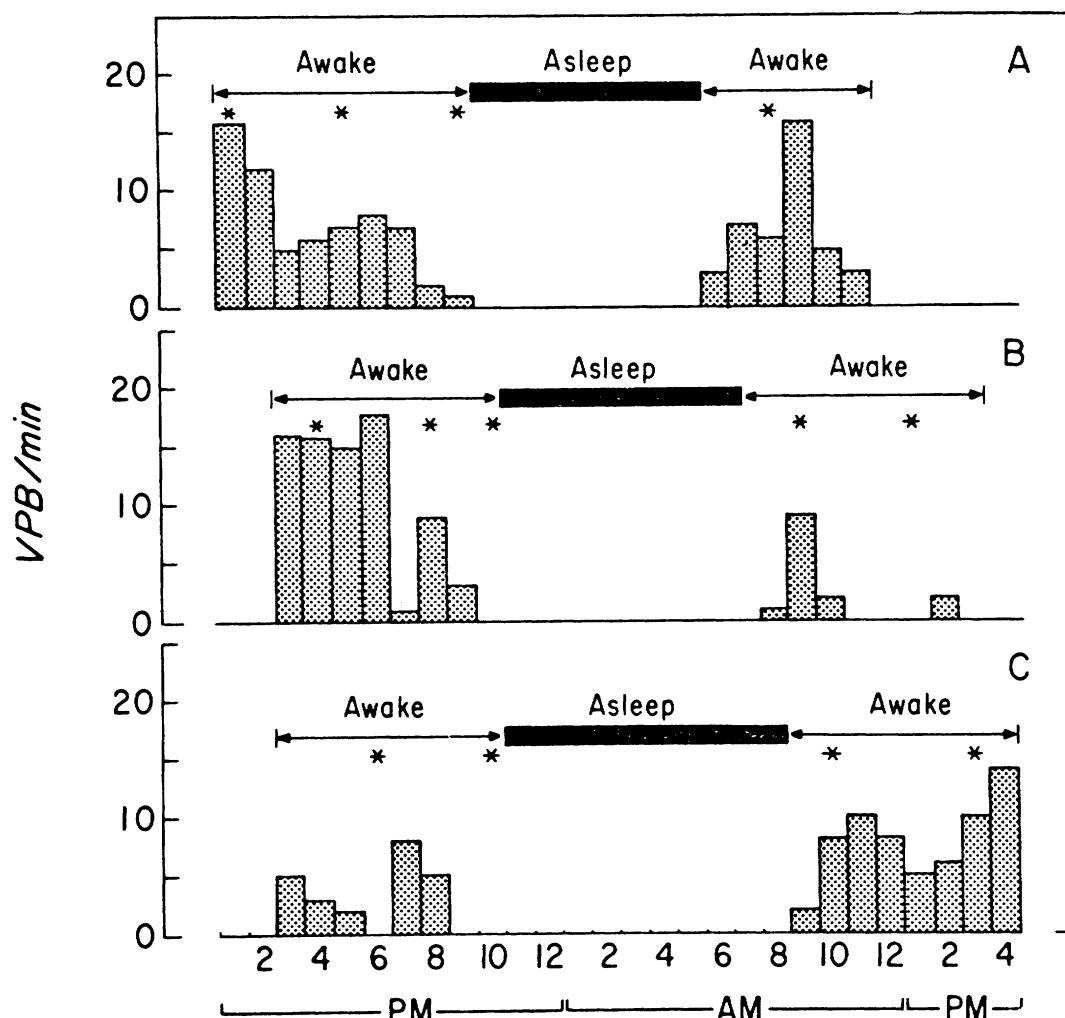


Figure 6

S.B. was monitored three successive 24-hr sessions at weekly intervals. With sleep there was nearly a total disappearance of VPBs. This change was greater than that observed following ingestion of antiarrhythmic drugs, the time for which is indicated by asterisks. (A) Patient received 0.4 g of quinidine. (B) Quinidine was continued, but 20 mg propranolol was added. (C) The dose of propranolol was increased to 40 mg.

stages enhanced accuracy of the comparison. It is unlikely that patients would have erred by more than one hour in defining onset of sleep. If such an error were made by each patient, which is highly improbable, and sleep had been adjudged to have occurred earlier than it actually did, the average incidence of ectopic activity during sleep would have been overestimated by about 14%. If, conversely, sleep actually occurred later, the average incidence of VPBs while awake would have been underestimated by about 7%. In either case, the error would have tended to bias against rather than for the reported result.

Patients slept at home and in their own beds. This afforded a great advantage over the unnatural

environment of a sleep laboratory. On the other hand, it accounts for a major limitation of the present study, namely, the absence of objective data on sleep and its stages. It is uncertain whether sleep was consistently maintained during the period indicated by the patient. However, if some of the patients had slept poorly or not at all, there might have been an increase in incidence and grade of VPBs during such periods. This would dilute the observation that sleep reduced ventricular ectopic activity.

Of the 54 subjects studied, 42 had heart disease; in the majority the process was stable and of prolonged duration. The finding of a reduction in VPBs with sleep may not apply when the cardiac

disease is acute and unstable. Indeed, a somewhat different result was obtained among patients convalescing from acute myocardial infarction (Kerzner and Lown, unpublished observation). In eight of 48 such patients (17%), there occurred either aggravation of pre-existing arrhythmia or development of ectopic mechanism during sleep not recorded while awake. In five of these eight, VPBs increased either in frequency or grade during sleep. The remaining three patients showed ventricular arrhythmia only while asleep; one patient had ventricular tachycardia, a second had bigeminy, while the third had occasional VPBs.

With sleep the heart rate decreases progressively throughout the night reaching its nadir at about the sixth hour.¹¹ One might therefore have anticipated a nocturnal increase rather than diminution in VPBs. Han et al.¹² have demonstrated that ventricular ectopic beats were more likely to develop in the experimental animal when the basic rate was slow. This was true whether the precipitating agency of ectopic activity was coronary occlusion, sudden elevation in left ventricular pressure or hypothermia. These investigators have also noted that temporal dispersion of refractory period duration was augmented by slow rates.¹³ Thus bradycardia would also favor repetitive ectopic activity on the basis of reentrant excitation. An association between slow heart rates and ventricular arrhythmia is known to occur in man under diverse clinical circumstances. Carotid sinus massage may provoke ventricular extrasystoles in patients with CHD.¹⁴ Digitalis intoxication-induced ventricular ectopic rhythms can be exposed by a diversity of measures which slow the basic frequency including vagal stimulation,^{15, 16} administration of rauwolfia alkaloids,¹⁷ beta adrenergic blocking drugs,¹⁸ and the injection of succinylcholine.¹⁹ In patients with atrial fibrillation, early ectopic beats develop more frequently after relatively long ventricular cycles.²⁰ Complete heart block is associated with a high incidence of ventricular arrhythmia promptly subdued by accelerating the heart rate. In sleep, this prevalent tendency associating slow heart rates with ventricular ectopic activity appears to be diminished or annulled.

The reduction in VPBs during sleep was most marked in patients without heart disease. Thus three out of seven of these subjects lost all ectopic activity while asleep. This was observed in only nine of the 28 patients with CHD and in none of the nine patients with miscellaneous forms of heart disease. This latter group had the largest number of

patients with congestive heart failure. It may well be that reduction in cardiac work load during sleep is a contributory factor to the salutary effect on ventricular arrhythmia. During sleep, in addition to the slowing in rate, there is a reduction in blood pressure. In the normal young adult blood pressure reaches a nadir within 1.5 to 2.5 hr after onset of sleep; thereafter, it rises through the night to attain its basal level shortly before awaking.²¹ In normal as well as hypertensive patients, the fall in blood pressure has been ascribed to reduction in total peripheral resistance.²² A modest decrease in cardiac output has also been noted.²³ The above cited hemodynamic changes do not coincide temporally with the abatement of arrhythmia. The decrease in VPBs is noted with the very onset of sleep at a time when measurable hemodynamic alterations have not yet occurred. If a change in hemodynamic load was of importance in the present study, one would have anticipated phasic variation in ectopic activity throughout sleep coinciding with REM state, during which cardiac work is augmented. This was not observed. Hemodynamic variables are probably not the decisive factors accounting for the lessening in VPBs during sleep.

Heart rate changes and other cardiac alterations during sleep are mediated by both sympathetic and parasympathetic neural outflow^{24, 25} and are abolished after complete cardiac denervation.²⁴ Cardiac automaticity and excitability, like heart rate, are carefully tuned by sympathetic discharge.²⁶ Because of partial sympathetic withdrawal during sleep there is a rise in threshold to artificial pacing. In a patient with complete heart block, pacing ceased with sleep only to be restored immediately upon awaking.²⁷ In the present study, the observed reduction during sleep in VPB incidence and grade may therefore be related to lessened sympathetic tone. If this is indeed a key factor, it is hard to account for the failure of large doses of propranolol to reduce VPBs in three patients, though such a result was observed with sleep alone.

While the specific neural mechanism responsible for altered ventricular ectopic activity with sleep remains to be defined, there can be little doubt that higher nervous activity is implicated. Furthermore, it appears that this neural effect is highly potent, for in a number of patients sleep reduced VPBs when antiarrhythmic drugs such as quinidine, procaine amide, and propranolol were without effect. It may be that for many patients with paroxysmal ventricular arrhythmia the pharmacologic focus should be

in restraining the neurophysiologic trigger rather than in attempting to protect the cardiac target.

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