Disordered Breathing and Hypoxia during Sleep in Coronary Artery Disease*

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The occurrence of breathing disorders and hypoxia during sleep was studied in 17 male patients with coronary artery disease, demonstrated by coronary angiography, who did not have symptomatic pulmonary disease. Thirteen patients (76 percent) experienced disordered breathing during sleep; of these, 11 had obstructive apnea and the other two had Cheyne-Stokes breathing. There was an average of 20 episodes of disordered breathing per hour during sleep among the 13 patients, with a mean duration of 24 seconds per episode; significant oxygen desaturation occurred in ten of these 13 patients. There was no episode of angina pectoris, myocardial infarction or sudden death. Although cardiac arrhythmias occurred in 12 patients, disordered breathing with hypoxia was not proven to be causative. Therefore, obstructive disordered breathing and nocturnal oxygen desaturation commonly occurred during sleep in patients with coronary artery disease. Although no immediate ill effects were noted, the longterm effects remain to be determined.

Coronary artery disease afflicts approximately four million Americans, with a predominance in men and increased incidence with age. Disordered breathing and oxygen desaturation during sleep also have a strong predominance in men correlating positively with increased age. This has been reported in normal subjects, as well as in a variety of conditions such as the Pickwickian syndrome, the syndrome of hypsomolence and periodic apnea, and in chronic obstructive pulmonary disease. The simultaneous occurrence of disordered breathing during sleep, with or without oxygen desaturation, and coronary artery disease has not been previously studied, although the common occurrence of angina pectoris, myocardial infarction or sudden death during sleep in patients with disease of the coronary arteries suggests that there may be an association. Block has recently hypothesized that nocturnal oxygen desaturation is likely to occur in patients with cardiovascular diseases and may contribute to the progression of those diseases as well.

This study was designed to investigate the incidence and short-term effects of disordered breathing and oxygen desaturation during sleep in patients with coronary artery disease.

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Methods

Seventeen patients with coronary artery disease, demonstrated by coronary angiography, were selected from the Medical Service of the Medical University Hospital and the Charleston Veterans Administration Hospital. All patients had symptoms of coronary insufficiency and seven occasionally complained of nocturnal chest pain. Since the occurrence of disorders of sleep and nocturnal hypoxia are well established in chronic obstructive pulmonary disease, patients were selected for this study who did not have a symptomatic coexistent pulmonary disorder. Patients with mild spirometric abnormalities were not excluded provided they did not have symptoms of chronic pulmonary disease. A 12-lead electrocardiogram was recorded in every subject while awake. Spirometric tests of pulmonary function were performed in 88 percent and analysis of arterial blood gases while awake, breathing room air, in 82 percent. The patients were admitted to the sleep laboratory of the General Clinical Research Center at the Medical University Hospital on the afternoon of the study. The details of the procedure were explained, after which the patients signed a consent form which had been approved by the Human Research Committee. That evening, following a light supper, they were connected to the various recording devices. The patient remained alone in a quiet, well ventilated, dimly lit room. All monitoring equipment was located in an adjacent room where at least one of the investigators was in constant attendance during the entire period of study. The patient was constantly observed by means of a one-way mirror and sound was transmitted by an intercommunication system. The following functions were monitored during sleep: 1) arterial oxygen saturation was continuously measured by ear oximetry (Hewlett-Packard 47201A); 2) airflow at the nose and mouth was detected by nasal and oral thermistors (Grass Instruments Company, model TCT 1-R); 3) chest wall and abdominal movements were monitored using external pneumographs; 4) a continuous electrocardiogram (MCL-1) was displayed on an oscilloscope (Hewlett-Packard, model 7803B) and with the other variables was continuously recorded on a multiple channel strip recorder (Hewlett-Packard, model...
myocardial infarct (one patient), unifocal premature ventricular contractions (two patients), sinus bradycardia (one patient) and early repolarization (one patient). Normal sinus rhythm was present in all of the patients except one who had atrial flutter-fibrillation. All of the patients had significant coronary artery disease as shown by coronary angiography. Five patients (29 percent) had one vessel disease with at least 50 percent occlusion, five patients (29 percent) had two-vessel disease, and seven patients (41 percent) had triple vessel disease. Eleven patients were taking propranolol (mean dose 142 mg/day) for control of angina pectoris. Two were taking quinidine (mean dose 300 mg/day) as an antiarrhythmic agent and seven were receiving digitalis (mean dose .25 mg/day).

The incidence of disordered breathing, oxygen desaturation and cardiac arrhythmias which occurred during sleep is shown in Table 1. All of the patients slept for a total period of at least 90 minutes, as shown by electroencephalographic analysis. Thirteen patients (76 percent) experienced disordered breathing during sleep; of these, 11 had obstructive apnea and the other two had Cheyne-Stokes breathing. There was no instance of central apnea. There was an average of 20 episodes of disordered breathing per hour during sleep among the 13 patients, with a mean duration of 24 seconds per episode (range = 11 to 72 seconds). Significant oxygen desaturation occurred in ten of the 13 patients who had disordered breathing. The average fall in oxygen saturation was 11 percent (range 6 percent-15 percent). Significant oxygen desaturation did not occur in the absence of disordered breathing.

Cardiac arrhythmias occurred in 12 patients (71 percent) during sleep. The types of arrhythmias found are shown in Table 1. In six of the 11 patients who had premature ventricular contractions (PVCs) during sleep, the PVCs occurred infrequently (four per hour or less); in the other five patients, the frequency of PVCs ranged from 18 to 42 per hour (mean of 28/hour). Every patient who had cardiac arrhythmias associated with hypoxemia and/or disordered breathing also had arrhythmias occurring independent of both phenomena. Five of the total of 17 patients (29 percent) had some of their cardiac arrhythmias associated with significant falls in oxygen saturation resulting from disordered breathing during sleep (range 9-11 percent saturation). None of the five had ectopic activity on the control ECG and only one was receiving an antiarrhythmic drug (quinidine). In seven patients, some of the arrhythmias were associated with disordered breathing without oxygen desaturation. No signifi-
sides may be the predominant initiating event precipitating direct and chemoreceptor-induced changes in heart rhythm, pulmonary and systemic pressures.\textsuperscript{13,14} Cardiac arrhythmias, pulmonary hypertension and systemic hypertension are all part of the sleep apnea syndrome and hypoxemia appears to play a central role in the production of those abnormalities.\textsuperscript{5,13,14} Nocturnal oxygen desaturation occurs frequently in chronic obstructive pulmonary disease (COPD)\textsuperscript{7-10} resulting in significant morbidity. Cardiac arrhythmias are common in patients with COPD.\textsuperscript{16} Those arrhythmias occur commonly at night during sleep, and hypoxemia may be responsible for the arrhythmias.\textsuperscript{17} Episodic nocturnal oxygen desaturation produces episodic pulmonary vasoconstriction and pulmonary hypertension\textsuperscript{18} and nocturnal oxygen desaturation could contribute to the progression of COPD leading to cor pulmonale.\textsuperscript{19,20}

Nocturnal oxygen desaturation could be detrimental to patients with cardiovascular diseases,\textsuperscript{12} particularly to those with coronary artery disease in whom hypoxemia poses potential threats. The adequacy of oxygen supply to the myocardium depends upon the adaptive response of the coronary circulation to increases in myocardial oxygen consumption and decreases in arterial oxygenation.\textsuperscript{21} Hypoxemia increases myocardial oxygen consumption either directly\textsuperscript{22} or as a result of increases in myocardial contractility through sympathetic stimulation.\textsuperscript{23,24} Normally, the coronary blood flow increases several times in response to hypoxia.\textsuperscript{25} In conditions of hypoxemia and narrowing of the coronary arteries, however, cardiac oxygen consumption and cardiac performance may become coronary flow-dependent. This is in contrast to the normal situation in which coronary flow is determined by the myocardial O\textsubscript{2} consumption.\textsuperscript{23} Studies in patients with coronary artery disease, in which the oxygen requirement of the myocardium was increased, have shown that in some of the patients myocardial hypoxia developed due to failure to increase total coronary blood flow.\textsuperscript{26} A recent study\textsuperscript{27} has shown evidence of myocardial damage produced by severe nocturnal oxygen desaturation in patients with the "blue and bloated" form of COPD, manifested by electrocardiographic abnormalities such as prolongation of QTc, ST-T changes and cardiac arrhythmias; interestingly, those abnormalities were not related to the dips in oxygen saturation, but rather to sustained nocturnal hypoxemia. The same study also showed that the cardiac abnormalities were less prominent in the group of patients with the "pink-puffer" type of COPD, most of whom did not present significant nocturnal oxygen desaturation.

\begin{table}[!h]
\centering
\begin{tabular}{|l|c|c|}
\hline
Type & No. & Percent \tablefootnote{Patients of Total} \\
\hline
Total patients studied & 17 & - \\
Disordered breathing & 13 & 76 \\
obstructive apnea & 11 & 65 \\
Cheyne-Stokes & 2 & 12 \\
central apnea & 0 & 0 \\
Oxygen desaturation & 10 & 59 \\
Cardiac arrhythmias & 12 & 71 \\
a) associated with disordered breathing & 5 & 29 \\
with oxygen desaturation & \\
b) associated only with disordered & 7 & 41 \\
brather than with disordered & \\
breathing without oxygen desaturation & \\
c) associated with neither disordered & 12 & 71 \\
breathing nor oxygen desaturation & \\
Types of cardiac arrhythmias: & & \\
premature ventricular contractions & 11 & 65 \\
premature atrial contractions & 5 & 29 \\
sinus arrhythmia & 2 & 12 \\
no arrhythmias & 5 & 29 \\
\hline
\end{tabular}
\caption{Disordered Breathing and ECG Changes During Sleep}
\end{table}

\textbf{DISCUSSION}

The results of this study indicate that disordered breathing, particularly of the obstructive type, and significant oxygen desaturation are common occurrences during sleep in patients with stable coronary artery disease who do not have associated symptomatic pulmonary disease. The incidence is consistent with the findings in normal men in the same age group.\textsuperscript{8} Obstruction of the upper airway during sleep produces alveolar hypoventilation, respiratory acidosis and hypoxia in a repetitive manner.\textsuperscript{5,13} Cyclic hypoxemia occurring during the apneic epi-
In the present study, significant arterial oxygen desaturation associated with repetitive episodes of disordered breathing was frequently observed. The range of fall in oxygen saturation was equivalent to an ascent from sea level to an altitude up to 15,400 feet and the patients spent a significant portion of their sleeping time under such hypoxic conditions. However, except for cardiac arrhythmias and slight prolongation of the QTc, the patients did not show evidence of myocardial hypoxia. A possible explanation is that in contrast with the "blue and bloated" COPD patients, the patients in the present study had a baseline SaO2 located high on the flat portion of the oxyhemoglobin dissociation curve and the patients did not experience sustained nocturnal hypoxemia, but rather frequent dips of oxygen desaturation. In addition, most of the patients were taking propranolol which is known to reduce myocardial oxygen requirements.

Although angina pectoris, myocardial infarction and sudden death are known to occur during sleep in patients with coronary artery disease,11 none of these events occurred in this study. The absence of angina pectoris could be coincidental, but could also be attributed to the use of propranolol by most of the patients. The occurrence of cardiac arrhythmias during sleep in patients with coronary artery disease has been previously studied and evidence exists for both the association and lack of association between arrhythmias and sleep.29-32 Our results showed that cardiac arrhythmias occurred frequently during sleep, but a cause-and-effect relationship between disordered breathing with intermittent hypoxia and the development of arrhythmias could not be established. Since no difference in the FEV1/FVC ratio was found between the group of patients who had arrhythmias and those who did not, exclusion of patients with mild-to-moderate obstructive spirometric changes would not have altered the results.

Although no immediate ill effects resulted from sleep disordered breathing (SDB) and intermittent nocturnal oxygen desaturation in this group of patients with coronary artery disease, one night of study may understate the potential long-term consequences of intermittent nocturnal hypoxia. It is possible that nocturnal hypoxemia may contribute to the progression of coronary artery disease. Hypoxia appears to accelerate experimental atherosclerosis.33-34 It has been shown that urinary catecholamines in patients with sleep disorders, including sleep apnea, are elevated.35 Catecholamines may contribute to the process of atherosclerosis36 and thus nocturnal hypoxemia, by increasing catecholamines, could contribute to the progression of atherosclerosis and coronary occlusion.

A cause-and-effect relationship could exist between SDB and systemic hypertension.37,38 Almost half of the patients had systemic hypertension, a proportion similar to that found in patients with sleep apnea.38 Since systemic hypertension is considered to be an atherogenic factor,39 this could be another indirect way by which SDB could contribute to the progression of coronary artery disease.

In conclusion, although disordered breathing of the obstructive type with associated hypoxia commonly occurred during sleep in patients with stable coronary artery disease, no short-term ill effects resulting from those abnormalities were noted in this study. As pointed out by Block,12 it is conceivable that SDB and nocturnal hypoxemia in the long run may contribute to the progression of coronary artery disease, but the long-term effects of SDB await further study.

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