**Myocardial Stress**

*Exercise versus Sleep in Patients with COPD*

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Epidemiologic investigation has revealed that patients with pulmonary disease are at increased risk of dying during the early morning hours. To provide a pathophysiologic explanation for these excessive nocturnal mortality statistics, we tested the hypothesis that episodes of arterial O₂ desaturation during sleep can produce as severe a stress on the maintenance of myocardial O₂ balance as maximal exercise in patients with chronic obstructive pulmonary disease (COPD). Thirty-one subjects with COPD underwent both overnight sleep and treadmill exercise study to their dyspnea-limited maximum. During both activities, systemic blood pressure was directly recorded and myocardial oxygen consumption (MVO₂) estimated from the pulse rate (HR) = systolic blood pressure (SBP) product. Arterial O₂ content (CaO₂) was calculated from hemoglobin concentration and arterial O₂ saturation (SaO₂) measured by ear oximetry. Using these data and the Fick principle, myocardial blood flow (MBF) was continuously estimated during both exercise and sleep. During sleep, mean SaO₂ was 98 ± 2 percent while the average of the lowest SaO₂ recorded for each subject was 71 ± 14 percent. Episodes of nocturnal oxyhemoglobin desaturation produced consistent elevations in SBP frequently accompanied by an increase in HR. Because this hemodynamic response resulted in increased MVO₂ at precisely the times when arterial O₂ contents were low, high demands for MBF were generated. The average of the highest individual values for MBF during sleep was 244 ± 144 (ml/100 g LV/min). This value was not significantly different from the value of MBF = 281 ± 91 (ml/100 g LV/min) determined for maximal exercise. This finding suggests that the demand for coronary blood flow during episodes of nocturnal hypoxemia can be transiently as great as during maximal exercise in patients with COPD.

Exercise and sleep are important physiologic states representing two poles of the spectrum of human activity. In patients with regional limitations to MBF, exercise-induced elevations in myocardial O₂ demand are commonly associated with the development of myocardial ischemia with ventricular arrhythmias and sudden death being an infrequent, but tragic sequelae to the physiologic stress of exercise on the heart. In patients with COPD, exercise capacity is limited by the sensation of dyspnea with sudden death a rare accompanying event. In contrast, chronobiologic studies have suggested that sleep is associated with an increased risk of dying. Investigation of human mortality rates as a function of time of day has revealed that patients with pulmonary disease are at increased risk of dying between 0100 and 0700 in the morning. Although the incidence of sudden death during sleep in patients with COPD has not been determined, the report of the Nocturnal Oxygen Therapy Trial Group suggests that it may be substantial. They reported that nine patients with COPD experienced sudden unexpected death in bed out of 64 total deaths. The present studies have attempted to provide a pathophysiologic basis for nocturnal mortality in COPD by studying the impact of nocturnal O₂ desaturation on myocardial O₂ balance during sleep and comparing it to the stress imposed by maximal exercise.

The physiologic relationship between MVO₂, MBF and the arterial-to-coronary sinus O₂ content difference (CaO₂-ESC₃O₂) is widely appreciated (Eq 1) as is the ability of exercise to induce myocardial ischemia by increasing MVO₂ in patients whose coronary artery disease limits their capacity to increase MBF.

\[
MBF = \frac{MVO_2}{(CaO_2 - ESC_3O_2)} \quad \text{Eq 1}
\]

Less widely appreciated is the fact that arterial hypoxemia is similarly capable of inducing myocardial ischemia. Rothchild and Kissin showed that arterial hypoxemia induced by inhalation of hypoxic gas mixtures caused angina pectoris as well as ST segment deviation on the electrocardiogram. Barach and Steiner subsequently reported that breathing 10 percent oxygen produced angina in 17 of 29 patients with heart disease at arterial O₂ saturations ranging from 60-86 percent. Arterial O₂ desaturation into and below this range has been frequently reported in patients with COPD during sleep.

Nocturnal hypoxemia leading to myocardial hypoxia is a pathophysiologic mechanism which may contribute to nocturnal death in patients with COPD. The present studies evaluated the magnitude of the stress placed on the coronary circulation to maintain myocardial.
dial O₂ delivery adequate to meet myocardial O₂ demand during sleep and compared this demand to that of maximal exercise.

METHODS

Patients

Thirty-three male patients with clinically stable COPD were recruited from the veteran population of the VA Medical Center, St. Louis. Routine spirometric tests were performed in each patient using a wedge spirometer (Med-Science, St. Louis). Thoracic gas volumes at functional residual capacity (FRC) were determined with a body plethysmograph (Warren E. Collins, Brantree, MA). Values were expressed as a percentage of previously published normal values.¹³ Patients with total lung capacity (TLC) ≥80 percent of predicted and ratios of forced expired volume in 1 sec to forced vital capacity (FEV/FVC) ≤70 percent were eligible for inclusion in this study. Patients with malignancy, renal or hepatic failure, clinically manifest left ventricular dysfunction, unstable angina, orthopedic and/or neurologic limitations to treadmill exercise were excluded from study. Two subjects found to have obstructive sleep apnea were excluded from analysis. Following informed consent for the performance of both an exercise stress test and overnight polygraphic sleep study, all patients underwent venipuncture for hematocrit, hemoglobin, and electrolyte determination. In addition, a 12-lead ECG was obtained along with a standard chest radiograph.

Exercise Study

Treadmill exercise was performed at least 2 h after a light meal. Workloads were adjusted according to a continuous multistage schedule and each level of work was maintained for 3 min. Treadmill grade and speed were incrementally increased until the patient indicated he could not perform any higher level of exercise. Exercise was performed under continuous ECG and arterial blood pressure monitoring. Arterial blood pressure was directly monitored via a 20 gauge Teflon catheter percutaneously inserted into a radial artery under local lidocaine (Xylocaine) anesthesia. An Intraflo continuous flush system was used with heparinized normal saline solution (5 units/ml) to maintain the patency of the arterial line. The pressure transducer (Statham P231D) used to monitor systemic blood pressure was maintained at the level of the fourth intercostal space in the mid-clavicular line throughout the study. A Hewlett-Packard for Medicine VR-6 recorder using a V2206 pressure amplifier with systolic pressure meter was used to record blood pressure with the upper frequency response filter set at 10 Hz. Direct manometric calibration of the system was performed prior to each study. Expired gas was collected in a 200L meteorologic balloon connected to a mouthpiece via a non-rebreathing J valve (102 ml deadspace) during both the rest period and final minute of exercise at the maximum tolerated workload. The fractional concentrations of CO₂ and O₂ in expired gas were measured with Beckman LB-2 and OM-14 gas analyzers, respectively, calibrated with appropriate standard gases. Expired gas volumes were measured under ATS conditions with a Tissot 120L1 volumeter and volumes corrected to BTPS. Oxygen consumption and CO₂ production were computed under STPD conditions using standard equations. Arterial blood was sampled at rest and during the final minute of exercise for measurement of PaO₂, PaCO₂ and pH with an Instrumentation Laboratories model 813 blood gas analyzer calibrated daily with known standards. Arterial O₂ saturation and hemoglobin concentration were measured with an Instrumentation Laboratories model 182 CO-oximeter.

Sleep Study

All patients underwent an overnight polygraphic sleep study which included monitoring of arterial O₂ saturation (Hewlett-Packard 4720A ear oximeter), respiratory airflow with both oral and nasal thermistors, thoracoabdominal movement by impedance pneumography, electrocardiographic activity using chest leads CC₁ and CM₁, and systemic arterial pressure by radial artery catheterization. All of the above cardiopulmonary data including both the continuous (analog) blood pressure as well as the signal from the systemic blood pressure meter were recorded with a Hewlett-Packard VR16 recorder and the data stored on electromagnetic tape (Amplex PR500) for subsequent analysis. Arterial blood was drawn in the supine position prior to the onset of sleep for direct measurement of PaO₂, PaCO₂, pH, SaO₂ and hemoglobin concentration as above.

In 19 patients, electroencephalographic activity using standard central leads (C₃-A₂/C₄-A₁), chin electromyographic activity and electro-oculographic activity were recorded all night with a Beckman dynagraph B411 polygraph. Sleep was scored according to standard criteria.¹³ A time code signal generated with a Hewlett-Packard real time clock, system 9835 desk top computer and model 6940 multiprogrammer, was simultaneously recorded on both the electromagnetic tape and sleep record. This signal permitted accurate identification of the segments of the taped cardiopulmonary data which occurred during rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. In the 12 patients in whom sleep staging was not performed, only the segments of the cardiopulmonary data both free of movement artifact and during times when the sleep technician considered the subject to have been asleep were analyzed. The taped data for each patient was carefully reviewed and all technically inadequate segments, usually related to damped blood pressure recordings, were identified and excluded from analysis.

Analysis of Sleep Data

The taped data for the continuous (analog) recording of the blood pressure signal, the systolic blood pressure (SBP) from the systemic pressure meter and the arterial oxyhemoglobin saturation (SaO₂) from the ear oximeter, were played back in real time through a Honeywell VR-16 4205 tape interface amplifier. The analog blood pressure signal was then processed through a model V1208A tachometer amplifier to determine heart rate (HR). The voltage signals for HR, SBP and SaO₂ were then put into a Hewlett-Packard 6050B multiprogrammer for analog to digital conversion and input to the 9835 desk top computer. The digital voltages for HR, SBP and SaO₂ were determined every 1 sec and converted to their actual physiologic values using standardized calibration signals recorded on each patient tape. Because the accuracy of the Hewlett-Packard ear oximeter has not been verified at extremely low saturations, recorded values for SaO₂ of less than 50 percent were arbitrarily limited to a minimum value of 50 percent for use in all subsequent computations. To minimize beat-to-beat variability in HR and SBP, the values for HR and SBP used to compute MVO₂ in Eq 2 below were the continuously updated moving average of the ten values obtained at 1 sec intervals over the preceding 10 sec. A maximum value for HR of 150 per min was used in the software to prevent early premature beats from spuriously elevating HR. The regression equation published by Nelson et al⁴⁸ (Eq 2) was selected to estimate MVO₂ in the present study because it was based on peripheral measurement of SBP and found to have an excellent correlation (r = 0.86) with measured values for MVO₂ over a wide range of heart rates and systolic pressures in man.

\[
\text{MVO}_2 (\text{ml/100 g LV/min}) = 0.0017 (\text{HR} \times \text{SBP}) - 5.31 \quad \text{Eq 2}
\]

Because CaO₂ can be closely estimated from knowledge and hemoglobin concentration (Hgb) and SaO₂, Eq 3, MBF was estimated using Eq 4 assuming a normal coronary sinus O₂ saturation of 30 percent.⁴⁸

\[
\text{CaO}_2 (\text{ml O}_2/\text{ml blood}) = 0.0139 \times \text{Hgb} \times \text{SaO}_2 \quad \text{Eq 3}
\]

\[
\text{MFB} (\text{ml/100 g LV/min}) = \frac{\text{MVO}_2}{\text{CaO}_2 - \text{CVO}_2} = \frac{0.0017 (\text{HR} \times \text{SBP}) - 5.31}{0.0139 \times \text{Hgb} \times \text{SaO}_2 - 0.30} \quad \text{Eq 4}
\]
MVO\(_2\) and MBF were calculated every second using the 10 sec moving averages for HR and SBP along with the value for SaO\(_2\). Hemoglobin concentration was assumed to remain constant throughout the study. Mean values were determined for each of the above variables, as well as the minimum value of SaO\(_2\) and maximal values for HR, SBP, MVO\(_2\), and MBF during sleep. Equations 2 and 4 were similarly used to compute MVO\(_2\) and MBF from the resting and maximal exercise data for HR, SBP, SaO\(_2\), and Hgb.

**Statistical Analysis**

The paired t-test (two-tail) was used to test for significant differences between exercise and sleep. Correlation coefficients were computed according to the method of Pearson.

**RESULTS**

The anthropometric, spirometric and arterial blood gas data (Table I) indicate that the study group had moderately severe obstructive airways disease based on the FEV\(_1\)/FVC ratio of 50 percent and hyperinflation indexed by the elevation in residual lung volume to 169 percent of predicted normal. The study population demonstrated moderate arterial hypoaxemia, PaO\(_2\) = 62 ± 10 mm Hg, and mild hypercapnia, PaCO\(_2\) = 45 ± 9 mm Hg, awake at rest in the supine position. All patients had a positive smoking history that averaged 56 pack years. Major coexisting medical diagnoses were hypertension, coronary artery disease and diabetes in nine, three and three subjects, respectively. Medications consisted of theophylline, β-agonists, diuretics and steroids in 28, 13, 12 and three subjects, respectively.

During exercise, the subjects walked on the treadmill at an average speed of 2 mph and elevation of 4 percent. Dyspnea was the predominant symptom limiting further exercise. Chest pain considered to be cardiac in origin was not reported by subjects nor was ST segment depression greater than 1 mm occurring 80 msec after the J point observed in any subject. Oxygen consumption increased 338 percent with exercise from a resting level of 0.385 ± 0.090 L/min to 1.303 ± 0.651 L/min. At maximal exercise, minute ventilation averaged 43.0 ± 20.2 L/min which represented 87 percent of the measured maximal breathing capacity for the group while HR increased to 124 ± 16 beats/min or 77 percent of the age predicted maximal heart rate.

Total sleep time averaged 220 ± 80 min for the entire group and was not significantly different between the sleep-staged and non-sleep-staged subjects. In three of the 19 sleep-staged subjects, no REM sleep was observed. The remaining 16 patients spent an average of 16 percent of their total sleep time in REM sleep. Cough, discomfort related to the monitoring equipment and the necessity to urinate were most commonly cited by the subjects as reasons for nocturnal awakening. Arousals associated with the symptom of dyspnea were not related to episodes of O\(_2\) desaturation and conversely, arousals following episodes of severe O\(_2\) desaturation did not result in the complaint of dyspnea. Although nonspecific ST and T wave changes were observed during episodes of severe O\(_2\) desaturation, significant ST changes were not observed nor was chest pain reported by any of the subjects.

In the seven subjects in whom SaO\(_2\) fell below 60 percent, the mechanisms responsible were an apnea lasting 75 sec during REM sleep in one subject and prolonged desaturations associated with decreased thermistor deflections (presumed hypoventilation) in the remaining six subjects. These latter episodes which lasted from 2 to 5 min were all documented to occur during REM sleep in the subjects who were sleep-staged. Figure 1 illustrates the time-course of the relationships between SaO\(_2\), SBP, HR, MVO\(_2\) and MBF for one of these major REM related episodes of O\(_2\) desaturation. Although the values for SaO\(_2\) recorded by the ear oximeter decreased to an oxyhemoglobin saturation of only 10 percent during this episode, the tracing shown reflects the lower limit of 50 percent set for SaO\(_2\) to compensate for the ear oximeter's underestimation of SaO\(_2\) at these low values. As a result, the values for SaO\(_2\) depicted in the figure were those used in computing MBF. During this period of O\(_2\) desaturation, a progressive, sustained rise in SBP was observed and accompanied by a fluctuating but generalized increase in HR toward the end of the event. The combined effect of these elevations in HR and SBP on MVO\(_2\) are shown along with the computed values for MBF. Three curves for MBF have been generated to illustrate the impact of assuming three levels of coronary sinus blood oxyhemoglobin saturation (S\(_{\text{a}}\)O\(_2\)) on MBF. For comparison, the three straight lines below the sleep MBF data are the subjects

| Table 1—Anthropometric, Arterial Blood Gas, and Spirometric Data for 31 Male Subjects with COPD |
|--------------------------|------------------|------------------|------------------|------------------|------------------|
| Age                      | 58±8 yrs (37-77) | TLC              | 101±14% (80-134) |
| Height                   | 174±7 cm (160-188) | FRC              | 130±28% (82-179) |
| Weight                   | 84±19 kg (52-124) | RV               | 169±47% (85-292) |
| PaO\(_2\) (awake, supine)| 62±10 mm Hg (39-83) | FVC              | 58±20% (21-89) |
| PaCO\(_2\) (awake, supine)| 45±9 mm Hg (35-80) | FEV\(_1\)         | 40±16% (15-71) |
| pHa (awake, supine)      | 7.43±0.04 (7.35-7.54) | FEV/FVC         | 50±11% (30-69) |
|                          |                   | FEF\(_{25-75}\)  | 26±15% (9-71)   |
|                          |                   | MBC              | 46±20% (19-99)  |

Data are mean ± SD (range)

Spirometric data are expressed as a percentage of predicted normal values with the exception of the FEV/FVC ratio.
calculated values for MBF during maximal exercise at the correspondingly labeled levels of $S_{\text{a}O_2}$. The length of the straight lines on the time scale represent the 3 min duration of the maximal exercise period. For each assumed level of $S_{\text{a}O_2}$, the calculated values for MBF during this episode of severe $O_2$ desaturation clearly exceed those computed for maximal exercise.

Figure 2 compares the HR and SBP data obtained during the exercise and sleep studies for the entire group. During sleep, highest HR recorded averaged 113 beats/min compared to an average HR of 124 beats/min at maximal exercise. Highest SBP recorded during sleep averaged 160 mm Hg compared to an average SBP of 181 mm Hg at maximal exercise. Although the mean highest values for HR and SBP recorded during sleep were significantly lower than the respective values obtained at maximal exercise, they were quantitatively only 10 percent lower. In fact, ten of the 31 subjects had SBPs recorded during sleep which equaled or exceeded the systolic pressures recorded during maximal exercise.

Figure 3 compares the rate-pressure product estimates for MVO$_2$ during exercise and sleep. The average of the highest MVO$_2$ values observed in the individual subjects during sleep was 22 ml/100 g LV/min compared to an average MVO$_2$ of 33 ml/100 g LV/min at maximal exercise. Despite the fact that mean highest MVO$_2$ observed during sleep was 33 percent lower than at maximal exercise, highest MVO$_2$ during sleep nearly doubled the overall mean sleep MVO$_2$ value of 12 ml/100 g LV/min. In five patients, highest MVO$_2$ during sleep was equal or greater than the value

**Figure 1.** Prolonged episode of oxyhemoglobin desaturation during REM sleep with hemodynamic responses. See text for discussion of results.

**Figure 2.** Heart rate and systolic blood pressure data for both sleep and exercise studies in 31 subjects with COPD. Overall mean values obtained during sleep are compared with the values obtained awake at rest prior to treadmill exercise. Mean highest values during sleep are compared with the values obtained at maximal exercise. Data are mean ± SEM. P values compare data in immediately adjacent bars.
obtained during maximal exercise.

Figure 4 presents the data for SaO₂. Awake at rest, SaO₂ averaged 93 percent compared to a mean SaO₂ of 88 percent during sleep, p<0.001. During sleep, the average of the lowest recorded SaO₂ for each patient was 71 percent compared to an average SaO₂ of 88 percent during maximal exercise. This substantial 17 percent difference in saturation was highly significant. Because hemoglobin concentrations measured prior to the beginning of the exercise and sleep studies were 14.7±1.5 and 14.8±1.4 g/dl, respectively, percentage changes in SaO₂ reliably reflect changes in CaO₂.

Figure 5 presents the exercise and sleep data for MBF. Mean MBF during sleep was found to be 22 percent less than the mean value obtained awake at rest, p<0.02. In contrast, no difference was detected between the mean highest demand for MBF during sleep and the demand generated by maximal exercise. In nine subjects, highest MBF during sleep exceeded MBF at maximal exercise. These subjects all had severe nocturnal O₂ desaturation and relatively high myocardial O₂ demands during sleep. The hemodynamic response of increased SBP and HR to the stimulus of nocturnal O₂ desaturation was identified as the major physiological mechanism elevating MVO₂ during sleep.

DISCUSSION

Although direct measurements of MBF, MVO₂ and the oxyhemoglobin saturation of coronary sinus blood (Sco₂O₂) have been successfully undertaken in man, the available methodologies are invasive and incapable of providing continuous information during sleep. Consequently, established physiologic principles have been integrated with ear oximetry and the rate-pressure product method of estimating MVO₂ to derive continuous estimates for MBF.

Figure 6 graphically illustrates the hyperbolic relationship that exists between MBF and SaO₂ as a function of MVO₂ with the assumption that Sco₂O₂=30 percent and for the measured average hemoglobin concentration of 14.7 g/dl. It can be seen that increasing MVO₂ while holding SaO₂ constant would result in progressive increments in MBF as one moves to progressively higher MVO₂ isopleths. In contrast, decreasing SaO₂ while maintaining MVO₂ constant is graphically shown to follow a constant MVO₂ isopleth.
Figure 6. Graphic plots of the relationship, 
\[ \text{MBF} = \frac{\text{MVO}_2}{(0.0139)(\text{Hgb})(\text{SaO}_2 - \text{ScS\textsubscript{O}_2})} \]
between myocardial blood flow (MBF) and arterial oxygen-hemoglobin saturation (SaO\textsubscript{2}) for four levels of myocardial O\textsubscript{2} consumption (MVO\textsubscript{2}), assuming a coronary sinus O\textsubscript{2} saturation of 30 percent and hemoglobin concentration of 14.7 g/dl. Superimposed data are results from the sleep (mean and Smax) and exercise (rest and Emax) studies for SaO\textsubscript{2} and MBF. See text for discussion.

requiring progressively greater increments in MBF as SaO\textsubscript{2} approaches S\textsubscript{cS\textsubscript{O}_2} due to the hyperbolic nature of the relationship between MBF and SaO\textsubscript{2} when S\textsubscript{cS\textsubscript{O}_2} is held constant.

In the present study, exercise increased the demand for MBF predominantly by increasing MVO\textsubscript{2}, as indicated by the nearly vertical rise from the point labeled Rest to Emax. The 5 percent fall in SaO\textsubscript{2} alone would have had minimal impact on increasing MBF requirements as shown by the dotted line connecting the point labeled Rest with point A along the awake resting MBF = 17 ml/100 g LV/min isopleth.

During sleep, the observed fall in SaO\textsubscript{2} from its mean of 88 to 71 percent would have necessitated only a relatively small increase in MBF if MVO\textsubscript{2} had remained constant. This increase would have been equivalent to the vertical rise in the dashed line connecting the mean sleep data point and point B along the mean sleep MVO\textsubscript{2} = 12 ml/100 g LV/min isopleth. However, because of the hemodynamic response of increased rate-pressure product to arterial O\textsubscript{2} desaturation, mean highest MBF during sleep was computed to have increased to the point indicated by Smax on the appropriately higher MVO\textsubscript{2} isopleth. The difference in MBF between Smax and point B reflects the additional MBF required to meet the increased O\textsubscript{2} demands of the myocardium generated by the hemodynamic response to hypoxemia.

It is important to recognize that the calculated values for MBF are significantly influenced by our assumptions: 1) that S\textsubscript{cS\textsubscript{O}_2} remains constant at 30 percent; and 2) that SaO\textsubscript{2} does not decrease below 50 percent. Because the term (SaO\textsubscript{2} - S\textsubscript{cS\textsubscript{O}_2}) in the denominator of equation 4 approaches 0 as SaO\textsubscript{2} decreases toward S\textsubscript{cS\textsubscript{O}_2}, the calculated value for MBF will asymptotically increase toward infinity as the lower limit S\textsubscript{cS\textsubscript{O}_2} is approached. Therefore, our assumption that SaO\textsubscript{2} does not fall below 50 percent limits the decrease in the term (SaO\textsubscript{2} - S\textsubscript{cS\textsubscript{O}_2}) preventing tremendously high calculated values for MBF as well as compensating for the oximeter's tendency to underestimate SaO\textsubscript{2} at low levels. The assumption that S\textsubscript{cS\textsubscript{O}_2} remains constant at a normal value of 30 percent was made because of the basic behavior of the coronary circulation. In general, the response of the coronary circulation to hypoxia is vasodilatation with increased MVO\textsubscript{2}. This behavior functions to keep S\textsubscript{cS\textsubscript{O}_2} and the partial pressure of O\textsubscript{2} in end-capillary blood near normal, thereby maintaining the partial pressure gradient for O\textsubscript{2} diffusion into the metabolically active myocytes. However, as the flow reserves of the coronary circulation become exhausted, myocardial O\textsubscript{2} extraction eventually increases and S\textsubscript{cS\textsubscript{O}_2} falls in order to maintain adequate O\textsubscript{2} delivery. Because this pattern of response has been observed in man during studies of the coronary circulation with exercise,\textsuperscript{16} we have assumed that the coronary vascular beds of our subjects would behave similarly and maintain normal values for S\textsubscript{cS\textsubscript{O}_2} especially during the low levels of exercise they are capable of achieving. Even patients with coronary insufficiency and a limited capacity to increase MBF have been documented to show only modest reductions in S\textsubscript{cS\textsubscript{O}_2} of 5 to 6 percent with exercise.\textsuperscript{17,18} Unfortunately, direct measurements of MBF, MVO\textsubscript{2} and S\textsubscript{cS\textsubscript{O}_2} have not been published for patients with COPD and we are not aware of any reports documenting the behavior of S\textsubscript{cS\textsubscript{O}_2} in man during progressive systemic hypoxemia. However, systemic hypoxemia has been shown to increase MBF in human volunteers.\textsuperscript{19}

Although we have assumed that S\textsubscript{cS\textsubscript{O}_2} remains constant for purposes of calculating the MBF which would be required to meet myocardial O\textsubscript{2} demands and maintain S\textsubscript{cS\textsubscript{O}_2} = 30 percent, we actually believe that
$S_aO_2$ decreased below this value in at least four different subjects in each of the exercise and sleep studies. In these subjects, the calculated values for MBF exceeded 400 ml/100 g LV/min, which is considered to be the physiologic upper limit for MBF in man based on studies using dipyridamole to maximally dilate the coronary circulation. Therefore, MBF may well have increased to its physiologic upper limit in these few individuals followed by increased myocardial $O_2$ extraction and decreased $S_aO_2$ to maintain myocardial $O_2$ delivery. However, because the average values for highest MBF during sleep and MBF with exercise, respectively, averaged only 61 and 70 percent of the MBF upper limit of 400 ml/100 g LV/min, the flow reserves of the coronary circulation were unlikely to have been exhausted in the majority of patients and major desaturation of coronary sinus blood would not have been required to provide adequate $O_2$ delivery. Consequently, our calculated values for MBF must be interpreted as the quantity of MBF required to meet existing $O_2$ demands and maintain $S_aO_2$ equal to 30 percent. This latter requirement was the same for both the exercise and sleep studies. Assuming a lower value for $S_aO_2$ would have reduced the calculated values for MBF in both studies, as shown in Figure 1.

The validity of utilizing the rate-pressure product to estimate $MVO_2$ in man has been documented by multiple investigators under a variety of experimental conditions including supine exercise, upright exercise, combined static and dynamic exercise, as well as under propranolol induced alterations in ventricular contractility. The regression equation used to estimate $MVO_2$ was based on data derived from the peripheral measurement of SBP and showed a high degree of correlation, $r = 0.86$, between direct measurement of $MVO_2$ and the rate-pressure product. Because differences in cardiac dimensions, which are known to affect wall tension and $MVO_2$, are likely to have existed between selected subjects in the present study and the subjects used to establish this regression equation, errors were undoubtedly made in the absolute estimation of $MVO_2$. However, because each patient served as his own control (exercise versus sleep), errors due to variations in ventricular geometry would tend to be proportional and cancel each other in the paired analysis. If anything, ventricular dimensions and therefore $MVO_2$ would probably have been greater during sleep for any given level of SBP because of the greater preload in the supine position compared to the upright condition.

Although the contractile state of the myocardium is increased during exercise by the endogenous release of catecholamines, arterial hypoxemia also stimulates catecholamine release and likely plays a mediating role in the observed heart rate-systolic pressure response to $O_2$ desaturation. It is unlikely that significant differences in contractile state, independent of the rate-pressure product, could have existed during sleep compared to exercise which would have invalidated use of the rate-pressure product to estimate $MVO_2$.

The methods employed to determine $CaO_2$ have several sources of error that were probably minimal at $SaO_2$ above 60 percent, but are less well defined for saturations below 60 percent. Ignoring the small quantity of $O_2$ dissolved in arterial blood introduces less than 1 percent error in the computation of $CaO_2$ while the spectrophotometric method used to measure hemoglobin concentration is reproducible to within ± 0.1 g/dl. The accuracy of the HP oximeter has been verified during acute progressive and steady-state hypoxia over the saturation range of 60-100 percent. Values obtained with the instrument employed in the present study at saturations above 60 percent have repeatedly shown excellent agreement with direct measurements of $SaO_2$ in patients under steady-state conditions. At saturations below 60 percent, Douglas et al have reported that the HP oximeter progressively underestimates $SaO_2$. For this reason, a minimum arterial saturation of 50 percent was employed in the present study as a conservative lower limit for $SaO_2$ to compensate for the oximeter's tendency to underestimate $SaO_2$ at low values. In the five subjects in whom $SaO_2$ was arbitrarily limited to a minimum value of $SaO_2 = 50$ percent for the computation of MBF, the lowest values for $SaO_2$ actually recorded by the ear oximeter were 45, 44, 25, 10, and 0 percent.

Because the uncomfortable nature of the monitoring techniques reduced sleep duration, thereby limiting the time spent in REM sleep when the major desaturations occur, the data may actually underestimate the severity of oxyhemoglobin desaturation during unmonitored sleep. Nevertheless, the values obtained for $SaO_2$ during sleep in the present study were similar to values previously reported. Flick and Block, Wynne et al and Fleetham et al have reported mean lowest arterial saturations on the order of 67-72 percent in their subjects with COPD. Douglas et al have observed that seven of ten subjects with COPD, classified as blue bloaters, desaturated to less than 50 percent, and three to less than 30 percent during sleep. Similar findings were reported by Tirilapur and Mir and are consistent with the findings in the present study.

Although the methods employed in this study to estimate $MVO_2$ and MBF were indirect, it is difficult to escape the basic conclusion that a certain percentage of patients with COPD experience demands for MBF during episodes of severe nocturnal hypoxemia which exceed those associated with maximal exercise. This is because the heart rate-systolic blood pressure product has been documented to increase into the ranges observed with maximal exercise at times when the $O_2$ contents of arterial blood are substantially lower than
the levels associated with maximal exercise. The duration of these high demands for MBF during sleep were generally brief, but occasionally lasted for up to 5 min (Fig 1) corresponding to the duration of the O₂ desaturation and accompanying tachycardic-hypertensive response.

The finding of essentially equivalent maximal MBF demands during sleep and at maximal exercise in this group of subjects is attributable in part to the low exercise HRs associated with their limited exercise capacity. Furthermore, as COPD progresses, exercise becomes progressively curtailed by the unpleasant sensation of dyspnea while deteriorations in gas exchange during sleep cannot be avoided. Eventually, there are no exercise data for patients with "end-stage" disease, only data awake at rest to be compared with the mean and maximal stress sleep data. In several patients we have studied, whose disease severity prohibited them from performing treadmill exercise, we have observed mean rate-pressure products (MVO₂ demands) during sleep which exceeded those awake at rest. In fact, mean MVO₂ values during sleep were equal or greater than awake resting MVO₂ values in four subjects in the present group. Since mean arterial O₂ saturations during sleep were considerably lower than the awake resting values, the mean estimated demands for MBF during sleep were also greater. Consequently, we believe that sleep increasingly becomes the activity state associated with the greatest physiologic stress being placed on the coronary circulation to maintain myocardial O₂ delivery in COPD patients.

In summary, episodes of nocturnal O₂ desaturation were found to increase the O₂ demands of the myocardium as reflected by increases in the rate-pressure product. Increases in MVO₂ concomitant with reductions in CaO₂ were calculated to produce substantial demand for MBF during sleep. In nine (29 percent) of the subjects studied, the maximal demand for MBF during sleep exceeded the demand for MBF during maximal treadmill exercise. These physiologic data suggest that the hypoxicemiac stress placed on the coronary flow reserves to maintain myocardial O₂ delivery during sleep may contribute to nocturnal mortality in patients with COPD.

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