The Rate of Fall of Arterial Oxyhemoglobin Saturation in Obstructive Sleep Apnea*

Eugene C. Fletcher, M.D., F.C.C.P.; Constantino Costarangos, M.D.; and Trey Miller, M.A.

During breath holding, correlations have been demonstrated between the rate of fall of arterial oxyhemoglobin saturation (dSaO₂/dt) and the following: thoracic gas volume at apnea onset, resting oxygen consumption, preapneic arterial oxyhemoglobin saturation (SaO₂), and obesity. A key factor influencing dSaO₂/dt is mixed venous oxyhemoglobin saturation (SVO₂) as recently demonstrated in an animal model of obstructive apnea. The purpose of the present study was to see if dSaO₂/dt was related to SVO₂ during sleep in a group of subjects with severe obstructive sleep apnea (OSA) and varying levels of SVO₂. Eight OSA subjects were studied during sleep with indwelling arterial and central venous catheters. Continuous SaO₂ was measured by ear oximetry while continuous SVO₂ was measured through the fiberoptic bundle of a Shaw Opticath catheter. Thirty percent or more of all obstructive apneas were scored for duration, preapneic SaO₂, SVO₂ and dSaO₂/dt. Least squares regression was used to examine the relationship between dSaO₂/dt and other measured variables. The dSaO₂/dt showed a consistent negative correlation with preapneic SVO₂ and was not related to duration. Mean dSaO₂/dt during sleep correlated to some degree with the degree of gas exchange (QSa/Qt) abnormality prior to sleep. It is concluded that in humans, SVO₂ plays a substantial role in determining dSaO₂/dt. Potentially, the presence of gas exchange abnormalities (eg, found in intrinsic lung disease) causing hypoxemia and low SVO₂ may steepen dSaO₂/dt, lowering the nadir level of apneic desaturation for the same duration of apnea found in a patient with more normal gas exchange. (Chest 1999; 96:717-22)

Rapid falls in oxyhemoglobin saturation (SaO₂) occur in patients with obstructive sleep apnea (OSA) and may lead to profound hypoxemia. The depth of each desaturation episode is dependent upon the duration of the apnea and the rate of fall of SaO₂ (dSaO₂/dt). Factors determining the duration of an apnea are probably related to neural reflexes, central chemosensitivity, and sleep stage. Several studies have examined the relationship between thoracic gas volume at apnea onset (preapnea) and dSaO₂/dt. It has been demonstrated that obesity, resting functional residual capacity (FRC) and resting oxygen consumption (VO₂) all correlate with the nadir SaO₂ during fixed duration apneas, hence dSaO₂/dt. Differences in awake supine PaO₂ and expiratory reserve volume (obesity) may influence severity of hypoxemia during apneas. These studies indicate that preapneic oxygen stores play a major role in determining dSaO₂/dt.

While 25 percent of the body's total oxygen stores are in the lung and 15 percent in the tissue, 60 percent are contained in the blood by virtue of the storage capacity of hemoglobin. Several studies have examined SaO₂ at apnea onset, showing a negative correlation between preapneic SaO₂ and dSaO₂/dt. An observation made in our laboratory during sleep in one patient with OSA in whom mixed venous oxyhemoglobin saturation (SVO₂) was continuously monitored showed an inverse relationship between SVO₂ and dSaO₂/dt. Because of this observation, the oxygen storage capacity of blood, and the known relationship between SaO₂ and SVO₂, it was felt that changes in preapneic SVO₂ may explain variations in dSaO₂/dt in the setting of different levels of VO₂ and SaO₂. This prompted a study examining the correlation between SVO₂ and dSaO₂/dt in an animal model where apnea duration and preapneic SVO₂ could be rigidly controlled. In that study, the level of preapneic SVO₂ was a strong predictor of dSaO₂/dt. The rationale for the present study was to see if this relationship could be confirmed during sleep in human OSA where apnea duration and SVO₂ may vary greatly. The following hypotheses were examined: 1) apnea duration is not a predictor of dSaO₂/dt, 2) preapneic SVO₂ is strongly correlated with dSaO₂/dt in an individual on a given night, and 3) a group of OSA subjects, mean SVO₂ is predictive of dSaO₂/dt.

For editorial comment see page 716

*From the Department of Medicine, Pulmonary Disease Section, Houston Veterans Administration Medical Center, and Baylor College of Medicine, Houston.
Manuscript received December 5; revision accepted February 8.
Reprint requests: Dr. Fletcher, VA Medical Center (111), 2002 Holcombe Blvd, Houston 77030

CHEST / 96 / 4 / OCTOBER, 1989 717
METHODS

Eight obese male subjects with previously established diagnoses of OSA were recruited from the Houston Veterans Administration Medical Center chest clinics. All subjects signed informed consents. There was a wide range of values for arterial blood gases and resting SVO₂ levels (Tables 1 and 2) due to the presence of concomitant lung disease in six patients. All subjects performed spirometry and body plethysmography prior to study except one (I) who became claustrophobic in the body box. All subjects were clinically stable and free of edema at the time of study. Each subject was polysomnographically monitored at least two nights in our laboratory: one for diagnosis of OSA and another for continuous SVO₂ measurement. Polysomnographic measurements included electroencephalography, electro-oculography, electromyography, air flow and thoraco-abdominal motion using pneumobelts. Continuous SₐO₂ was measured with an ear oximeter (fast response mode) (Biox IIIA, Boulder, CO). On the night of SVO₂ measurement, a No. 7.5 Fr balloon tipped fiberoptic catheter (Shaw Opticath, Mountain View, CA), was inserted percutaneously prior to the sleep study. The proper position was ascertained by pulmonary artery pressure curves. An indwelling radial artery catheter was used to draw initial supine arterial blood gas (Table 1) and to monitor systemic pressure. All subjects also underwent gated cardiac radionuclide studies to evaluate right (RVEF) and left (LVEF) ventricular ejection fraction prior to study. Five patients were classified as having had at least one episode of right ventricular failure on the basis of history, compatible signs and symptoms, and reduced RVEF in the face of a normal LVEF (Table 1).

Variables measured included apnea duration to the nearest 0.5 s, preapneic SₐO₂ and SVO₂, and dSₐO₂/dt analyzed from the linear portion of the curve (Fig 1). More detailed discussion of the technique for measurement of dSₐO₂/dt is found elsewhere. Thirty percent or more of the apneas from the heart catheterization night were scored in each patient. Apneas for scoring were selected on the following basis: 1) absolute certainty of absent airflow, 2) regard for a representative distribution of apnea durations, and 3) regard for a representative distribution of preapneic SₐO₂ and SVO₂ levels.

Accuracy of the Biox IIIA ear oximeter for this laboratory has been calculated for the steady state by comparing the oximeter readings from 82 samples (40 patients) of arterial blood analyzed by oximeter (OSM II, Radiometer, Copenhagen). The correlation coefficient for steady state samples was 0.933. Correlation between ear oximeter and oximeter under non-steady state conditions was examined in four subjects by comparing sequential oximeter readings during progressive hypoxia with six to eight consecutive samples of arterial blood. Samples were drawn every 2 s during application of a hypoxic gas mixture (FIo₂ = 10 percent) down to an SₐO₂ of 70 percent. Correlation coefficients for these subjects were r = 0.999, 0.995, 0.987, and 0.974. We have published figures on the accuracy of the Shaw Opticath down to and below an SVO₂ of 50 percent. The correlation between bench oximeter and the Shaw Opticath was 0.944.

Table 1—Anthropomorphic and Pulmonary Function Data

<table>
<thead>
<tr>
<th>Subj, Age</th>
<th>% Ideal Weight</th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>Q̇Va/Qt (%)</th>
<th>FEV₁ (L)</th>
<th>FEV₁ (%)</th>
<th>FEV₁/FVC (%)</th>
<th>RV (%)</th>
<th>RVEF (%)</th>
<th>LVEF (%)</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 67</td>
<td>148</td>
<td>57.5</td>
<td>56.4</td>
<td>19.8</td>
<td>1.45</td>
<td>44</td>
<td>40</td>
<td>—</td>
<td>19/53</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>2, 46</td>
<td>148</td>
<td>76.0</td>
<td>40.0</td>
<td>10.5</td>
<td>2.48</td>
<td>64</td>
<td>78</td>
<td>90</td>
<td>44/75</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>3, 49</td>
<td>137</td>
<td>103.0</td>
<td>41.6</td>
<td>0.0</td>
<td>2.10</td>
<td>54</td>
<td>81</td>
<td>78</td>
<td>44/56</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>4, 56</td>
<td>139</td>
<td>74.0</td>
<td>46.0</td>
<td>10.9</td>
<td>2.05</td>
<td>69</td>
<td>53</td>
<td>160</td>
<td>37/53</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>5, 69</td>
<td>142</td>
<td>62.4</td>
<td>38.2</td>
<td>18.2</td>
<td>1.73</td>
<td>60</td>
<td>71</td>
<td>147</td>
<td>26/55</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>6, 63</td>
<td>190</td>
<td>65.1</td>
<td>40.9</td>
<td>21.6</td>
<td>2.60</td>
<td>68</td>
<td>69</td>
<td>144</td>
<td>43/59</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>7, 58</td>
<td>167</td>
<td>57.5</td>
<td>49.4</td>
<td>19.7</td>
<td>1.85</td>
<td>53</td>
<td>69</td>
<td>171</td>
<td>35/64</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>8, 67</td>
<td>150</td>
<td>84.7</td>
<td>36.0</td>
<td>6.3</td>
<td>1.28</td>
<td>60</td>
<td>60</td>
<td>149</td>
<td>50/49</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Mean, 59</td>
<td>153</td>
<td>72.5</td>
<td>43.7</td>
<td>13.4</td>
<td>1.94</td>
<td>59</td>
<td>65</td>
<td>134</td>
<td>37/58</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>

Arterial blood gases are single values drawn from a radial artery catheter just prior to sleep (supine). Q̇Va/Qt is venous admixture calculated according to published formulas. Right and left ventricular ejection fractions (RVEF, LVEF) were calculated from resting gated equilibrium radionuclide studies performed during periods of clinical stability. Other abbreviations: subj = subject; RV = residual volume, percent predicted; CHF = congestive heart failure. Although patients 2 and 3 have FEV₁ % predicted below 70%, their FEV₁/FVC is greater than 75%, indicating the low FEV₁ may be due to restrictive disease, in this case, probably caused by massive obesity. The other patients with obstruction all show air trapping evidenced by increased RV.

Arterial Oxyhemoglobin Saturation Fall in OSA (Fletcher, Costarangos, Miller)
Table 2—Sleep Data from Catheterization Night

<table>
<thead>
<tr>
<th>Subj</th>
<th>TST (Min)</th>
<th>Total Apneas</th>
<th>Apneas Sampled</th>
<th>Average Duration (S)</th>
<th>Shortest (S)</th>
<th>Longest (S)</th>
<th>*Mean SaO₂ (%)</th>
<th>*Mean SVO₂ (%)</th>
<th>Mean dSaO₂/dt (%/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>232</td>
<td>139</td>
<td>42</td>
<td>28.1</td>
<td>19.4</td>
<td>44.2</td>
<td>85.5</td>
<td>64.0</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>322</td>
<td>128</td>
<td>53</td>
<td>23.7</td>
<td>12.0</td>
<td>50.0</td>
<td>96.3</td>
<td>70.9</td>
<td>0.46</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>82</td>
<td>33</td>
<td>29.1</td>
<td>11.6</td>
<td>62.4</td>
<td>95.2</td>
<td>76.1</td>
<td>0.42</td>
</tr>
<tr>
<td>4</td>
<td>413</td>
<td>280</td>
<td>96</td>
<td>38.1</td>
<td>16.0</td>
<td>82.5</td>
<td>96.5</td>
<td>75.2</td>
<td>0.47</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>150</td>
<td>60</td>
<td>41.5</td>
<td>15.5</td>
<td>83.2</td>
<td>97.4</td>
<td>83.2</td>
<td>0.73</td>
</tr>
<tr>
<td>6</td>
<td>338</td>
<td>140</td>
<td>41</td>
<td>24.5</td>
<td>13.5</td>
<td>38.5</td>
<td>98.0</td>
<td>76.2</td>
<td>0.60</td>
</tr>
<tr>
<td>7</td>
<td>283</td>
<td>345</td>
<td>103</td>
<td>23.1</td>
<td>14.5</td>
<td>69.0</td>
<td>89.0</td>
<td>60.0</td>
<td>1.03</td>
</tr>
<tr>
<td>8</td>
<td>271</td>
<td>312</td>
<td>96</td>
<td>33.9</td>
<td>15.0</td>
<td>60.0</td>
<td>94.0</td>
<td>70.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean</td>
<td>292</td>
<td>197</td>
<td>30.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
</tbody>
</table>

Abbreviations: TST = total sleep time. Mean SaO₂, SVO₂ (*preapneic values) and dSaO₂/dt are averages of all measured values from the individual on the night of right heart catheterization.

Using simultaneously drawn arterial and venous blood to ascertain gas tensions and saturation and assuming a normal respiratory quotient of 0.82, venous admixture (Qva/Qt) was calculated for each subject in the awake supine position according to previously published formulas. Variables were compared by least squares regression for each subject's apneas during the catheterization night (intra-subject) and for the mean of all subjects (inter-subject) on all nights. The null hypothesis was rejected at p<0.05.

RESULTS

The mean age of the eight subjects was 59.4 ± 8.6 years and each was overweight with a mean percentage of ideal body weight for the group of 153 percent. Other morphometric, blood gas, and pulmonary function data are given in Table 1. Six subjects had symptoms (cough, exertional dyspnea, wheezing), arterial blood gases, spirometry, and plethysmography compatible with moderate COPD. One subject (1) had severe expiratory airflow obstruction and required tracheostomy and supplemental oxygen treatment for severe cor pulmonale.

The average sleep time for the eight subjects with the catheters in place was 4.9 hours giving a mean apnea index of 40.2/h. The number of apneas sampled, average and range of apnea duration, mean pre-apnea SaO₂ and SVO₂, and dSaO₂/dt are shown in Table 2. The mean dSaO₂/dt for all apneas sampled was 0.58 with a range of 0.42 percent/s to 1.03 percent/s.

The intra-subject relationship between dSaO₂/dt vs SaO₂ and dSaO₂/dt vs SVO₂ are described in Figure 2, panels A and B. Except for subject 1, the correlation coefficients for dSaO₂/dt vs SVO₂ were significant at p<0.02 or better. The dSaO₂/dt vs SaO₂ showed a less consistent relationship. The correlation between dSaO₂/dt and duration was poor, although it was statistically significant in two cases at 0.37 and −0.23 (Fig 3).

Using the mean preapneic SaO₂ and SVO₂ for the whole night in each individual vs the mean dSaO₂/dt (N = 8), SVO₂ correlated significantly with dSaO₂/dt (r = 0.79, P<0.02) while the correlation coefficient for SaO₂ and dSaO₂/dt was r = 0.57 (P = 0.16). The correlation coefficient between Qva/Qt and dSaO₂/dt was 0.62 (P = 0.09).

DISCUSSION

These data indicate that variability of dSaO₂/dt during OSA is negatively correlated to preapneic SVO₂. This relationship has previously been demonstrated during the rigid study conditions of an obstructive breath hold in supine, spontaneously breathing baboons. It has not been demonstrated during sleep in humans where varying apnea duration and recovery periods between apneas produce wide fluctuation in preapneic SVO₂. It confirms the finding that dSaO₂/dt is independent of apnea duration during a single night. It also demonstrates that on a given night for one individual, there is a strong negative correlation between variation in preapneic SVO₂ and dSaO₂/dt.

This information is important from a clinical standpoint because of the increasing number of reports that patients with coexisting lung disease and OSA have worse cardiopulmonary hemodynamic disturbances than patients with OSA alone. Both pre-existing daytime hypoxemia and transient nocturnal hypoxic episodes are likely to contribute to these disturbances. The data in the present study provides one possible explanation (lower SVO₂) for worse nocturnal desaturation in patients with lung disease and OSA. This is further suggested by the correlation (r = 0.62) between awake Qva/Qt and dSaO₂/dt which would probably have reached significance with a slightly larger study group. As previously demonstrated by Findley et al, normal gas exchange may play a role in dSaO₂/dt in longer duration apneas. Conceivably, gas exchange abnormalities in the form of intrinsic lung disease, existing prior to apnea onset, could
further aggravate nocturnal desaturation by causing a greater fall in SaO₂ for the same duration apnea.

Following the onset of a breath hold, oxygen removal from the lung, transport, and tissue utilization occur in a closed system and therefore must be directly interdependent. The dSaO₂/dt for a given apnea must be a function of oxygen stores within the various lung, blood, and tissue compartments. While lung stores play a major role in determining dSaO₂/dt, blood oxygen stores should play an equally important role since 60 percent of total body oxygen stores are found in the blood. In man, about 75 percent of the total blood volume is venous and 25 percent arterial.¹⁷

Thus, by virtue of volume alone, central venous blood oxygen level should play a major role in determining dSaO₂/dt. Other factors which affect dSaO₂/dt aside from thoracic gas volume should do so through their effect upon SvO₂. For example, increased VO₂ would cause greater tissue oxygen extraction, thereby lowering SvO₂, causing more rapid depletion of alveolar oxygen, and hastening the fall in SaO₂.⁰⁻¹⁰

With the exceptions of Shepard³ and Strohl et al, other investigators examining factors affecting dSaO₂/dt during either relaxed or obstructive breath holds have done so in normal, awake volunteers where apnea duration, FRC, and to some extent, SaO₂ could be
Figure 3. Least squares regression analysis of dSaO2/dt vs apnea duration, one night each for eight subjects with OSA. Correlation coefficient and p value shown for each subject in the lower right hand corner of each panel.

Moreover, four of their patients received supplemental oxygen during the night. This will lessen the dSaO2/dt by increasing alveolar as well as blood oxygen stores at apnea onset and widen the range of SaO2 being tested, both of which will improve SaO2 vs dSaO2/dt correlations for those patients. It is likely that the SaO2 vs dSaO2/dt relationship that Strohl et al observed is a reflection of the SVO2 vs dSaO2/dt relationship. That is, varying levels of preapnic SaO2 may reflect varying levels of SVO2. Thus, a patient with a low preapnic SaO2 has a steeper dSaO2/dt by virtue of a lower preapnic SVO2 depleting alveolar oxygen stores at a greater rate.

Possible sources of error in our data could be the accuracy and tracking characteristics of the Biox IIA ear oximeter and the Opticath SVO2 catheter. Our oximeter has an averaging window of 3 seconds, as mentioned above, and could affect the measurement of a short curve. However, all our slope measurements were made on apneas of 12 s or greater duration. Furthermore, the accuracy of our instruments was checked in steady and non-steady conditions showing a high correlation in both circumstances. We have not checked the dynamic accuracy of the Shaw Opticath catheter. However, steady state samples (SVO2 maintained at a particular level for >5 s) have been shown to be accurate between 80 and 50 percent. It was not considered necessary to examine dynamic accuracy for this study since SVO2 slope was not a measured variable.
While other variables such as changing $\dot{V}O_2$ and cardiac output could have affected $d$SaO$_2$/dt, their effect should have been mainly through changing SVO$_2$. Thus, lack of these data does not detract from the present study. We attempted to measure cardiac output at the beginning and end of apneas in several of the subjects. Because of the unpredictability of apnea duration and disturbance of sleep created by being in the room and injecting iced saline solution, attempts at systematic collection of such data were successful in only two subjects 4, 5. One showed a mean cardiac output drop from 7.8 L/min (apneic) to 6.32 L/min (end apnea), and the other 9.0 to 8.1 L/min.

Thoracic gas lung volume at apnea onset was not measured in this study. Theoretically, marked changes in FRC at apnea onset could have affected $d$SaO$_2$/dt. There is no reason to suspect that FRC at apnea onset during non-REM sleep varied substantially. One study has examined variation in FRC at apnea onset and found a systematic decrease of about 6 percent between the first through third preapneic FRC values. To our knowledge, no data are available examining variability of FRCs in the last preapneic breath during the whole night. There could be a difference in FRC volumes between NREM and REM sleep since normal subjects undergo neuronal inhibition of respiratory muscles during REM sleep and may therefore show decreased thoracic gas volume. This effect would in turn cause a decrease in the alveolar oxygen stores and possibly influence the $d$SaO$_2$/dt. The difference in $d$SaO$_2$/dt between REM and NREM apneas in patients 1, 4, and 5 were examined, but there were insufficient numbers of REM sleep apneas in other subjects to allow statistical analysis. A significant difference in $d$SaO$_2$/dt slopes between NREM and REM $d$SaO$_2$/dt was not found for either patient 1 or 5, but was found in subject 4 ($p = 0.0001$).

In conclusion, $d$SaO$_2$/dt is independent of apnea duration, but is strongly related to preapneic SVO$_2$. Preapneic SVO$_2$ in turn, may be affected by preexisting lung disease and by the close repetitiveness of apneas not allowing sufficient time for recovery of SVO$_2$.8

REFERENCES

6 Cherniack NS, Longobardo GS. Oxygen and carbon dioxide gas stores of the body. Physiol Rev 1970; 50:196-243
11 Fletcher EC, Miller T, Thornby JI. Accuracy of the central venous 02 saturation catheter below 50 percent. J Appl Physiol 1985; 64:2220-23
18 Fletcher EC. Cardiac output and mixed venous oxygen during obstructive apnea. Clin Res 1985; 33:77A
19 Guilleminault D, Motta J, Milm F, Melvin K. Obstructive sleep apnea and cardiac index. Chest 1986; 89:331-34
21 Henderson-Smart DJ, Read DJ. Reduced lung volume during behavioral active sleep in the newborn. J Appl Physiol 1979; 46:1081-95