Total Oxygen Uptake with Two Maximal Breathing Techniques and the Tidal Volume Breathing Technique

A Physiologic Study of Preoxygenation

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Background: Three common methods for preoxygenation are 3 min of tidal breathing, four deep breaths taken within 30 s (4DB), and eight deep breaths taken within 60 s (8DB). This report compares these three techniques in healthy volunteers.

Methods: Five healthy subjects breathed through a mouthpiece and wore a nose clip; oxygen was delivered at 180 l/min via a low-resistance T-piece. Each subject repeated each of the three oxygenation techniques four times. The end-tidal fraction of oxygen was measured, and the oxygen uptake at the mouth was measured breath by breath. The additional difference between oxygen uptake at the mouth during the period of breathing oxygen (as compared with that during air breathing) was taken to represent the total oxygen sequestered into body stores.

Results: The mean ± SD maximum end-tidal fraction of oxygen after the 4DB method was 0.83 ± 0.09, which was significantly less than either the 3-min method (0.92 ± 0.01; P < 0.04) or after the 8DB method (0.91 ± 0.04; P < 0.05). The mean additional oxygen taken up during oxygenation with the 4DB method was 1.67 ± 0.45 l, which was significantly lower than with the 3-min method (2.23 ± 0.85 l; P < 0.04) or with the 8DB method (2.53 ± 0.74 l; P < 0.01). There were no significant differences for these variables between the 3-min and 8DB methods.

Conclusions: For the physiologic measurements that were made, both the 3-min and the 8DB method are superior to the 4DB method. The 3-min and 8DB methods seem to be equally effective.

Preoxygenation with 100% oxygen before induction of anesthesia is standard practice and delays the onset of arterial hypoxemia during subsequent apnea. Three methods of preoxygenation are commonly used: 3 min of normal tidal breathing 100% oxygen (3-min method),1 four deep vital capacity breaths of oxygen taken within 30 s (4DB method),2 and eight deep vital capacity breaths of oxygen taken within 60 s (8DB method).3 Various endpoints have been used to compare these methods: minimum end-tidal nitrogen fraction,4–6 maximum arterial oxygen tension (Pao2),7 maximum end-tidal oxygen fraction (FE O2),7 and time taken for hemoglobin to desaturate to a certain level after anesthetic-induced apnea.5,8 The results obtained have often been conflicting.

Three studies using maximum Pao2 as the endpoint concluded that the 3-min and 4DB methods were equally effective.1,9,10 In contrast, Russell et al.,11 using FEO2, concluded that the 4DB method was inferior to the 3-min method.11 However, Winship and Skinner7 and McCrory and Matthews12 reported similar FEO2 values after 3 min of tidal breathing and after four deep breaths. Other studies have used the time for hemoglobin to desaturate to arterial oxygen saturation (SaO2) 95% (or 93%) and found 4DB to be inferior to the 3-min method.5,8,13,14 Furthermore, McCarthy et al.14 observed that although Pao2 values were similar after 4DB and 3-min protocols, the times to desaturation were significantly longer in the 3-min group. Because theoretically the time to desaturation is more directly related to the available body stores for oxygen than is Pao2, this might suggest that it is a more suitable endpoint for preoxygenation studies. Baraka et al.5 confirmed these findings with respect to the superiority of the 3-min versus the 4DB method when time to desaturation was used as the endpoint but, in contrast to the result of McCarthy et al.,14 found that Pao2 was higher after the 3-min method as compared with the 4DB method. Baraka et al.5 emphasized that all of these measures (FEO2, Pao2, and time to desaturation) were “surrogate markers” of oxygen uptake into body stores, although the last of these is probably the most clinically relevant measure.

There are other technical reasons why the results of previous studies might differ. Some studies have used oxygen flow of 5 l/min in a circle system5; others have used oxygen flow rates of 20 l/min in Mapleson D circuits7 or 10 l/min through a Magill (Mapleson A) circuit.12 In addition, Benumof has suggested that an important reason for failure to achieve maximum oxygenation is the occurrence of leaks around the facemask. The influence of differences between the type of patients studied (e.g., the obese,10,16 pregnant,9,11,17 or elderly13,14) has also been considered.

We planned to eliminate these technical problems and to use healthy subjects in repeated studies. We wished to estimate the actual amount of oxygen taken up by the body using an analysis of net gas exchange at the mouth. Therefore, this was a physiologic rather than a clinical study, which aimed to assess which of the methods of oxygenation was best in ideal laboratory circumstances, rather than in the clinical situation.
Materials and Methods

Subjects
This study had the approval of the Central Oxford Research Ethics Committee (Oxford, United Kingdom). We used five healthy male subjects, and all gave written, informed consent.

Equipment
Subjects were seated in a chair, wore nose clips, and breathed through a mouthpiece that was connected to the gas supply via low-resistance tubing (resistance 0.1 mm H₂O · min⁻¹ · l⁻¹). The arrangement may be described as a simple T-piece, with the expiratory limb being a large funnel-shaped tube (volume ~3 l) open to the atmosphere. The total gas flow was high to prevent rebreathing (180 l/min). Inspired and expired gas at the mouth were sampled continuously by a mass spectrometer (Airspec 3000; Airspec Ltd., Biggin Hill, Kent, United Kingdom) and analyzed for inspired and end-tidal fractions and partial pressures of oxygen and carbon dioxide (body temperature, ambient pressure, and saturated with water vapor [BTPS]). Respiratory volumes were measured by a turbine volume-measuring device and flows by a pneumotachograph in series with the mouthpiece (dead space 90 ml). Data regarding experimental time, gas flow, and gas composition were stored every 20 ms in a data acquisition computer, which used a program to locate inspiratory and end-expiratory values. For each breath, net oxygen uptake at the mouth was calculated breath by breath (standard temperature and pressure, dry [STPD]) as described previously. Briefly, the records of carbon dioxide and oxygen composition at the mouth were aligned in time with the record of respiratory flow, as measured by the pneumotachograph, using the measured delay of the mass spectrometer. Second, the as yet uncalibrated values of flow from the pneumotachograph were adjusted for changes in gas viscosity due to changes in gas composition. Then, for each half breath, the respiratory flow from the pneumotachograph was calibrated using the volume measurement from the turbine device. Finally, for each gas species, the difference between the amount breathed in and the amount breathed out was calculated.

Protocols
There were three oxygenation protocols. Before each protocol, subjects breathed room air for 3 min, which enabled calculation of their basal (metabolic) oxygen uptake (Basal_32). This was taken to be the average value of oxygen uptake at the mouth (in l/min) over this period. Then, the inspired gas was changed surreptitiously to 100% O₂ at end-expiration, and subjects undertook one of the following breathing protocols:

- For the 3-min protocol, subjects continued to breathe normally at tidal volumes for 3 min. The inspired gas was then restored to room air, and the experiment continued until FE_2 had returned to its starting value.
- For the 4DB protocol, on tapping their shoulder, subjects took four deep vital capacity breaths within 30 s. After the end of expiration after the fourth breath, signaled again by a tap on the shoulder, the inspirate was changed back to room air, and the subject returned to normal breathing at tidal volumes until FE_2 had returned to its starting value.
- For the 8DB protocol, on tapping their shoulder, subjects took eight deep vital capacity breaths within 60 s. After the end of expiration after the last breath, signaled again by a tap on the shoulder, the inspirate was changed back to room air, and the subject returned to normal breathing at tidal volumes until FE_2 had returned to its starting value.

Each subject repeated each of the three protocols four times, in random order on separate days, yielding a total of 60 individual experimental periods. If a subject undertook more than one protocol on any given day, the interval between protocols consisted of at least 2 h of air breathing.

Data Analysis
There were two values of interest. First, for each protocol, the maximum FE_2 (BTPS) attained by each subject in each protocol was measured, and these values averaged to give the mean for the group.

Second, the additional oxygen uptake (in excess of Basal_32) over the course of each protocol (STPD) was calculated in the following manner. It was assumed that breathing oxygen would not itself influence Basal_32. If, for any breath during oxygenation, the measured oxygen uptake at the mouth (Breath_2, l/min) exceeded Basal_32, it was assumed that this excess oxygen uptake represented sequestration of oxygen into body stores. As body stores for oxygen became saturated, it was expected that Breath_32 would approximate Basal_32. If, for any breath (e.g., after the period of oxygenation), the measured Breath_32 was less than Basal_32, it was assumed that this represented loss of oxygen from body stores.

Thus, for each breath during the period of oxygenation, the difference: Breath_32 – Basal_32 yielded the amount of oxygen taken up by (or lost from) the body for that breath (in l/min). This value multiplied by the duration of the breath yielded the amount of oxygen taken up during that breath (in liters). The sum of these values for all breaths during the period of oxygenation gave the total amount of oxygen taken up (Total_32; liters). For each protocol, individual subject values for Total_32 were calculated, and these subject values averaged to obtain the mean value for the group.

Statistics
The individual subject values for Basal_32, FE_2, and Total_32 were first subjected to ANOVA (Minitab for Win-
dows version 9.2, State College, PA). There were two factors: subject (five levels) and protocol (three levels). The interactive term between subject and protocol indicated whether there were any influences of the protocol within subjects. If ANOVA suggested significant effects, then post hoc paired t tests were undertaken to assess the statistical significance of the differences between the mean results of each protocol. Statistical significance was taken at $P < 0.05$.

**Results**

The mean (range) age of the subjects was 20.8 (20–23) years, height was 1.79 (1.69–1.88) m, and weight was 74 (61–92) kg. Table 1 shows the BasalO$_2$ values for subjects in the three protocols. ANOVA suggested significant differences between subjects ($P < 0.001$), but not between protocols ($P < 0.21$). One subject (1222) had rather low values, but these were consistent across all three protocols for this subject. The interactive term did not indicate a significant influence of protocol within subjects (ANOVA, $P < 0.28$).

Table 1. Basal (Metabolic) Oxygen Uptake Breathing Air for Each of the Three Protocols

<table>
<thead>
<tr>
<th>Subject</th>
<th>Basal Oxygen Uptake Breathing Air, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 min</td>
</tr>
<tr>
<td>156</td>
<td>0.40 (0.03)</td>
</tr>
<tr>
<td>205</td>
<td>0.46 (0.10)</td>
</tr>
<tr>
<td>206</td>
<td>0.43 (0.08)</td>
</tr>
<tr>
<td>1,222</td>
<td>0.22 (0.05)</td>
</tr>
<tr>
<td>1,223</td>
<td>0.46 (0.05)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.39 (0.10)</td>
</tr>
</tbody>
</table>

Values are mean (SD) and standard temperature and pressure, dry. There were no significant differences between the protocols (ANOVA, not significant).

Fig. 1. Graphs of inspired oxygen fraction (FIO$_2$; unfilled circles) and end-tidal oxygen fraction (FEO$_2$; filled circles) for each of the three protocols (BTPS). Each graph is a single representative experimental period from one subject, and each point represents a single breath. The start of oxygenation for each protocol is arbitrarily time = 0. For the 3-min protocol (3 min), the period of oxygenation was 180 s. For the 4DB protocol (4DB), the four breaths took approximately 20 s in this experimental period. For the 8DB protocol (8DB), the eight breaths took approximately 55 s in this experimental period. Note that the time scales for the 4DB and 8DB graphs are the same, but different from the time scale for the 3-min graph. $O_2$ = oxygen.

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The mean (SD) breath volumes for vital capacity breaths achieved were 3.53 (0.53) l for 4DB and 3.57 (1.15) l for 8DB (NS). The mean end-tidal PCO$_2$ during 3 min was 39.9 (2.4) mmHg, and the mean minimum for 4DB was 31.7 (3.2) mmHg ($P < 0.019$ vs. 3-min method; Student paired t test) and for 8DB was 27.1 (2.1) mmHg ($P < 0.026$ vs. 4DB).

Table 2 shows the quantitative values for FE O$_2$ and TotalO$_2$. For FE O$_2$, ANOVA indicated that there were significant influences of subject ($P < 0.001$), protocol ($P < 0.001$), and the interactive term ($P < 0.001$), which...
suggested that FE O₂ differed between subjects and between protocols and also that FE O₂ was influenced by protocol within subjects. Post hoc t tests suggested that the mean of the 4DB protocol was different from both the 3-min (P < 0.04) and 8DB (P < 0.01) protocols. Differences between the 3-min and 8DB protocols were not significant for either TotalO₂ (P < 0.20) or FE O₂ (P < 0.27).

Finally, we calculated that the mean (SD) total oxygen uptake by the fourth breath of the 8DB technique was 1.67 (0.75) l, which was identical to the TotalO₂ value for the 4DB method (table 2).

Discussion

The main finding of this study is that when technical factors that might limit oxygenation are eliminated and when the additional oxygen uptake at the mouth is used as the endpoint, the 3-min and 8DB methods of preoxygenation are equal in efficacy, and both are superior to the 4DB method.

Critique of Experimental Technique

Our subjects used a mouthpiece and a nose clip, which would not necessarily be applicable to clinical situations. However, it is of interest that some workers have used mouthpieces and nose clips in clinical scenarios with good results.⁷,19

Our method of calculating the additional uptake of oxygen at the mouth is perhaps a novel measure in preoxygenation studies. The method is not influenced by hard exercise,²⁰ electrically induced exercise,²¹,²² or sustained changes in the composition of inspired gases (including breathing hypercapnic¹⁸ and hyperoxic²⁰ gas mixtures). Taken together, these results confirm agreement of mean breath-by-breath calculations with steady state (i.e., Douglas bag) measurements,²³ but an additional issue is that of breath-to-breath variability. Various methods have been proposed to estimate breath-by-breath gas transfer.²³–²⁵ Because no direct measurement of gas transfer across the alveolus is possible, these different methods cannot be compared with a standard reference. All of the methods yield estimates of gas exchange with certain differences in breath-to-breath

Table 2. Maximum Oxygen Fraction and Total Oxygen Uptake

<table>
<thead>
<tr>
<th>Subject</th>
<th>3 min</th>
<th>4 DB</th>
<th>8 DB</th>
<th>3 min</th>
<th>4 DB</th>
<th>8 DB</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>0.91 (0.01)</td>
<td>0.67 (0.07)</td>
<td>0.84 (0.05)</td>
<td>3.22 (0.39)</td>
<td>1.32 (0.27)</td>
<td>2.51 (0.48)</td>
</tr>
<tr>
<td>205</td>
<td>0.93 (0.01)</td>
<td>0.87 (0.03)</td>
<td>0.94 (0.02)</td>
<td>1.39 (0.47)</td>
<td>2.14 (0.99)</td>
<td>3.33 (0.64)</td>
</tr>
<tr>
<td>206</td>
<td>0.93 (0.01)</td>
<td>0.81 (0.08)</td>
<td>0.93 (0.03)</td>
<td>2.94 (0.98)</td>
<td>2.11 (0.61)</td>
<td>3.21 (1.01)</td>
</tr>
<tr>
<td>1,222</td>
<td>0.93 (0.01)</td>
<td>0.90 (0.11)</td>
<td>0.91 (0.01)</td>
<td>1.38 (0.09)</td>
<td>1.62 (0.34)</td>
<td>1.67 (0.73)</td>
</tr>
<tr>
<td>1,223</td>
<td>0.91 (0.02)</td>
<td>0.90 (0.01)</td>
<td>0.92 (0.02)</td>
<td>2.22 (0.66)</td>
<td>1.15 (0.43)</td>
<td>1.95 (0.81)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.92 (0.01)*</td>
<td>0.83 (0.09)</td>
<td>0.91 (0.04)*</td>
<td>2.23 (0.85)*</td>
<td>1.67 (0.45)</td>
<td>2.53 (0.74)*</td>
</tr>
</tbody>
</table>

Values are mean (SD). Maximum oxygen fraction (body temperature, ambient pressure, and saturated with water vapor) and total oxygen uptake (standard temperature and pressure, dry).

* Significantly different from 4 deep breaths (DB) (P < 0.05, ANOVA and post hoc Student t test). Comparisons between 8 DB and 3 min were not statistically significant.
variability. It is currently impossible to assess whether this interbreath variability arises from artifacts in the computation methods or whether it is a true physiologic phenomenon. It is generally assumed that the method of calculation that yields the lowest variability given the same data set (or when compared against a model) is the one that minimizes computational error. We have previously tested our method with three other methods of analysis and found that our method yields the lowest interbreath variation (SD of breath-to-breath oxygen uptake of 20.8 ± 10.4%). Campbell and Beatty, using data from previous studies, have estimated that the maximum total body oxygen uptake is probably approximately 2.7 l after “ideal” preoxygenation. This compares well with our value of 2.5 l after the 8DB method (table 2), which suggests that our method yielded reasonable estimates for total oxygen uptake in this study.

Our measurement method indicates only the total amount of oxygen taken up. Not all of this amount may be available for use by the tissues during any subsequent apnea. Hence, for clinical purposes, the measure of most relevance is probably the time to desaturation.

Our subjects were seated; therefore, our results may not be applicable to situations in which patients lie flat. Baraka has reported that the seated position results in longer times to desaturation during postanesthetic apnea, but other workers have been unable to confirm this result.

There were a number of strengths of our study. The very high oxygen flow rates ensured that there was virtually no rebreathing (or air dilution), a factor that has probably dogged many other studies. Figure 3A shows the effect of oxygen supplied at 40 l/min during one preliminary trial of deep breathing, and the effects of rebreathing (air dilution) are self-evident. Figure 3B shows the dramatic effect of increasing the flow to 180 l/min.

An additional strength of this study was that we were able to perform repeated studies in our subjects to obtain values for both FEo2 and total oxygen uptake, which minimized the effects of random variability. Also, because this was a physiologic study, all of our subjects were able to undertake each of the three protocols; no matching of subject groups between protocols was necessary, and this further minimized bias.

There are some advantages to performing physiologic studies in cooperative subjects. Salem et al. criticized the methodology of some clinical studies. Although eight deep breaths are taken by the patient when awake, oxygenation often needs to be continued by active hand-facemask ventilation of the lungs for a period after induction of anesthesia (which can impart an additional 2–4 breaths). We avoided this problem.

**Comparison with Other Studies**

Our results are in agreement with those studies that have found the 3-min and 8DB methods to be superior to the 4DB method. Our results do not support the notion that the 4DB method is equal to other methods.

Comparison with the study of Baraka et al. is particularly interesting. We found that 8DB results in 860 ml more oxygen taken into body stores than 4DB (table 1). If we assume a mean basal (metabolic) oxygen consumption of 390 ml/min (table 1), this would suggest that the 8DB method might result in approximately 2.2 min longer time to hemoglobin desaturation to a given endpoint than the 4DB method. The results of Baraka et al. show that the time to hemoglobin desaturation to 95% is indeed 2.4 min longer with the 8DB than the 4DB method. This similarity might suggest that our novel measure of preoxygenation is also of some clinical relevance.

However, we cannot confirm the finding of Baraka et al. that the 8DB method is superior to the 3-min method. Although the total oxygen uptake was greater with 8DB by 300 ml, this did not reach statistical significance in our study (table 2). However, we did observe that in 15
of 20 experimental periods, the net additional oxygen uptake (BreathO2 – BasalO2) had a small positive value for the last breath of the 8DB protocol (fig. 2). This suggests that in these instances, the body stores for oxygen were not fully saturated at eight breaths. Further oxygen uptake may therefore have continued had more breaths been taken, and it is therefore possible that a 10- or 12-deep-breath technique might produce values for oxygen uptake somewhat greater than those for the 3-min technique.

**Conclusion**

Results from clinical studies are likely to be influenced greatly by the limitations of the equipment used. Physiologically, in a setting where such technical limitations are minimized, we have shown that the 8DB and 3-min methods are equally effective and that both are superior to the 4DB method. It would be desirable to repeat our methodology in a clinical setting, using time to desaturation as an additional endpoint.

We might speculate on the physiologic basis for our results. Traditionally, the view is held that the largest contribution to the oxygen store is that contained in the functional residual capacity of the lung. Therefore, if methods differ, it is likely that this is because the methods result in different functional residual capacities, and it is plausible that deep breathing might increase functional residual capacity. However, if this is the case, it is does not explain how the 3-min method results in higher oxygen uptake than the 4DB method (table 2). A number of authorities have suggested that differences in oxygen carriage by blood (including venous blood) or tissue stores might be important.27–31 Benumof has suggested that the presumed respiratory alkalosis induced by the 8DB method might increase oxygen carriage by the blood, and consistent with this, we found lower end-tidal PCO2 values for 8DB as compared with 4DB. Other possibilities include interaction of the preoxygenation method with cardiac output. Our data do not yield any further insight into which of these suggestions is the most important factor in our results. Future studies might measure oxygen carriage by blood or measure functional residual capacity, but it would seem important for any results to be meaningful that technical factors, which might otherwise contribute to apparent differences in oxygenation methods, be minimized.

**References**