Impact of periodic breathing on measurement of oxygen uptake and respiratory exchange ratio during cardiopulmonary exercise testing

Darrel P. FRANCIS*,†, L. Ceri DAVIES*,†, Keith WILLSON†, Roland WENSEL†, Piotr PONIKOWSKI‡, Andrew J. S. COATS*† and Massimo PIEPOLI*

*National Heart & Lung Institute, London SW3 6LY, U.K., †Heart Failure Unit, Royal Brompton Hospital, Sydney St, London SW3 6NP, U.K., and ‡Military Hospital Wroclaw, Weigla 5, PL 50-981 Wroclaw, Poland

ABSTRACT

Metabolic exercise testing is valuable in patients with chronic heart failure (CHF), but periodic breathing may confound the measurements. We aimed to examine the effects of periodic breathing on the measurement of oxygen uptake ($V_{\text{O}_2}$) and respiratory exchange ratio (RER). First, we measured the effects of different averaging procedures on peak $V_{\text{O}_2}$ and RER values in 122 patients with CHF undergoing cardiopulmonary exercise testing. Secondly, we studied the effects of periodic breathing on $V_{\text{O}_2}$ and RER in healthy volunteers performing computer-guided periodic breathing. Thirdly, we used a Fourier analysis to study the effects of periodic breathing on gas exchange measurements. The first part of the study showed that 1 min moving window gave a mean peak $V_{\text{O}_2}$ of 13.8 ml·min⁻¹·kg⁻¹ for the CHF patients. A 15 s window gave significantly higher values. The difference averaged 1.0 ml·min⁻¹·kg⁻¹ ($P < 0.0001$), but varied widely: 41% of subjects showed a difference greater than 1.0 ml·min⁻¹·kg⁻¹. RER values were also higher by an average of 0.09 ($P < 0.0001$); in 20% of subjects the difference was greater than 0.10. In the second part of the study, we found artefactual elevations of peak $V_{\text{O}_2}$ (without averaging) of 2.9 ml·min⁻¹·kg⁻¹ ($P < 0.01$) and of peak RER of 0.13 ($P < 0.001$), which were still significant when 30 s averaging was applied [$\Delta (\text{peak } V_{\text{O}_2}) = 1.8 \text{ ml·min}^{-1}·\text{kg}^{-1}, \ P < 0.01; \Delta \text{RER} = 0.08, \ P < 0.001$]. The third, theoretical, part of the study showed that values of carbon dioxide output and $V_{\text{O}_2}$ oscillate with different phases and amplitudes, resulting in oscillations in their ratio, RER. Averaging over 15 s or 30 s can be expected to give only 10% or 36% attenuation respectively. Thus periodic breathing causes variable artefactual elevations of measured peak $V_{\text{O}_2}$ and RER, which can be attenuated by using longer averaging periods. Clinical reports and research publications describing peak $V_{\text{O}_2}$ in CHF should be accompanied by details of the averaging technique used.

INTRODUCTION

Peak oxygen uptake ($V_{\text{O}_2}$) during cardiopulmonary exercise [1] has been identified by several studies [2–7] as one of the most powerful prognostic markers available to the clinician for patients with chronic heart failure (CHF). Wider realization of the clinical value of this measure of integrated physiology is leading to its greater availability and inclusion in epidemiological reports and therapeutic studies.

However, experience with the use in CHF patients of standard respiratory gas exchange measurement techniques developed in healthy individuals has revealed difficulties. Healthy individuals show only small variations in ventilation, which are high frequency (breath-to-breath) and random. The conventional tech-
The implicit assumption is that and can be applied in different co-operating centres. The or 1.05. Such a criterion is useful because it is objective if the respiratory fluctuation in healthy individuals, in that it is slow (cycle time typically 1 min), consistent rather than random, and prominent. Assumptions based on observations in healthy individuals may therefore not be applicable in patients with periodic breathing: the peak value of \( \dot{V}_O_2 \) obtained may be unrepresentative of true metabolic performance.

The second important variable is the respiratory exchange ratio (RER) of carbon dioxide output (\( \dot{V}_{CO_2} \)) to \( \dot{V}_O_2 \) i.e. RER = \( \dot{V}_{CO_2} / \dot{V}_O_2 \). For a valid measurement of maximal aerobic capacity, it is frequently required that RER rises above a predetermined threshold, such as 1.00 or 1.05. Such a criterion is useful because it is objective and can be applied in different co-operating centres. The implicit assumption is that \( \dot{V}_{CO_2} \) and \( \dot{V}_O_2 \) are affected in the same way by periodic breathing, so that RER should be unaffected, yet proof of this is lacking. If this assumption is incorrect, then care should be taken in establishing validity criteria for RER.

The size of this problem in the measurement of \( \dot{V}_O_2 \), \( \dot{V}_{CO_2} \) and RER in routine clinical practice in relation to CHF has not been formally addressed. The present study examines this issue by using three approaches. First, we examine the effects of different averaging periods on the values of peak \( \dot{V}_O_2 \) and RER obtained from a series of 122 consecutive clinical cardiopulmonary exercise tests in patients with CHF. Secondly, to study the specific effects of periodic breathing in more controlled circumstances, healthy volunteers performed voluntary periodic breathing while exercising at three workloads corresponding to low, intermediate and high levels in CHF. The effects of periodic breathing on \( \dot{V}_O_2 \) and RER could thus be observed in isolation from changes in workload. Thirdly, a Fourier-analytical approach to gas exchange is used to develop a generalizable understanding of the effects of periodic breathing on the measured parameters.

**METHODS**

**Clinical cardiopulmonary exercise tests in patients with CHF**

**Patients and clinical exercise protocol**

We retrospectively examined data from 122 consecutive patients with CHF (peak \( \dot{V}_O_2 < 20 \text{ ml \cdot min}^{-1} \cdot \text{kg}^{-1} \)) who had undergone cardiopulmonary exercise testing for clinical purposes at the Brompton Hospital. CHF was diagnosed on the basis of a history of fatigue or breathlessness on exercise, with evidence of fluid retention, left ventricular dysfunction on radionucleide ventriculography or echocardiography, and a peak \( \dot{V}_O_2 < 20 \text{ ml \cdot min}^{-1} \cdot \text{kg}^{-1} \). Patients exercised on a treadmill according to a modified Bruce protocol [additional stage 0: 1 mile/h (1.61 km/h), 5% gradient]. Ventilation, \( \dot{V}_O_2 \) and \( \dot{V}_{CO_2} \) were measured on-line breath-by-breath using a standard Amis 2000 metabolic cart (Innovision, Odense, Denmark), which used a respiratory mass spectrometer [9].

**Impact of averaging on peak \( \dot{V}_O_2 \) and RER in clinical tests**

We studied the effects of different-sized averaging windows on the peak values of \( \dot{V}_O_2 \) and RER. For each subject, peak \( \dot{V}_O_2 \) and RER were determined using moving-average window widths of 15, 30 and 60 s, and the differences between the values obtained using the different averaging widths were calculated.

**Voluntary periodic breathing during exercise in healthy volunteers**

**Voluntary periodic breathing**

Six healthy male volunteers (age 32 ± 5 years) underwent exercise tests at three workload levels with free breathing and also with computer-guided periodic breathing. All volunteers gave informed consent for the study, which was approved by the Ethics Committee.

To enable volunteers to perform periodic breathing reliably, the signal from the pneumotachograph was monitored on-line by a second computer with custom-designed software which displayed their breathing in the form of a moving bar, in association with a target that the subject had to follow. We programmed this system with a fluctuating ventilatory pattern, whose tidal volume varied sinusoidally with a period of oscillation of 60 s, and with a controllable mean and amplitude. The software compared the volunteer’s respiratory rate and
tidal volume with those of the programmed target. It continuously computed and cumulated the difference between intended and actual ventilation, and modified the target accordingly. The subject was thus automatically guided to correct undershoots or overshoots (of rate and/or volume) [9], yielding a reproducible sinusoidal ventilation pattern.

Free breathing and voluntary periodic breathing during exercise

Subjects were familiarized with the equipment before metabolic monitoring commenced. Treadmill slope and speed were increased gradually to identify the slopes and speeds at which the $\dot{V}O_2$ was 10 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$ (henceforth referred to as ‘low’ workload), 15 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$ (‘intermediate’) and 20 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$ (‘high’). These three workloads are intended to correspond to typical workloads that occur during exercise in patients with moderate to severe CHF, in whom not only is periodic breathing common, but also results of exercise physiology may have important therapeutic implications. Gas exchange recordings were then made for 8 min at each of four workload levels (rest, low, intermediate and high), while the subjects breathed spontaneously without any guidance (free breathing). Mean ventilation, $\dot{V}O_2$, $\dot{V}CO_2$ and RER at each workload were calculated. The same workload levels were repeated while the subject was guided to perform periodic breathing. At each level, the computer guided the subject to breathe with an oscillatory pattern whose mean matched the individual’s ventilation during free breathing at that level, but with an amplitude of oscillation of ventilation of 30% of that value. The mean and amplitude of the oscillations in ventilation, $\dot{V}O_2$, $\dot{V}CO_2$ and RER were calculated.

Effectiveness of time-averaging in attenuating oscillations in ventilation

Time-averaging (with window widths of 10, 15, 30 and 60 s) was applied to the data recorded from subjects performing voluntary periodic breathing, and the size of the residual oscillations was assessed. In general, artefacts are problematic when they are large in relation to the size of the signal being measured. We therefore calculated a simple noise-to-signal ratio for each ventilatory parameter: for each subject, the peak-to-trough difference in the measured variable due to voluntary periodic breathing divided by the increment in that variable from low to high workload.

Mathematical effect of periodic breathing on $\dot{V}O_2$ and $\dot{V}CO_2$

The physiology of gas exchange fluctuations during periodic breathing can be addressed mathematically by a Fourier analysis of respiratory gas exchange that we have developed [10], which enables a broad spectrum of physiological situations to be considered with ease. The mathematical dependency of gas-exchange parameters on ventilatory oscillations can be derived.

Statistical analysis

The Statview 4.5 package was used for statistical analysis. Mean (S.D.) values are given. The paired-sample $t$ test was used to assess the difference between pairs of measurements in the same subjects. A $P$ value of $< 0.05$ was considered significant.

RESULTS

Clinical measurements in patients with CHF

Patient characteristics

The mean age of the CHF patients was 58 (S.D. 12) years. Of the 122 patients, 81 had an ischaemic aetiology, 35 had dilated cardiomyopathy and six had heart failure secondary to valvular disease. The mean left ventricular ejection fraction, as assessed by radionuclide ventriculography, was 26% (S.D. 10%) ($n = 87$).

Effectiveness of time-averaging in attenuating oscillations in ventilation

Upper panel: difference between using 15 s and 60 s windows. In 41% of patients, this difference exceeded 1 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$. Lower panel: difference between using 30 s and 60 s windows. In 6% of patients, this difference exceeded 1 ml $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$.

Figure 2 Frequency distribution, in 122 patients with CHF, of difference in peak $\dot{V}O_2$ obtained by averaging exercise data with different window widths

© 2002 The Biochemical Society and the Medical Research Society
Effects of different averaging window widths on \( \dot{V}O_2 \) and RER

The peak \( \dot{V}O_2 \) when measured with a 15 s window, averaged 14.8 (S.D. 3.9) ml \cdot min^{-1} \cdot kg^{-1}. With longer windows of 30 s, 45 s and 60 s, peak \( \dot{V}O_2 \) was 14.2 (3.8), 14.0 (3.8) and 13.8 (3.8) ml \cdot min^{-1} \cdot kg^{-1} respectively.

On an individual patient basis, selecting a 15 s averaging period rather than one of 60 s consistently gave a peak \( \dot{V}O_2 \) that was higher, by an average of 1.0 (S.D. 0.79) ml \cdot min^{-1} \cdot kg^{-1} \( P < 0.0001 \). Even 30 s averaging gave significantly higher peak \( \dot{V}O_2 \) values than 60 s averaging, by 0.43 (0.38) ml \cdot min^{-1} \cdot kg^{-1} \( P < 0.0001 \).

However, these means conceal considerable inter-patient variation (Figure 2) in the size of the disparity between averaging widths. Thus values from 15 s averaging differed from those from 60 s averaging by more than 1.0 ml \cdot min^{-1} \cdot kg^{-1} in 50 out of the 122 patients (41%). In comparison, 30 s averaging gave fewer values differing from 60 s averaging by more than 1.0 ml \cdot min^{-1} \cdot kg^{-1}, i.e. seven out of the 122 patients (6%).

The peak RER averaged 1.05 (S.D. 0.01) using a 60 s window. Because RER is the ratio between \( \dot{V}CO_2 \) and \( \dot{V}O_2 \), it might be expected to be little affected, if at all, by ventilatory irregularities. However, the peak RER values with 15 s and 30 s averaging were higher than those with 60 s averaging by 0.09 (S.D. 0.12) \( P < 0.0001 \) and 0.04 (0.05) \( P < 0.0001 \) respectively.

Again, some subjects showed larger discrepancies between averaging methods than others, as shown in Figure 3. Thus 15 s and 30 s averaging gave results that differed from that with 60 s averaging by more than 0.10 in 24 (20%) and 10 (8%) of the total of 122 patients respectively.

Effects of controlled voluntary periodic breathing on \( \dot{V}O_2 \) and RER

All volunteers were able to complete the protocol of free breathing and periodic breathing during exercise successfully. Mean ventilation and mean \( \dot{V}O_2 \) were not significantly different between the free-breathing and voluntary periodic breathing tests at matched workloads, as shown in Table 1. Figure 4 shows an example of the patterns of the size and phase of the oscillations in the six subjects. Tables 2 and 3 show the means of amplitudes and phases respectively of the oscillations in the six subjects.

Effectiveness of time-averaging in attenuating oscillations due to periodic breathing

The effects of averaging of data (using different periods from 10 s to 90 s) on the size of the oscillations due to periodic breathing as well as on the noise-to-signal ratio (calculated as described in the Methods section) are
Impact of periodic breathing on O₂ uptake and respiratory exchange ratio

Figure 4  Voluntary periodic breathing in a representative healthy control subject at rest and at the three exercise levels
Panels show the oscillations in ventilation, V̇O₂, V̇CO₂ and RER with computer guidance of respiration to maintain periodic breathing with a period of 60 s and an amplitude of 30% of mean ventilation (see the Methods section). Note that the oscillation in V̇O₂ becomes relatively smaller and shifts to an earlier phase as workload increases (see Tables 2 and 3 for measurements). This does not occur for V̇CO₂. The oscillation in RER therefore becomes larger.

shown in Table 2. Narrow windows, such as 10 s and 15 s, gave very little attenuation of the oscillations, and resulted in relatively large noise-to-signal ratios. Longer windows (30 s and 45 s) gave better attenuation; when the window was as long as the period of oscillation (60 s), attenuation was almost complete. When the window was even longer (90 s), some of the oscillation recurred.

At high workloads, voluntary periodic breathing caused an artefactual elevation in V̇O₂ of 2.6 ml · min⁻¹ · kg⁻¹ when conventional 15 s averaging was used. The effect of periodic breathing on RER was even larger, as a proportion of the size of the change that occurred in the variable due to increasing workload. The noise-to-signal ratio for RER with the standard 15 s window width was 2.7. The window had to be widened to 45 s for this ratio to fall to a more acceptable 0.9.

Theoretical basis for the effect of periodic breathing on RER
Oscillation in ventilation causes oscillation in lung gas stores, the effect of which on measured V̇O₂, V̇CO₂ and RER can be evaluated mathematically (as described in the Appendix). The larger the variation in ventilation due to periodic breathing (as a proportion of the mean ventilation), the larger are the resultant oscillations in V̇O₂, V̇CO₂ and RER (as a proportion of their corresponding...
and phases of the relative oscillations in ventilation, and are different in phase. Figure 5 (left panel) shows how the amplitudes of oscillation in ventilation (marked with a star) is represented by the distance from the centre of the diagram (length of the arrows). The timing, or phase, relative to that of ventilation (marked with a star) is represented by the angle, with one complete circle equivalent to one period of oscillation.

The relationships of the sizes and phases are dependent on both mean ventilation and cardiac output, but a useful general appreciation can be gained by considering that both of these parameters increase proportionally with increasing workload. Based on this assumption, Figure 5 (right panel) shows the effects of increasing workload. In this diagram, the vectors are represented by points rather than arrows (allowing many to be shown on the same diagram). At low workloads, the artefactual fluctuations in \( \Delta V_{\text{CO}} \) and RER are of similar relative amplitude to the ventilatory oscillations that are driving them. Consequently, the fluctuations in RER are relatively small. As workload increases (in the direction of the arrows), the oscillations in \( \Delta V_{\text{O}} \) become much smaller (and move to an earlier phase), while those in \( \Delta V_{\text{CO}} \) remain of a similar relative size and phase to the driving ventilatory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Low workload</th>
<th>Intermediate workload</th>
<th>High workload</th>
<th>Noise-to-signal ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta V_{\text{CO}} ) (ml \cdot min(^{-1}) \cdot kg(^{-1}))</td>
<td>Mean</td>
<td>114 ± 19</td>
<td>251 ± 28</td>
<td>309 ± 39</td>
<td>516 ± 31</td>
</tr>
<tr>
<td>Oscillatory amplitude</td>
<td>Without averaging</td>
<td>23 ± 5</td>
<td>64 ± 12</td>
<td>123 ± 20</td>
<td>154 ± 19</td>
</tr>
<tr>
<td>With averaging width:</td>
<td>10 s</td>
<td>22 ± 5</td>
<td>61 ± 11</td>
<td>117 ± 19</td>
<td>147 ± 18</td>
</tr>
<tr>
<td>15 s</td>
<td>21 ± 4</td>
<td>57 ± 11</td>
<td>110 ± 18</td>
<td>139 ± 17</td>
<td>0.74</td>
</tr>
<tr>
<td>30 s</td>
<td>18 ± 3</td>
<td>40 ± 7</td>
<td>77 ± 12</td>
<td>98 ± 11</td>
<td>0.52</td>
</tr>
<tr>
<td>45 s</td>
<td>8 ± 2</td>
<td>18 ± 3</td>
<td>36 ± 6</td>
<td>45 ± 6</td>
<td>0.24</td>
</tr>
<tr>
<td>60 s</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>0.02</td>
</tr>
<tr>
<td>90 s</td>
<td>5 ± 1</td>
<td>13 ± 3</td>
<td>25 ± 4</td>
<td>32 ± 4</td>
<td>0.17</td>
</tr>
<tr>
<td>( \Delta V_{\text{O}} ) (ml \cdot min(^{-1}) \cdot kg(^{-1}))</td>
<td>Mean</td>
<td>4.5 ± 0.4</td>
<td>10.0 ± 0.3</td>
<td>13.0 ± 0.5</td>
<td>19.9 ± 0.9</td>
</tr>
<tr>
<td>Oscillatory amplitude</td>
<td>Without averaging</td>
<td>1.4 ± 0.2</td>
<td>2.1 ± 0.1</td>
<td>2.3 ± 0.1</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>With averaging width:</td>
<td>10 s</td>
<td>1.4 ± 0.2</td>
<td>2.0 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>15 s</td>
<td>1.3 ± 0.2</td>
<td>1.9 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.6 ± 0.4</td>
<td>0.45</td>
</tr>
<tr>
<td>30 s</td>
<td>0.9 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.8 ± 0.3</td>
<td>0.31</td>
</tr>
<tr>
<td>45 s</td>
<td>0.4 ± 0.1</td>
<td>0.6 ± 0.0</td>
<td>0.7 ± 0.0</td>
<td>0.9 ± 0.1</td>
<td>0.15</td>
</tr>
<tr>
<td>60 s</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.01</td>
</tr>
<tr>
<td>90 s</td>
<td>0.3 ± 0.0</td>
<td>0.4 ± 0.0</td>
<td>0.5 ± 0.0</td>
<td>0.6 ± 0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>RER</td>
<td>Mean</td>
<td>0.81 ± 0.03</td>
<td>0.80 ± 0.03</td>
<td>0.84 ± 0.02</td>
<td>0.87 ± 0.02</td>
</tr>
<tr>
<td>Oscillatory amplitude</td>
<td>Without averaging</td>
<td>0.06 ± 0.01</td>
<td>0.10 ± 0.01</td>
<td>0.13 ± 0.01</td>
<td>0.13 ± 0.01</td>
</tr>
<tr>
<td>With averaging width:</td>
<td>10 s</td>
<td>0.06 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>0.13 ± 0.01</td>
</tr>
<tr>
<td>15 s</td>
<td>0.05 ± 0.00</td>
<td>0.09 ± 0.01</td>
<td>0.11 ± 0.01</td>
<td>0.12 ± 0.01</td>
<td>2.71</td>
</tr>
<tr>
<td>30 s</td>
<td>0.04 ± 0.00</td>
<td>0.06 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>1.90</td>
</tr>
<tr>
<td>45 s</td>
<td>0.02 ± 0.00</td>
<td>0.03 ± 0.00</td>
<td>0.04 ± 0.00</td>
<td>0.04 ± 0.00</td>
<td>0.90</td>
</tr>
<tr>
<td>60 s</td>
<td>0.01 ± 0.00</td>
<td>0.01 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.09</td>
</tr>
<tr>
<td>90 s</td>
<td>0.01 ± 0.00</td>
<td>0.02 ± 0.00</td>
<td>0.03 ± 0.00</td>
<td>0.03 ± 0.00</td>
<td>0.62</td>
</tr>
</tbody>
</table>

The noise-to-signal ratio is defined as the peak-to-trough difference divided by the difference between values at the low and high workloads.
Table 3  Phase of oscillations in measured $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and RER during voluntary periodic breathing with a period of 60 s at four workload levels
A positive phase indicates an oscillation whose peak precedes that of ventilation. Note that 360° = 1 cycle = 60 s in this study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Low workload</th>
<th>Intermediate workload</th>
<th>High workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation</td>
<td>$\dot{V}_{O_2}$</td>
<td>35 ± 11</td>
<td>35 ± 5</td>
<td>44 ± 6</td>
</tr>
<tr>
<td></td>
<td>$\dot{V}_{CO_2}$</td>
<td>26 ± 11</td>
<td>12 ± 3</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>RER</td>
<td>$-46 \pm 13$</td>
<td>$-33 \pm 6$</td>
<td>$-22 \pm 7$</td>
<td>$-28 \pm 3$</td>
</tr>
</tbody>
</table>

fluctuations. Consequently, the artefact in RER becomes larger and moves closer into phase with the periodic breathing.

Effect of time-averaging of metabolic data
Figure 6 shows the effect of increasing the width of the averaging window on the $\dot{V}_{O_2}$ trace. As the averaging window is widened, the size of the peak artefact is reduced, although if the window becomes wider than the period of oscillation then the oscillation reappears (in opposite phase).

In general, a variable oscillating sinusoidally with amplitude $A$ and period $T$, when averaged with a rectangular window of duration $t_a$, becomes attenuated, yielding a residual oscillation with amplitude given by:

$$Amplitude = A \cdot \frac{\sqrt{1 - \cos(2\pi t_a / T)}}{2 \sqrt{\frac{2\pi t_a}{T}}}$$

The size of this residual oscillation, as a proportion of the size of the underlying oscillation, is plotted in Figure 7. With a width of 15 s (one-quarter of a cycle), 90% of the amplitude remains; if the averaging width is widened to
The Fourier analysis reveals the reasons for fluctuations not only in VO₂ and VCO₂, but also in RER – which might have been expected to be resistant to fluctuation because it is the ratio of VCO₂ to VO₂. It also explains why the fluctuations in RER become more prominent (in relation to the size of the ventilatory oscillations) as workload increases.

**Clinical importance of oscillations in VO₂**

Periodic breathing is common in patients with CHF, especially in severe disease [11]; a quantitative explanation of its origin and treatment has been presented [12]. Determination of peak VO₂ is usually performed automatically by software that calculates moving averages for VO₂ (typically with 15 s or 30 s windows) and selects the highest such average value during exercise. If an individual has periodic breathing, the peak value thus obtained will exceed the true VO₂ by an amount equal to the amplitude of the oscillations. The extent of this overestimation, judging from the histogram in Figure 2, may be several ml · min⁻¹ · kg⁻¹ in some patients.

The important irony is that periodic breathing is associated with a poorer prognosis [13,14], but its effect on the measurement of peak VO₂ is to cause an artefactual elevation, which has two consequences. First, epidemiological studies will underestimate the prognostic value of peak VO₂ in CHF. Secondly, in a study of therapy, if a patient with stable breathing were later to develop periodic breathing without any change in true exercise capacity, there would appear to be an increase in peak VO₂, despite the development of an adverse prognostic feature. This problem may be important if treatment-associated changes in peak VO₂ are only of the order of 1–2 ml · min⁻¹ · kg⁻¹, since the artefact from periodic breathing may also be of the order of 1–2 ml · min⁻¹ · kg⁻¹. At the very least, the problem of periodic breathing adds to the time and cost of conducting the study, since the required study size (determined by power calculations) is quadrupled for every doubling of inter-test variability.

**Clinical significance of oscillations in RER**

The adequacy of exercise effort may be assessed in several ways, including identification of the anaerobic threshold by the V-slope method [15] and visual identification of a marked increase in ventilation (or fall in end-tidal CO₂) without a concomitant increase in VO₂. However, these techniques are not always successful [16] and show inter-observer variation. Confirming adequacy using a predetermined threshold for peak RER is therefore helpful in standardizing interpretation of therapeutic trials and whenever several centres (and therefore several observers) are involved.

Because RER is a ratio between two variables, which both depend on ventilation, it might be expected to be unaffected by ventilatory fluctuations. This is certainly
the case for the high-frequency breath-to-breath random variation in tidal volume that is typically seen in exercise testing of normal subjects. However, periodic breathing is a different phenomenon, characterized by slow and non-random oscillations.

The data from the normal control subjects performing voluntary periodic breathing (Table 2), and the results of the mathematical analysis, reveal that the oscillations in $\dot{V}_O$ and $\dot{V}_{CO_2}$ behave differently as workload increases. At low workloads, the oscillations in $\dot{V}_O$ and $\dot{V}_{CO_2}$ are of a similar size and are in phase. Their ratio, RER, is therefore relatively stable. As workload increases, the relative size of the oscillations in $\dot{V}_O$ becomes more attenuated than that of those in $\dot{V}_{CO_2}$; moreover, the phase of the $\dot{V}_O$ oscillations becomes earlier with respect to the phase of those in $\dot{V}_{CO_2}$. Consequently the oscillations in RER become paradoxically more prominent, despite its determinant factors becoming more stable. Even moderate ventilatory oscillations produce clinically significant fluctuations in RER at high exercise levels. For example, in the lower right panel of Figure 4, it can be seen that, despite an underlying RER of only 0.90, periodic breathing generated a peak RER of 1.10. Such artefactually high peak RER values may be wrongly interpreted to signify an adequate exercise test.

**Study limitations**

This study does not address or review the mechanism of periodic breathing itself, which has been analysed elsewhere [12]. Several years ago, clinical data showing a difference between patients with spontaneous periodic breathing and healthy control subjects simulating periodic breathing was interpreted to mean that the spontaneous oscillations in $\dot{V}_O$ in CHF patients could not arise from oscillatory ventilatory control [17]. However, we now recognize several aspects of the initial interpretation to be incorrect due to the absence of a mathematical framework to understand the effects of oscillatory ventilation on gas exchange. Once subjected to quantitative analysis with the mathematical framework, the data of Ben-Dov et al. [17] are shown [10] to be strongly suggestive of a ventilatory origin of oscillatory gas exchange.

**Implications for cardiopulmonary exercise testing in patients with CHF**

Conventional 15 s or 30 s averaging, while appropriate for subjects with stable ventilation, results in over-estimates of $\dot{V}_O$ and RER in patients with periodic breathing (which is common in CHF). This is because the characteristics of the ventilatory fluctuations in periodic breathing are fundamentally different from the high-frequency, breath-by-breath variations typically observed in normal subjects. This artefactual upward bias in $\dot{V}_O$ and RER values can be attenuated by using longer averaging periods. However, if the averaging period is made very long (e.g. several minutes) then the last averaging segment is centred on a time rather earlier than the end of exercise, which is a potential disadvantage if the values are continuing to rise throughout exercise.

One option would be to use short-term averaging if breathing is stable, and longer-term averaging if it is periodic. However, this option has the disadvantage of introducing subjectivity (distinction between periodic and stable breathing) into a test whose principal merit is its objectivity.

We therefore recommend a standardized averaging period similar to the length of the typical periodic breathing cycle, i.e. 60 s, regardless of whether breathing is periodic or stable. This would improve the physiological validity of the value obtained in subjects with periodic breathing, without adverse effects in subjects with stable breathing. The presence of periodic breathing could be assessed and reported separately, since it is a predictor of relatively poor prognosis: this assessment would of course be made on the raw data before 60 s averaging.

At the very least, reports of peak $\dot{V}_O$ and peak RER during exercise (both in clinical practice and in research publications) from patients with CHF ought to be accompanied by details of the averaging technique used. This is as important as knowing whether the exercise is on a treadmill or a bicycle and the protocol used (both of which are always reported). This information would assist in interpreting discrepancies between findings from different centres, for example when comparing the relative prognostic value of peak $\dot{V}_O$ against other parameters, or considering the effects of therapy on exercise capacity in patients with CHF.

**APPENDIX**

We use a single-compartment model of lung gas exchange [10] to consider sinusoidal oscillation in alveolar ventilation $\dot{V}_A$, with mean $\dot{V}_A$, amplitude $A_{\dot{V}_A}$ and frequency of oscillation $f_{\dot{V}_A}$ (typically 1/min). We define $\delta\dot{V}_A$ to be the displacement of alveolar ventilation away from its mean, so that $\dot{V}_A = \dot{V}_A + \delta\dot{V}_A$, where $\delta\dot{V}_A = A_{\dot{V}_A} \cdot \sin(2\pi f_{\dot{V}_A} t)$. We define $\dot{V}_{CO_2}$ similarly:

$$\dot{V}_{CO_2} = \dot{V}_{CO_2} + \delta\dot{V}_{CO_2}$$

$$= \dot{V}_{CO_2} \left(1 + \frac{\delta\dot{V}_{CO_2}/\dot{V}_{CO_2}}{\delta\dot{V}_A/\dot{V}_A} \cdot \frac{\delta\dot{V}_A}{\dot{V}_A}\right)$$

(A corresponding equation can be written for $\dot{V}_O$.) The term

$$\frac{\delta\dot{V}_{CO_2}/\dot{V}_{CO_2}}{\delta\dot{V}_A/\dot{V}_A}$$

encompasses a scaling effect and a change of phase. This combined effect is a complex number whose value can be found by Fourier analysis [10] and is dependent.

© 2002 The Biochemical Society and the Medical Research Society
on certain parameters of gas exchange physiology [10]. It can be expressed efficiently using variables that index ventilation and cardiac output for lung size, namely \( v = \dot{V}_A/(2\pi f_{TV} V_A) \) and \( q = \dot{Q} \dot{P}_B/(2\pi f_{TV} V_A) \), where \( V_A \) represents alveolar volume, \( Q \) is cardiac output, \( \beta \) is the capacitance coefficient for \( CO_2 \) in blood, \( P_b \) is atmospheric pressure and \( j \) is the square root of \(-1\):

\[
\frac{\delta \dot{V}_{CO_2}/\dot{V}_{CO_2}}{\delta V_A/V_A} = \frac{j + q}{j + (q + v)}
\]

\[
\frac{\delta \dot{V}_{O_2}/\dot{V}_{O_2}}{\delta V_A/V_A} = \frac{j}{j + v}
\]

RER is defined as \( \dot{V}_{CO_2}/\dot{V}_{O_2} \), so that:

\[
\text{RER} = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} \left( 1 + \frac{\delta \dot{V}_{CO_2}/\dot{V}_{CO_2}}{\delta V_A/V_A} \frac{\delta \dot{V}_A}{\dot{V}_A} \right)
\]

Thus the relative amplitude and phase of the fluctuation in RER (in comparison with the fluctuation in alveolar ventilation) are dependent on alveolar ventilation and cardiac output in the following way:

\[
\frac{\delta \text{RER}/\text{RER}}{\delta \dot{V}_A/\dot{V}_A} \approx \frac{\delta \dot{V}_{CO_2}/\dot{V}_{CO_2}}{\delta \dot{V}_A/\dot{V}_A} \frac{\delta \dot{V}_{O_2}/\dot{V}_{O_2}}{\delta \dot{V}_A/\dot{V}_A} = \frac{q \cdot v}{(j + v + q)(j + v)}
\]

This varies from 0 (i.e. RER unaffected by periodic breathing) at a theoretical state of zero cardiac output, to 1 (i.e. RER fluctuating in phase with, and in direct proportion to, the fluctuations in ventilation) when cardiac output is very high.

REFERENCES


Received 27 May 2002; accepted 6 September 2002