Oscillations in stroke volume and cardiac output arising from oscillatory ventilation in humans

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Oscillations in the cardiovascular system have been observed in patients with periodic breathing. It is not clear whether these are driven by primary oscillations in the respiratory system or whether an intrinsic cardiovascular instability is required, as previous studies with subjects performing voluntary periodic breathing have failed to produce the cardiovascular oscillations. We investigated whether cardiovascular oscillations occurred in healthy controls performing voluntary periodic breathing. Six healthy subjects performed voluntary periodic breathing with guidance from a real-time computer display. We measured ventilation, end-tidal partial pressures of O₂ (P₀₂) and CO₂ (P₀₂), heart rate, blood pressure (BP), arterial oxygen saturation and stroke volume and cardiac output by transthoracic impedance cardiography. Fourier analysis was used to quantify the size and phase of the periodic breathing-induced oscillations in these parameters. Periodic breathing (amplitude 30% of mean ventilation) induced oscillations in end-tidal P₀₂ (amplitude 0.8 kPa), end-tidal P₀₂ (amplitude 0.3 kPa), R–R interval (amplitude 32.6 ms), systolic BP (amplitude 3 mmHg), diastolic BP (amplitude 3 mmHg), stroke volume (amplitude 8.0 ml, mean 79.5 ml) and cardiac output (amplitude 0.6 1, mean 5.9 1 min⁻¹). The oscillations in stroke volume and cardiac output were nearly in phase with ventilation, with their peaks occurring 5.6 and 6.1 s, respectively, after the peak in ventilation. An oscillatory ventilatory pattern entrains the cardiovascular system in healthy controls into fluctuations, not only in heart rate and BP, but also in stroke volume and cardiac output. Experimental Physiology (2000) 85.6, 857–862.
METHODS

Subjects
Six healthy male volunteers were recruited. Their average age, height and weight (mean ± s.d.) were 33 ± 9 years, 1.77 ± 0.61 m and 79.2 ± 8.9 kg, respectively. All gave informed consent and the local Ethics Committee approved the study.

Physiological measurements
Blood pressure was measured non-invasively by a photoplethysmographic device (Finapres, Ohmeda, CA, USA), with the cuffed finger resting comfortably at heart level. Each subject underwent several minutes of familiarisation and the servo-adjust mechanism was turned off prior to recording. The ECG (Hewlett-Packard) was acquired from a limb lead with a large R wave. Respiratory volume and cardiac output were measured by a custom-designed software. The readings were saved onto disk and analysed off-line with custom-designed software. The program measured R-R intervals and beat-to-beat systolic blood pressure.

Impedance cardiography
Stroke volume and cardiac output were measured non-invasively by thoracic impedance cardiography (NCCOM 3, BoMed) as previously described and validated (Appel et al. 1986; Gotshall et al. 1989; Bogaard et al. 1997). Pairs of recording electrodes were placed at the base of the neck and at the level of the xiphisternum. Pairs of electrodes injecting a constant current (2.5 mA, 70 kHz) were placed 5 cm above the cervical electrodes and below the thoracic electrodes. Left ventricular stroke volume (SV) was calculated by the Sramek-Bernstein equation (Bernstein, 1986): $SV = (VEPT) \times (TPI) \times (EVI) \times (LVET)$ where VEPT is the volume of tissues electrically participating in thoracic impedance (Bernstein, 1986), TPI is the impedance of thoracic fluid volume, EVI is the ejection velocity index and LVET is the left ventricular ejection time (Fig. 1).

![Figure 1](image)

Figure 1
Example of impedance signal (Imp) and its first derivative (dImp/dt, t = time), indicating measurements made for calculation of left ventricular stroke volume.

The origin of impedance signals is still controversial, although several investigators have shown that there is a reasonable linear relationship between impedance change and the blood volume change in the aorta and that the lungs contribute little to any overall impedance changes (Fuller, 1994; Ouypek & Gersing, 1995; Newman & Callister, 1999).

Cardiac output was obtained as the product of stroke volume and heart rate. Both stroke volume and cardiac output were calculated on a beat-to-beat basis.

Voluntary periodic breathing
All subjects performed 8 min of voluntary periodic breathing. To enable volunteers to simulate PB, the signal from the pneumotachograph was monitored on-line by a second computer system (Carrera, UK) with custom-designed software which displayed a moving bar representing their breathing, in association with a target. We programmed this system with a fluctuating ventilatory pattern, whose tidal volume varied sinusoidally with a period of oscillation of 1 min, and with a controllable mean and amplitude. The respiratory frequency was kept constant. The software compared the volunteer’s respiratory rate and tidal volume with those of the programmed target. It continuously computed and cumulated any small differences between intended and actual ventilation. It used this information to modify the target presented to the volunteer. The subject was thus automatically guided to correct undershoots or overshoots (of rate and/or volume). The result achieved was a reproducible and stable sinusoidal ventilation pattern. For this study, an amplitude of oscillation in ventilation of 30% was chosen to ensure that episodic desaturations occurred and that the periodic breathing was relatively easy to perform.

Assessment of amplitude and phase of oscillations
This study focused on the fluctuations which occur in the measured physiological variables at the frequency of the periodic breathing (1/60 Hz). Six consecutive cycles of stable, artefact-free data were digitally resampled at 1 Hz and underwent Fourier transformation. The periodic breathing was deliberately regulated to a fixed and known frequency (1/60 Hz), and the length of the data segment studied was set to an exact multiple of the period of oscillation of interest (1 min), so that the direct Fourier transformation (Brigham, 1988) could be used to unambiguously quantify the amplitude and phase of the resultant cardiovascular oscillations. Amplitude was calculated as the square root of the spectral power in the band 0.010–0.040 Hz, which contains the PB frequency of 1/60 Hz. Phase was calculated using the arctangent formula applied to the real and imaginary parts of the component at 1/60 Hz, having regard to their signs (Cohen, 1995). Coherence between signals was assessed by the magnitude-squared method.

Statistical analysis
Numerical data of groups are summarised by the mean and standard error of the mean. Statistical analysis was carried out using Statview 4.5 (Abacus Concepts, Berkeley, CA, USA).

RESULTS

All subjects successfully performed the periodic breathing protocol and demonstrated periodic desaturations to a mean O2 saturation of 96.4 ± 0.4 %.

Size of oscillations
Fourier analysis of the data obtained during voluntary periodic breathing revealed that the ventilatory oscillations resulted in coherent oscillations in end-tidal O2 and CO2, R-R
interval, BP, stroke volume and cardiac output at the same frequency of 1/60 Hz, as shown in Fig. 2.

The mean values of these variables and the size of their oscillations are shown in Table 1.

It can be seen that the relative sizes of the cardiovascular oscillations are much lower than those in ventilation, with the amplitude of oscillation in ventilation (as a proportion of each subject's mean ventilation) averaging 28% and those in cardiac output averaging 10%. This oscillation in cardiac output was principally attributable to the 9.6% oscillation in stroke volume, since the oscillation in R–R interval was only 4%. (The relative amplitude of cardiac output is less than the sum of the relative amplitudes of stroke volume and R–R interval, because the latter two variables do not oscillate in phase.)

**Phase of oscillations**
The phase difference between the peak in cardiovascular oscillations and the peak in ventilation is shown in Fig. 3. Peak BP occurred approximately 1/4 cycle before peak ventilation (systolic BP at −134 ± 1.2 s, diastolic BP at −168 ± 10 s). The trough in end-tidal O₂ occurred after the trough in ventilation (9.4 ± 0.8 s). It can be seen that the trough in O₂ saturation occurred 17 s after the trough in end-tidal O₂. This delay is due to a combination of a vascular transit delay between the lungs and the earlobe oximeter probe and a short delay of 1–1.5 s attributable to the 2–3 s averaging performed by the device. Stroke volume peaked just after peak ventilation at 5.6 ± 2.0 s. R–R interval was longest just after, at 15.1 ± 4.3 s. Because the relative fluctuations in stroke volume were much larger than those in R–R interval, cardiac output peaked near the time of peak stroke volume, at 6.1 ± 2.7 s.

Coherence between the oscillations in the measured parameters and ventilation was calculated by the magnitude squared method. The value ranges between 0 (no consistent temporal relationship between the oscillations) and 1 (completely consistent temporal relationship between the oscillations) (Malliani et al. 1991). The mean coherences for the measured

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**Figure 2**
Example of voluntary periodic breathing showing the accompanying cardiovascular oscillations. (Oxygen saturation is measured at the earlobe.)
variables are shown in Table 2. All variables had a mean coherence with ventilation in excess of 0.50.

**DISCUSSION**

This study shows that when healthy volunteers breathe according to a controlled PB pattern, coherent oscillations are generated in stroke volume, R–R interval, cardiac output and blood pressure. The stroke volume oscillations, whilst smaller than the ventilatory oscillations, are larger than those in R–R interval and are the dominant contributor to the fluctuations seen in cardiac output. The oscillations in stroke volume and cardiac output are very nearly in phase with those of ventilation whilst the oscillations in blood pressure peak a quarter of a cycle before ventilation.

![Figure 3](image_url)

**Figure 3**

Phase of cardiovascular oscillations with respect to ventilation during voluntary PB. (Oxygen saturation is measured at the earlobe.)
Previous studies in subjects with spontaneous PB have observed simultaneous cardiovascular oscillations in cardiac output (as measured by radionuclide scintigraphy, Yajima et al. 1994), stroke volume (as measured by Doppler echocardiography, Maze et al. 1989), blood pressure (Dowell et al. 1971) and cerebral blood flow (Franklin et al. 1997). One study (Yajima et al. 1994) asked patients with chronic heart failure to perform PB voluntarily and observed that cardiac output was not entrained into oscillations. A second study (Ben-Dov et al. 1992) with normal controls performing voluntary PB failed to reproduce the oscillations in pulmonary gas exchange seen in patients with spontaneous PB. These two studies have been considered as evidence against a primary ventilatory origin for the cardiovascular oscillations seen in spontaneous PB, and a primary haemodynamic/metabolic oscillator has therefore been proposed (Ben-Dov et al. 1992, Yajima et al. 1994). The difficulty with such a proposal is that it has been observed that the pattern of cardiovascular oscillations in patients with PB is the same regardless of whether the aetiology is chronic heart failure or cerebrovascular disease with normal left ventricular function (Maze et al. 1989).

The failure to produce cardiovascular oscillations in controls performing voluntary PB in previous studies may reflect the extreme difficulty subjects have in performing stable PB voluntarily. There is a natural tendency towards a substantial increase in mean ventilation when PB is simulated without guidance, which can be seen in the published data (Ben-Dov et al. 1992, Yajima et al. 1994). While this increase in mean ventilation may have been assumed by previous workers to have no consistent effect on the physiology being studied, we have recently shown (Francis et al. 1999) that this assumption may not be correct. In addition, we showed that normal subjects performing voluntary periodic breathing closely matched the ventilatory and pulmonary gas exchange oscillations seen in patients with chronic heart failure exhibiting spontaneous periodic breathing. The results of the present study may therefore represent resting physiology more closely. The second difficulty with the previous studies is that since the oscillations in ventilation achieved were irregular, it was necessary to use visual assessment of amplitude and phase. In general, this leads to a greater degree of uncertainty in measurements and consequently a reduced statistical power to detect an effect. Our study arranged to have consistent ventilatory oscillations over a period of several minutes, so that the amplitudes, phases and coherences of the consequent oscillations could be quantified by a standard objective technique, namely, Fourier analysis.

The patterns of the cardiovascular oscillations found in our study were similar to those seen in studies with patients with spontaneous PB.

The Doppler studies by Maze et al. (1989) in patients with spontaneous PB showed oscillations in left ventricular outflow velocity approximately in phase with ventilation (although quantitative measurement of phase was not available); our study showed a similar concordance in phase between ventilation and stroke volume. Maze et al. (1989) estimated the stroke volume to have oscillated with an amplitude of 12.5% of its mean value; in our study the observed amplitude in stroke volume was 10%. They found no significant difference in heart rate between the two phases of the respiration cycle, our study did show oscillations in heart rate, but these were comparatively small (4%), and therefore, would be likely to be missed on a purely visual assessment.

The radionuclide studies of Yajima et al. (1994) in patients with spontaneous PB showed oscillations in left ventricular ejection fraction at rest and during exercise. They reported an average lag of about 30 s between ventilation and ejection fraction, which is in complete contrast to the findings of Maze et al. (1989) and of our study. However, from the data tracings (all 5 of which are displayed in the publication), it appears that the phase relationship was variable and unclear and that therefore the phase assessment performed (which was visual and based solely on the identification of peaks) may have been difficult. Our study was able to utilise a Fourier approach, which has the advantages of using all the available information to determine phase, rather than the peaks alone, and also of being observer independent.

It has been suggested (Hurst, 1985) that the reason for the fluctuation in cardiac output in patients with PB is that the hypoxic episodes cause transient disturbances in left ventricular function. In our current study, although the trough of cardiac output occurs near the peak of the oxygen saturation, it coincides very closely with the trough in end-tidal $O_2$. Whilst Maze et al. (1989) did not measure oxygen saturations, another study in heart failure patients with periodic breathing (Goldberger et al. 1984) showed that the trough in oxygen saturation coincided closely with the peak in ventilation. However, end-tidal gas partial pressures were not measured in this study, and there is no indication as to whether a delay due to vascular transit had been taken into account. Despite this, the oscillations seen in end-tidal $O_2$ and the fall in oxygen saturation are relatively small and are, therefore, unlikely to account for the relatively large oscillations in stroke volume and cardiac output. There does, however, remain the possibility that such a hypoxic effect could occur, but be over-

### Table 2. Coherence between the oscillations in ventilation (voluntary periodic breathing) and the resultant oscillations in the other measured variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coherence with ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal $O_2$ (kPa)</td>
<td>0.93 ± 0.03</td>
</tr>
<tr>
<td>End-tidal CO$_2$ (kPa)</td>
<td>0.86 ± 0.08</td>
</tr>
<tr>
<td>R–R interval (ms)</td>
<td>0.67 ± 0.06</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.81 ± 0.05</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.87 ± 0.02</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>0.72 ± 0.09</td>
</tr>
<tr>
<td>Cardiac output (l min$^{-1}$)</td>
<td>0.71 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M.
rendered by other simultaneous phenomena resulting from chemoreceptor or stretch receptor stimulation (Vatner & Rutherford, 1981). Clearly, the subjects in this study were healthy and it may be that the effect of oxygen desaturation on cardiac function may be more profound in patients with cardiovascular disease.

A further potential mechanism for the fluctuations seen in cardiac output and stroke volume could be related to the mechanical effects of respiration. Although we did not directly measure intrathoracic pressure changes during voluntary periodic breathing, it is likely that they also oscillated as the end-expiratory lung volumes varied throughout the cycle. This would have an effect on preload and afterload conditions resulting in oscillations in stroke volume. The effect of changes in intrathoracic pressure on cardiac performance will not necessarily be the same in patients with heart disease as in our study population.

In summary, we have shown that the imposition of voluntary periodic breathing in healthy subjects entrains coherent oscillations in cardiac output, attributable in large part to fluctuations in stroke volume and also to fluctuations in heart rate. Whilst this study is unable to rule out the presence of a cardiovascular oscillator as the cause of oscillations in stroke volume and cardiac output seen in chronic heart failure, the role of primary ventilatory oscillations should not be neglected.


Volume and cardiac output seen in chronic heart failure, the cardiovascular oscillator as the cause of oscillations in stroke rate. Whilst this study is unable to rule out the presence of a cardiovascular oscillator as the cause of oscillations in stroke volume and cardiac output seen in chronic heart failure, the role of primary ventilatory oscillations should not be neglected.


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