Very-low-frequency oscillations in heart rate and blood pressure in periodic breathing: role of the cardiovascular limb of the hypoxic chemoreflex

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A B S T R A C T

In chronic heart failure, very-low-frequency (VLF) oscillations (0.01–0.04 Hz) in heart rate and blood pressure may be related to periodic breathing, although the mechanism has not been fully characterized. Groups of ten patients with chronic heart failure and ten healthy controls performed voluntary periodic breathing with computer guidance, while ventilation, oxygen saturation, non-invasive blood pressure and RR interval were measured. In air, voluntary periodic breathing induced periodic desaturation and prominent VLF oscillations when compared with free breathing in both patients [RR interval spectral power from 179 to 358 ms^2 ($P < 0.05$); systolic blood pressure (SBP) spectral power from 3.44 to 6.25 $mmHg^2$ ($P < 0.05$)] and controls [RR spectral power from 1040 to 2307 ms^2 ($P < 0.05$); SBP spectral power from 3.40 to 9.38 $mmHg^2$ ($P < 0.05$)]. The peak in RR interval occurred 16–26 s before that in SBP, an anti-baroreflex pattern. When the patients followed an identical breathing pattern in hyperoxic conditions to prevent desaturation, the VLF RR interval spectral power was 50% lower (179.0 ± 51.7 ms^2; $P < 0.01$) and the VLF SBP spectral power was 44% lower (3.51 ± 0.77 $mmHg^2$; $P < 0.01$); similar effects were seen in controls (VLF RR power 20% lower, at 1847 ± 899 ms^2, $P < 0.05$; VLF SBP power 61% lower, at 3.68 ± 0.92 $mmHg^2$, $P = 0.01$). Low- and high-frequency spectral powers were not significantly affected. Thus periodic breathing causes oxygen-sensitive (and by implication chemoreflex-related) anti-baroreflex VLF oscillations in RR interval and blood pressure in both patients with chronic heart failure and normal controls.

INTRODUCTION

Patients with chronic heart failure may show discrete very-low-frequency (VLF) oscillations in heart rate and blood pressure with a period of approx. 1 min (frequency 0.010–0.040 Hz). This phenomenon may be linked to the presence of a fluctuating tidal volume of respiration (periodic breathing) [1–3] and episodic oxygen desaturation. Periodic breathing is associated with increased mortality in chronic heart failure [4,5]. Fluctuating ventilation may itself directly entrain heart rate and blood pressure into these slow rhythms. Alternatively, the oscillations in arterial partial pressure of oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}) which inevitably accompany

Key words: heart failure, periodic breathing, reflex.
Abbreviations: DBP, diastolic blood pressure; HF, high-frequency; LF, low-frequency; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide; SBP, systolic blood pressure; VLF, very-low-frequency.
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periodic breathing may also play a role. It has hitherto been difficult to study this phenomenon, for two reasons. Firstly, spontaneous periodic breathing is not completely regular. Its frequency (although usually approximately one cycle per min) and amplitude may vary over a short period of time. Secondly, interventions generally affect the nature of the fluctuations in all three parameters (ventilation, P_{O_2} and P_{CO_2}), so that their individual effects cannot easily be disentangled.

To overcome these limitations, we sought to study the role of periodic breathing in generating these slow oscillations under controlled circumstances, by imposing periodic breathing regulated to a fixed frequency with the aid of visual guidance from a computer. This enabled subjects to generate periodic breathing at will, and to have the same pattern regardless of the gas being inspired (room air or oxygen). We could therefore study the ability of voluntary periodic breathing to produce the VLF oscillations in heart rate and blood pressure, and examine the role of arterial desaturation in this phenomenon. We evaluated both patients with heart failure and a group of healthy young controls, to study whether any effects of periodic breathing could be found in normal cardiovascular physiology. We examined the effects of periodic breathing with and without hyperoxia in both groups of subjects, and made no statistical comparisons between the patients and healthy young controls.

METHODS

Study population

Ten patients with chronic heart failure were recruited from a specialist chronic heart failure clinic. Exclusion criteria included atrial fibrillation, ectopic beats in excess of two per minute, pacemaker implantation, and clinical instability within the previous 3 months. Six patients had an ischaemic aetiology. One patient was in NYHA class I, six were in class II, two were in class III and one was in class IV; their mean age was 57 (S.D. 10) years. On treadmill exercise, their peak oxygen uptake averaged 18.4 (S.D. 5.6) $ml \cdot min^{-1} \cdot kg^{-1}$. Their radionuclide left ventricular ejection fraction averaged 27 (S.D. 17) %. All patients were receiving treatment with angiotensin-converting enzyme inhibitors and diuretics. One was receiving digoxin. None was taking β-blockers, diltiazem or verapamil. Ten healthy controls were also studied; all were male, with a mean age of 33 (S.D. 6) years. They had no significant medical history, no abnormal findings on cardiorespiratory examination, and were not taking any regular medication.

All subjects gave informed consent, and the study was approved by the local Ethical Committee. The subjects were studied in standardized conditions, in a quiet room at a comfortable temperature. They were not allowed to smoke or to drink alcohol or caffeine-containing beverages for 12 h before the study.

Heart rate and blood pressure variability

Blood pressure was measured by a photoplethysmograph (Finapres model 2300; Ohmeda, Louisville, CO, U.S.A.) with the cuff wrapped around the index finger of the left hand, and the recordings were uninterrupted by the servo mechanism. The ECG was acquired from a limb lead with a clear R wave (usually lead II). Respiration was measured using a calibrated heated pneumotachograph, and end-tidal P_{CO_2} was monitored by a respiratory mass spectrometer (Amis 2000; Innovision). Oxygen saturation was measured with a pulse oximeter (Nellcor) set to fast mode, and equipped with an earlobe transducer. Data were sampled at 1000 Hz using an analogue-to-digital converter (National Instruments) interfaced to a personal computer running data acquisition software (Labview®; National Instruments). The readings were saved on to disk and analysed off-line with custom-designed software, which measured end-tidal gas concentrations and beat-by-beat values for the RR intervals, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Artefacts due to ectopic beats were corrected by linear interpolation with the previous and following beats.

Maintenance of periodic breathing

Subjects were guided to breathe at a constant respiratory rate with a tidal volume that oscillated sinusoidally, with a period of 1 min. This guidance was provided by a second computer system with custom-designed software that monitored the pneumotachograph signal on-line and displayed a moving bar in association with a target. This system could be programmed with any desired ventilatory pattern. We used this to create a regular respiratory rate and a sinusoidally varying tidal volume, whose period of oscillation was 1 min. The software monitored the subject's actual respiratory rate and tidal volume, and compared them with those of the programmed target. The difference between intended and actual ventilation was continuously computed and cumulated, and the result used to modify the tidal volume and rate of the visual target presented to the subject. Thus the subject was guided to correct undershoots or overshoots (in rate or volume, or both) and could match and maintain the desired oscillations in ventilation.

Each subject performed the periodic breathing twice: once while breathing room air, and once while breathing 100% oxygen.

Spectral analysis of power and phase

This study focused on the fluctuations that occur in the measured physiological variables at the frequency of

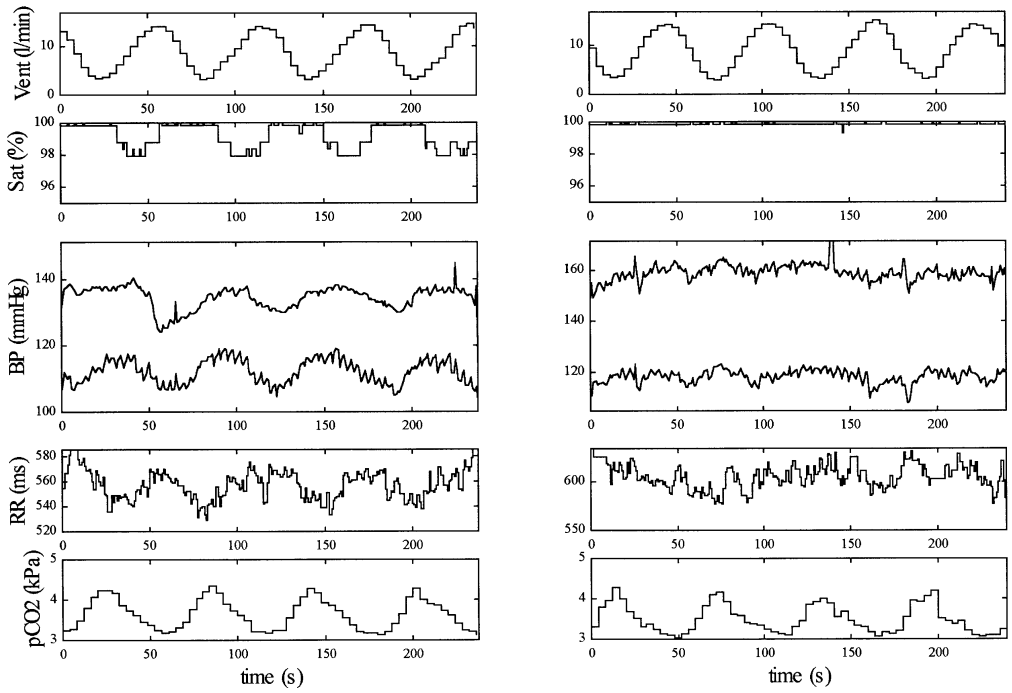

Figure 1 **Recordings from a representative patient performing periodic breathing in room air (left panel) and in oxygen (right panel)**

Vent, ventilation; Sat, saturation; BP, blood pressure; RR, RR interval.

periodic breathing (1/60 Hz), as shown in Figure 1. Eight consecutive cycles of artefact-free data were converted into an equidistant time series (by digital resampling at 1 Hz) and underwent Fourier transformation to obtain the power spectrum in the frequency domain. Because the periodic breathing was deliberately regulated to a fixed and known frequency (1/60 Hz), and the length of the data segment studied is an exact multiple of the period of oscillation of interest (1 min), the direct Fourier transformation [6] was used to quantify the spectral power and phase of the resultant cardiovascular oscillations. VLF spectral power was determined in the range 0.010–0.040 Hz, low-frequency (LF) power in the range 0.040–0.150 Hz, and high-frequency (HF) power in the range 0.150–0.450 Hz [3].

Statistical analysis

Numerical data of groups are summarized as means ± S.E.M. Spectral powers were log-transformed and compared between groups using Student's *t*-test.

Table 1 **Mean blood pressure and RR interval before periodic breathing, during periodic breathing in air, and during periodic breathing in hyperoxia**

Values are means (S.E.M.).

Parameter	Patients ($n = 10$)	Controls ($n = 10$)
SBP (mmHg)		
Before periodic breathing	118.4 (3.3)	114.9 (2.5)
Periodic breathing (in air)	116.0 (4.8)	122.6 (4.5)
Periodic breathing (in hyperoxia)	119.9 (4.6)	115.4 (3.5)
DBP (mmHg)		
Before periodic breathing	85.8 (5.0)	81.4 (3.1)
Periodic breathing (in air)	82.3 (4.5)	91.0 (4.4)
Periodic breathing (in hyperoxia)	89.1 (3.7)	87.6 (2.4)
RR interval (ms)		
Before periodic breathing	805 (52)	907 (37)
Periodic breathing (in air)	789 (57)	813 (37)
Periodic breathing (in hyperoxia)	812 (59)	842 (34)

RESULTS

Periodic breathing and VLF oscillations in cardiovascular variables

All subjects performed periodic breathing without any adverse effects. Most subjects required several minutes of practice before they became familiar with the breathing instructions being displayed by the computer.

During periodic breathing in air, all subjects showed episodic oxygen desaturations, with a mean trough of 96.6% (S.E.M. 0.5%) in patients and of 96.9% (S.E.M. 0.6%) in controls (Figure 1, left panel). VLF power increased with periodic breathing: in SBP it rose in patients from 3.44 to 6.25 mmHg^2 ($P < 0.05$) and in

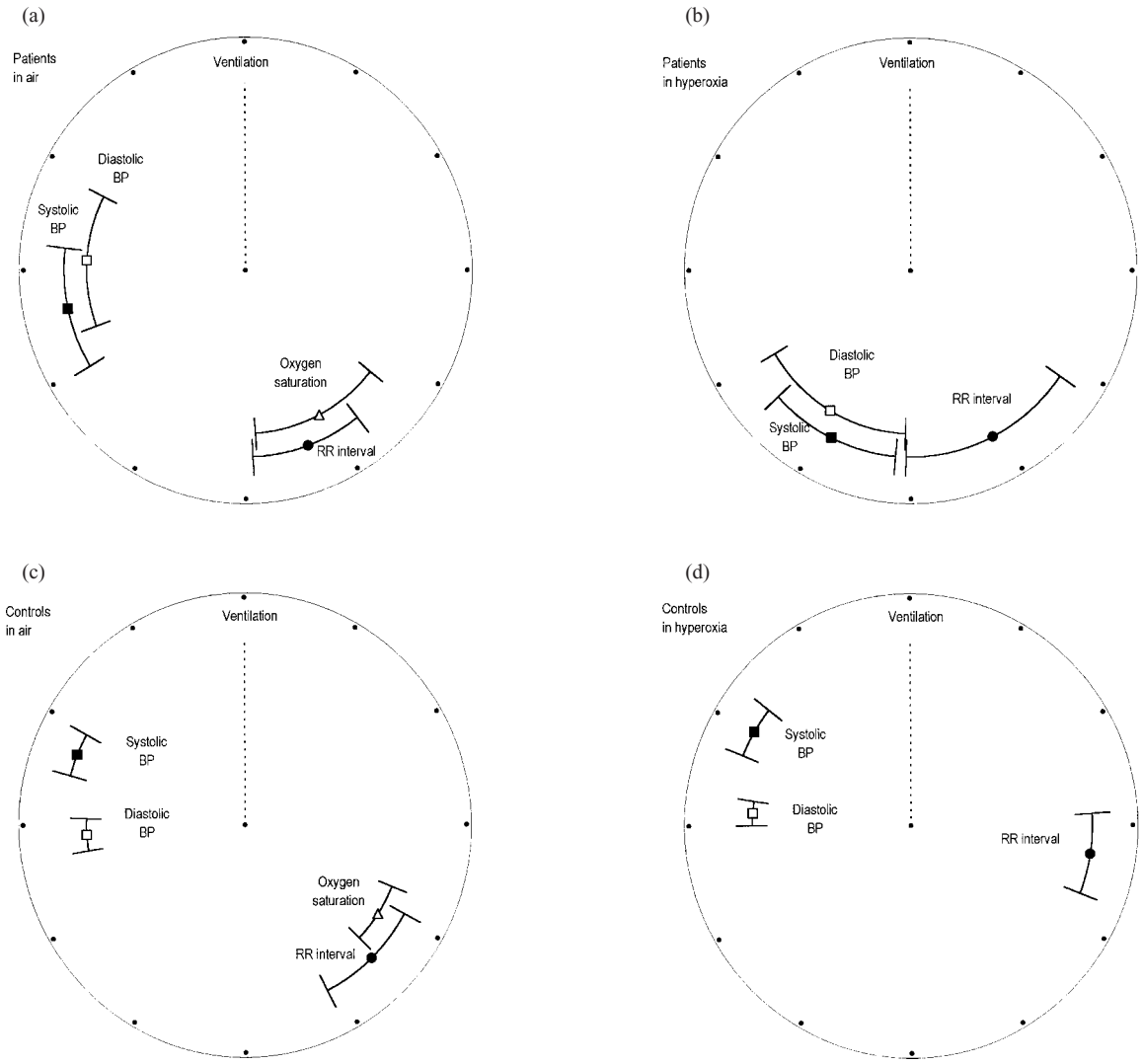

Figure 2 Phase plots showing the temporal relationship between the peaks of the VLF oscillations in patients performing periodic breathing in room air and in hyperoxia, and in controls performing periodic breathing in room air and in hyperoxia

Small dots around the circumference indicate 5 s intervals, and lines represent the standard errors of the group means.

controls from 3.40 to 9.38 mmHg^2 ($P < 0.05$); in DBP it rose in patients from 2.64 to 4.63 mmHg^2 ($P < 0.05$) and in controls from 2.56 to 13.31 mmHg^2 ($P < 0.001$); in RR interval it rose in patients from 178.8 to 357.8 ms^2 ($P < 0.05$) and in controls from 1040.1 to 2307.4 ms^2. Periodic breathing did not cause any significant change in LF power for any of the three variables in patients or controls ($P > 0.05$). The only significant change seen in the HF band was in the control group, where the HF spectral component increased from 1.70 to 3.38 mmHg^2 in SBP and from 0.50 to 1.72 mmHg^2 in DBP ($P < 0.05$ for both).

There was no significant effect of imposition of periodic breathing on mean SBP, DBP or RR interval, and nor was there a significant effect of hyperoxia (Table 1). The amplitudes of oscillation of end-tidal P_{O_2} and P_{CO_2} averaged 0.93 kPa and 0.47 kPa respectively in patients, and 0.98 kPa and 0.54 kPa respectively in controls.

Temporal relationships between ventilation, saturation, heart rate and blood pressure during periodic breathing

To determine the temporal relationships between the VLF oscillations in blood pressure, RR interval and oxygen saturation, the phase of each was determined (in relation to ventilation) from its Fourier transform.

In the patients, the peak of oxygen saturation occurred 25 s after the peak of ventilation, with the longest RR intervals also at approximately this time (27 s). The peak in blood pressure occurred late in the cycle (43 s for SBP and 46 s for DBP), and the fastest heart rate (57 s) coincided with the trough of oxygen saturation (55 s).

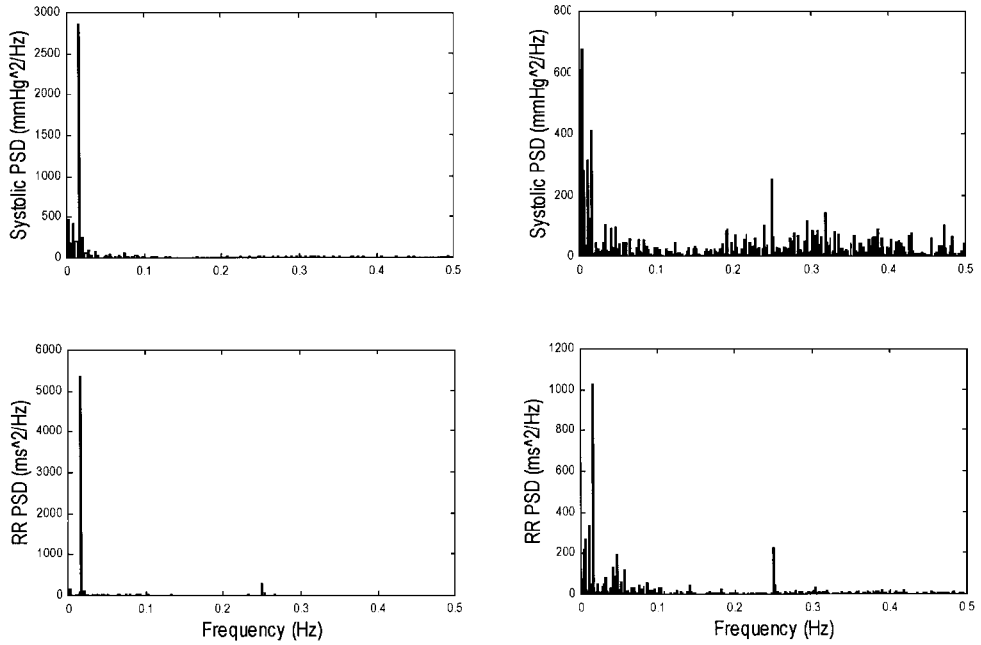

Figure 3 **Power spectral density (PSD) plots of SBP and RR interval from a patient performing periodic breathing in room air (left panels) and in oxygen (right panels)**

Note the difference in vertical scale between the left and right panels.

Table 2 **Comparison of ventilation, oxygen saturation and power spectral analysis of SBP, DBP and RR interval in air and under hyperoxic conditions in patients and controls**

Values are means (S.E.M.). Significance of differences compared with air breathing: $^{*}P < 0.05$; $^{**}P < 0.01$.

	Patients ($n = 10$)		Controls ($n = 10$)	
Parameter	Air	Oxygen	Air	Oxygen
Ventilation (l/min)				
Mean	8.1 (0.5)	8.1 (0.5)	6.9 (0.7)	7.0 (0.7)
Amplitude	4.6 (0.4)	4.5 (0.4)	4.3 (0.3)	4.4 (0.3)
Oxygen saturation (%)				
Peak	100.0 (0.1)	100.0 (0.1)	99.8 (0.2)	100.0 (0)
Nadir	96.6 (0.5)	99.3 (0.3)**	96.9 (0.6)	99.4 (0.2)**
SBP spectral power ($mmHg^2$)				
VLF	6.25 (1.16)	3.51 (0.77)**	9.38 (2.14)	3.68 (0.92)**
LF	2.62 (0.79)	2.28 (0.62)	2.97 (0.69)	2.28 (0.28)
HF	2.51 (0.54)	2.81 (0.88)	3.38 (1.00)	2.20 (0.33)
DBP spectral power ($mmHg^2$)				
VLF	4.63 (1.18)	2.33 (0.40)*	13.31 (2.45)	6.07 (1.50)*
LF	1.37 (0.46)	1.43 (0.50)	3.12 (0.61)	2.26 (0.22)
HF	1.27 (0.26)	0.93 (0.18)	1.72 (0.41)	1.09 (0.23)
RR interval spectral power (ms^2)				
VLF	357.8 (103.2)	179.0 (51.7)**	2307.4 (779.6)	1847.0 (898.8)*
LF	166.2 (96.8)	152.2 (67.3)	1032.1 (209.9)	1035.8 (201.1)
HF	102.7 (23.8)	94.1 (25.3)	949.3 (187.8)	835.3 (133.4)

The situation was similar in the control group, with blood pressure peaking late in the cycle (49 s for SBP and 44 s for DBP) and coinciding with the fastest heart rate (53 s) and the trough of oxygen saturation (51 s).

Figure 2 shows these phase relationships in circular plots, where the top of the circle represents the time of peak ventilation and the small dots around the circumference indicate successive 5 s intervals.

Clearly, significant coherences were observed between the physiological variables and ventilation during periodic breathing in air, which averaged (in patients and controls respectively) 0.83 and 0.86 for saturation, 0.56 and 0.80 for SBP, 0.77 and 0.87 for DBP, and 0.78 and 0.83 for RR interval. In hyperoxic conditions (in patients and controls respectively), the coherences averaged 0.60 and 0.51 for SBP, 0.64 and 0.79 for DBP, and 0.63 and 0.80 for RR interval.

Effect of oxygen on spectral power of VLF oscillations

In the frequency domain, the VLF oscillations were localized to the 1/60 Hz (0.0167 Hz) frequency, corresponding to the periodic breathing. In the presence of oxygen, the power in the VLF regions in heart rate and blood pressure was decreased (Figure 3 shows an example). There was no significant effect of oxygen on HF or LF spectral powers of BP or RR interval in patients or controls. The results are shown in Table 2.

DISCUSSION

This study shows that voluntary periodic breathing entrains heart rate and blood pressure into prominent VLF rhythms. Secondly, this effect occurs not only in patients with chronic heart failure, but also in healthy controls. Thirdly, at this frequency, RR interval and blood pressure, rather than being in phase as would be expected from baroreflex mechanisms, are close to being in antiphase. This indicates the presence of a mechanism which can overcome the baroreflex arc, not only when it is attenuated by heart failure [7] but also in healthy controls. Finally, when oxygen desaturation is prevented, there is a large decrease in the spectral power of these VLF oscillations in heart rate and blood pressure.

Anti-baroreflex patterns of regulation of heart rate and blood pressure at VLF have previously been reported in resting recordings from patients with chronic heart failure [2]. When they occur during attempts to measure baroreflex sensitivity by the phenylephrine method, they may be taken to signify a negative baroreflex gain [8]. Although theoretical mechanisms involving valvular dysfunction and pulmonary or right-heart stretch receptors [8] can be postulated to contribute a negative component to baroreflex gain, the net baroreflex gain must remain positive to be compatible with life.

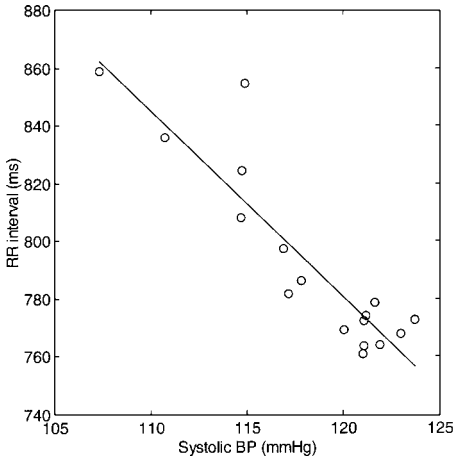

Figure 4 Example of RR interval plotted against SBP from half a cycle of periodic breathing in one patient, showing an apparent negative baroreflex gain

The present study suggests that periodic breathing generates desaturations which have a powerful influence on the cardiovascular system and which can overcome the homoeostatic effects of the baroreflexes, even in young healthy control subjects whose reflexes have not been attenuated by age or by disease. Thus, when anti-baroreflex movements in RR interval and blood pressure are seen during attempts to measure baroreflex sensitivity, it is important to entertain the possibility that these changes are a result of periodic breathing, as shown in Figure 4. This consideration is particularly important when studying patients with chronic heart failure, in whom periodic breathing is common.

Previous studies have attributed cardiovascular VLF rhythms to feedback oscillations in the thermoregulatory control system [9] or to fluctuations in the renin–angiotensin system [10], but it has become clear that there is a large neurogenic component in their genesis [10]. Cardiovascular VLF rhythms are frequently seen in patients with periodic breathing [3,11]. The present study supports the hypothesis that periodic breathing is a relevant mechanism for their origin. However, the phenomenon of periodic breathing contains three physiological oscillations from which VLF cardiovascular rhythms might originate. Firstly, periodic breathing consists of regular fluctuations in tidal volume: this has reflex cardiovascular effects [12], mediated by lung afferents [13,14]. Secondly, there are associated fluctuations in end-tidal P_{CO_2} with the same period. Elevations in P_{CO_2} cause an increase in blood pressure and tachycardia (independently of the effect on ventilation) [15]. Thirdly, falls in arterial oxygen saturation are frequently seen during periodic breathing. Localized hypoxia at the carotid bodies [16,17] (which are responsible for almost all of the ventilatory response to hypoxia) causes bradycardia with widespread reflex

vasoconstriction. In contrast, when hypoxia is applied to the entire body, the response is tachycardia and a rise in blood pressure [17]. Hypoxia therefore consistently causes a rise in blood pressure, but the integrated physiological response of heart rate is complex [18] and depends on the interplay of more than one influence [19]. The implication is that sensors other than the carotid bodies are important for the integrated cardiovascular response to hypoxia.

The principal difficulty in distinguishing the roles of these facets of periodic breathing in the genesis of VLF rhythms is that interventions altering any one of them affect all three factors. For example, application of oxygen modifies the ventilatory reflexes such that periodic breathing itself becomes less pronounced [26], making it difficult to quantify the direct effect of oxygen on the cardiovascular oscillations. In our study, therefore, we used visual guidance to arrange constant periodic breathing regardless of whether the subject was breathing room air or oxygen. This showed that when the hypoxic episodes were removed by adding oxygen, the VLF oscillations were substantially attenuated. The residual oscillations are therefore presumably mediated by fluctuations in P_{CO_2} or by a direct mechanical effect of periodic breathing.

Study limitations

The present study provides indirect evidence for an important component of neural mediation in the VLF cardiovascular rhythms that occur during periodic breathing. A more direct answer could be obtained by performing a similar study in cardiac transplant recipients, whose hearts would be denervated.

Clinical implications

Periodic breathing and Cheyne–Stokes respiration [20] during the daytime [21] and during sleep [4] have been reported to predict poor survival in chronic heart failure, independently of conventional risk markers [5]; the mechanism of this association is not clear. The recurrent phases of tachycardia with concurrent transient hypertension and arterial hypoxaemia are repetitive imbalances between myocardial oxygen supply and energy demand. This cardiovascular response would appear to be a maladaptive one, which contrasts with the bradycardic and afterload-reducing responses seen in diving mammals [22] which are well suited to life patterns requiring episodic breathing with long intervals of apnoea [23].

In the present study the desaturations were small, and might easily be compensated for by small changes in oxygen extraction and/or coronary blood flow. However, in clinical Cheyne–Stokes respiration, oxygen saturation frequently reaches nadir values below 90%; such deeper troughs may be less easily compensated for by transient adaptations in myocardial physiology.

These repetitive insults can occur hundreds of times per night in chronic heart failure and could potentially aggravate deterioration of myocardial function [24], which may partly explain the associated poor prognosis. This hypothesis should be treated with caution, however, since direct evidence is lacking. The contribution of episodes of oxygen desaturation to these cardiovascular oscillations is prominent: when excess oxygen is applied to prevent desaturations, the same periodic breathing pattern yields much less powerful cardiovascular VLF oscillations. These results may illuminate some conflicting clinical observations. Nocturnal oxygen therapy in Cheyne–Stokes respiration has been found to have favourable effects on daytime cardiovascular performance [25], although the direct effect on the severity of the overnight respiratory disturbance may be small [26]. A unifying hypothesis might be that the hypoxic chemoreflex, despite perhaps playing only a minor part in destabilizing ventilatory control, may have a pre-eminent role (through its cardiovascular efferent limb) in the haemodynamic consequences of periodic breathing.

If the cardiovascular consequences of Cheyne–Stokes respiration are to be a target for treatment [27], then oxygen should not be forgotten [28,29] as a simple, inexpensive and acceptable method not only for preventing the repetitive declines in myocardial nutrient supply but also for reducing the prominence of the spikes in blood pressure and heart rate that cause increases in myocardial workload. Oxygen may be administered alone or as an adjuvant to techniques that may be more potent in attenuating the respiratory disturbance itself, such as continuous positive airway pressure.

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