Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in chronic heart failure

Do Cheyne and Stokes have an important message for modern-day patients with heart failure?

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Oscillatory ventilation in chronic heart failure

Periodic breathing consisting of alternating hyperpnoea and hypopnoea (Fig. 1) was recognized in heart failure patients in the 19th century by John Cheyne and William Stokes. The clinical observation of Cheyne–Stokes respiration has been subsequently confirmed.

Initially, attention was focused on the occurrence of oscillatory breathing during sleep and severity of heart failure, suggesting that the former had a potent role in causing further deterioration in cardiovascular function. Episodic apnoea during the night with concomitant hypoxaemia and arousal, characteristic features of Cheyne–Stokes respiration, resulted in patients complaining of dyspnoea and daytime somnolence and was associated with sympathetic overactivity and precipitation of ventricular arrhythmias. A recent study has shown that heart failure patients with oscillatory ventilation while sleeping have more ventricular arrhythmias than patients whose breathing is normal. The high rate of unpredictable sudden death in heart failure has stimulated the search for potential triggers of arrhythmias. This has resulted in interest in the pathophysiological meaning of the Cheyne–Stokes phenomenon during sleep.

However an oscillatory pattern of respiration may also be present during spontaneous breathing while awake and during exercise (Fig. 2, Table 1). Twelve years ago, Kremser et al., described marked periodic breathing during moderate exercise in six of 31 patients with dilated cardiomyopathy. Oscillatory hyperventilation was defined as cyclic fluctuations in minute ventilation lasting longer than 66% of the exercise protocol. The amplitude was more than 15% of the average value at rest, and the amplitude of ventilatory oscillations increased in the transition from rest to light exercise and diminished with heavy exercise. The ventilatory oscillation was associated with cyclic changes in arterial oxygen (O2) and carbon dioxide (CO2) tensions, and with a significant reduction in arterial CO2 tension: the magnitude of this oscillatory breathing during exercise correlated with the severity of heart failure.

In the same year, Ribiero et al., described a periodic breathing pattern during exercise in five of 32 patients with severe heart failure (New York Heart Association functional class III and IV). Yajima et al., studying 48 consecutive patients with reduced left ventricular function, found five patients with clear ventilatory oscillations during exercise. Miyagi et al., reported that in patients with severe heart failure the detection of anaerobic threshold is masked by the early occurrence of anaerobic metabolism and the presence of irregular or oscillatory respiration.

More recently it has been observed that while oscillatory ventilation during sleep in heart failure patients seems to present little or no prognostic impact, the same ventilatory pattern present during the day is associated with a strong possibility of dying within a few months; the same authors suggested that the negative prognostic implication of the oscillatory respiratory

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Aetiology and pathophysiological implications

Despite the clinical implications, the origin of periodic breathing at rest and on exercise in heart failure is still unclear. Several hypotheses can be formulated and probably more can be speculated upon. More than one mechanism may be involved in the generation of oscillations in individuals.

Instability of the ventilatory control system

Oscillatory ventilation can be seen as a consequence of instability in the feedback systems controlling ventilation. The potential for instability and oscillatory fluctuations is inherent in any feedback control system, and such oscillations are more likely to occur when several feedback systems interact. The following factors could be responsible for the oscillatory changes: delay in information transfer, increase in controller gain, and reduction in system damping. In heart failure all these three components are present: prolonged circulatory time (delay in information transfer), overactivity of chemoreceptors and ergoreceptors (increase in controller gain), cardiopulmonary and arterial baroreflex impairment (reduction in system damping).

The presence of a prolonged circulatory time secondary to cardiac insufficiency as a cause of oscillatory ventilation was first suggested almost 50 years ago. There is a loss of control resulting from the time delay about the current state of the system being received by the controller. In effect, in heart failure the prolonged circulation time can delay changes in arterial blood gas tension being recognized by the sensors in the carotid bodies and in the medulla. The circulatory delay is reflected in lung-to-ear circulatory time, and could promote unstable respiratory control, leading to periodic respiration with alternating hyperpnoea and hypopnoea.

This theory is based on the finding that patients with Cheyne–Stokes respiration have a more depressed cardiac index than those without an oscillating respiratory pattern. Effective medical therapy or heart transplantation in patients with Cheyne–Stokes respiration has been shown to eliminate the abnormal breathing pattern in conjunction with clinical improvement. However, this could not be nominated as the leading factor in all cases: recent reports have suggested that circulatory delay is similar in heart failure patients with and without oscillatory ventilation.
Chemoreceptors

An increased chemoreceptor drive may indicate high controller gain, and small changes in $O_2$ and $CO_2$ can result in appropriate alterations of the system’s output$^{14,25}$. In an experimental model, Lahiri et al.$^{25}$ demonstrated that the peripheral chemoreflex can play a critical role in the development of cardiopulmonary oscillations: the augmentation of peripheral chemoreceptor responses (induced by infusion of a peripheral dopamine receptor blocker) led to the expression of oscillations in blood pressure and ventilation which were abolished by hyperoxia.

In a clinical setting of heart failure patients, augmented chemoreceptor activity has been described by our group$^{26-28}$. Hypoxic, peripheral hypercapnic chemosensitivity and central hypercapnic chemosensitivity were compared in patients with moderate to severe heart failure (radionuclide left ventricular ejection fraction $25 \pm 2\%$) and in healthy control subjects at rest and
Table 2 Hypothesized mechanisms of oscillatory ventilation in chronic heart failure

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<td>(B)</td>
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<td>(C)</td>
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during exercise. Heart failure patients, together with reduced peak O₂ consumption, showed enhanced hypoxic and central hypercapnic chemosensitivity, which correlated significantly with the ventilatory response to exercise. Hypoxic chemosensitivity was augmented during exercise in patients and in control subjects but remained higher in the former. The peripheral hypercapnic chemosensitivity of patients at rest and during exercise was similar to that in control subjects, consistent with its lesser contribution to overall carbon dioxide chemosensitivity[26]. In a heart failure population, an augmented peripheral chemoreflex was associated with increased severity (reduced peak O₂ consumption, reduced left ventricular ejection fraction and worse New York Heart Association functional class), with more marked exercise hyperpnoea (increased ventilation/CO₂ regression slope), and non-sustained ventricular tachycardia[57]. It is interesting to observe that in a substantial proportion of these patients this reflex favoured the expression of slow heart rate rhythms (‘very low frequency’ oscillation) which frequently coincided with slow respiration rhythms and blood pressure fluctuations[28–30]. More important, the presence of enhanced chemosensitivity has been shown to be associated with the presence of oscillatory breathing at rest, and the modulation of peripheral chemosensitivity can reduce or abolish the abnormal respiratory pattern[19].

The cause of augmented peripheral chemoreflex in heart failure is not known and several hypotheses have been proposed: reduced blood flow to the carotid chemoreceptors[31], impaired baroreflex sensitivity (by its inhibitory interaction with chemoreflex)[32,33], enhanced central or peripheral inputs to the ventilatory control centre.

In addition, activation of the peripheral chemoreflex may also contribute to neurohumoral and sympathetic stimulation in heart failure, by virtue of its excitatory action on the nucleus of the tractus solitarius in the medulla[34,35]. In agreement with this hypothesis, peripheral chemosensitivity correlates inversely with heart rate variability within the low frequency band (an index of sympathetic activity) and inversely with baroreflex sensitivity. Transient inactivation of chemoreflex (100% O₂ breathing) increases heart rate variability and improves baroreflex sensitivity, suggesting a causal link between increased peripheral chemoreflex and impaired autonomic control[32].

Ergoreceptors (skeletal muscle afferents)

The ergoreceptors, afferents sensitive to the metabolic state of the exercising muscles, contribute to hyper-ventilation, sympathetic activation, parasympathetic withdrawal, hypertension, and vasoconstriction of exercise[36]. Due to the metabolic abnormalities present in heart failure skeletal muscle, (e.g. early acidification, phosphocreatinine depletion, K⁺ production), the ergoreceptor system is overactivated[37]: this control gain may contribute to oscillatory hyperventilation in exercise either by being rhythmically stimulated itself or by increasing chemoreflex sensitivity centrally by a direct facilitatory input. This hypothesis is currently under investigation.

Impaired cardiopulmonary and arterial baroreflex functions

The role of the carotid arterial baroreceptor in physiological fluctuations has been described[38]. The cyclic changes in blood pressure, due to respiratory activity, are sensed and buffered by carotid baroreceptors which modulate heart-rate inducing respiratory sinus arrhythmia. After elimination of R-R interval fluctuations (and thus of the baroreflex buffering effect), arterial pressure fluctuations increase[39]. It may be hypothesized that in heart failure, when a cardiopulmonary and arterial baroreflex function is impaired[40], other systems (i.e. chemoreceptors) controlling respiratory function may stimulate oscillation in heart rate. This theory is supported by the finding of an inverse correlation between peripheral chemosensitivity and baroreceptor activity; the inactivation of chemoreceptors (by transient hypoxia) increases baroreflex sensitivity[32].

Central nervous system

The spontaneous firing rates of medullary motor neurones are transmitted to systems controlling heart rate, blood pressure and respiration[41,42]. A ‘central oscillator’ has been described as a medullary neuronal network which presents spontaneous and regular oscillations in firing rates that are maintained even when all afferent inputs are interrupted[43–45]. It has been hypothesized that these oscillations, when entrained by afferent stimuli from receptors in the lungs and thoracic wall in time with respiration, may result in heart rate oscillations generating respiratory sinus arrhythmia[46]. However, recent findings have challenged this theory. Ben-Dov et al[47] found that O₂ uptake oscillations in chronic heart failure patients were greater in magnitude than those induced by simulated periodic breathing in healthy subjects: they surmised that oscillations in O₂ uptake could not be explained entirely by primary changes in respiratory centre output or by changes in lung gas stores. Moreover, a dominant role of the ‘central oscillator’ as the origin of physiological
fluctuations has been disputed by studies that selectively suppressed central and peripheral control mechanisms.

Pulmonary blood flow oscillation

Ben-Dov et al. first speculated that fluctuations in pulmonary blood flow might be responsible for gas exchange oscillations, but no direct measurements of haemodynamic changes were performed to support this hypothesis. More recently, Yajima et al. continuously evaluated gas exchange and left ventricular ejection fraction, with a computerized cadmium telluride detector. They found oscillatory changes both in ejection fraction and in ventilation during exercise in heart failure patients with periodic breathing, and it was postulated that these patients have oscillations in pulmonary blood flow, as reflected in left ventricular ejection fraction. An association between ventilation and pulmonary blood flow (or cardiac output) has been reported. However, no direct causal relationship between changes in left ventricular ejection fraction and the occurrence of oscillatory breathing has been demonstrated: it is difficult to explain how changes in pulmonary blood flow or cardiac output can consistently cause periodic changes in ventilation.

Increased pulmonary dead space

The abnormal ventilatory response to exercise in heart failure has been traditionally attributed to increased dead space ventilation related to pulmonary congestion. Interstitial oedema may stimulate pulmonary afferents, therefore inducing hyperventilation, and consequently hypocapnia and ventilatory instability. However, this theory of a leading role for the overstimulation of pulmonary receptors in heart failure has been challenged by more recent studies that showed them to be impaired or abolished. The hypothesis of a leading role for impaired lung function and exercise gas exchange in exercise limitation in heart failure has been recently supported by Wasserman and co-workers: they suggested that hyperpnoea on exercise can be caused by an increase in physiological dead space with a high ventilation/perfusion mismatch. Chronic pulmonary hypertension may cause pulmonary restriction in heart failure patients, resulting in changes in respiratory mechanics similar to those observed in patients with restrictive lung disease. This theory may not be valid in all cases as other studies have shown no increase in dead space in heart failure patients during exercise. Ventilatory oscillations, in particular, seem not to be associated with abnormalities in spirometric data or alveolar hyperventilation. Finally the presence of periodic changes in dead space should be hypothesized to explain the phenomenon of oscillatory ventilation on exercise, but to our knowledge, no demonstration exists of these changes.

A unifying hypothesis

Several factors may contribute to the genesis of oscillatory breathing. However, on the basis of present knowledge, a unifying general hypothesis can be proposed (Fig. 3).

In heart failure, the presence of cardiac insufficiency induces skeletal and respiratory muscle myopathy determining a peripheral catabolic state, i.e. increases in lactate production, acidosis (therefore contributing to a ‘reduction in exercise tolerance’). Lactic acidosis, directly or mediated by other metabolites, may stimulate hyperventilation by acting on reflex controls, hyper-ventilation at rest and on exercise and reduction of arterial CO2 tension (‘abnormal ventilatory response to exercise’). Stimulation of chemoreceptors either directly or mediated by other receptors (such as ergoreflex) may induce well known slow oscillation in respiration, heart rate, and blood pressure cerebral circulation (‘oscillatory ventilation’).

Cardiac insufficiency may also induce slow circulation, which by itself may lead to an oscillation in physiological parameters, including respiration. A slow circulation also determines delayed transmission of metabolic ventilatory stimuli to the chemoreceptors: as a consequence, the controllers tend to produce ‘the wrong response at the wrong time’, reinforcing rather than dampening the effects of disturbances on the system. Thus the presence of a slowed circulation time may cause a delay in information transfer between the sensors in the carotid body and medulla, and the appropriate ventilatory response may be affected, so enhancing the oscillations in breathing.

This phenomenon is perpetuated and develops a vicious loop: these reflexes, although at the beginning activated as compensatory mechanisms to maintain cardiac output and circulation to the more vital organs, contribute to the state of sympatho-excitation and vagal withdrawal which maintains the clinical status and causes it to deteriorate. In fact the activation of these reflexes and their responses correlate with the severity of the syndrome, and with the activity (exercise). While in less severe heart failure pH and arterial CO2 tension tend to be kept constant, in more severe conditions, particularly during exercise, arterial lactate rises and arterial CO2 tension and pH are reduced.

Therapeutic implications

Evaluation of the pathophysiology of oscillatory hyper-ventilation at rest, or on exercise could uncover important diagnostic and prognostic implications for the management of heart failure patients: exercise training,
ventilatory inhibitors, reflex system modulators, or oxygen supplementation. Some of these therapeutic approaches will be reviewed.

(1) Physical training not only improves exercise tolerance but also reduces abnormal hyperventilation on exercise, by reducing the ventilation/CO₂ ratio⁵⁸. This beneficial effect could also be mediated by reduced stimulation of peripheral reflex mechanisms: exercise conditioning reverses muscle metabolic abnormalities by reducing early acidification and phosphocreatinine depletion⁵⁹. An improved peripheral metabolism may reduce peripheral reflex mechanism stimulation by chemoreceptors or ergoreceptors, for example³⁷.

(2) Suppression of chemosensitivity by oxygen supplementation⁶⁰ or opiate administration (dihydrocodeine⁶¹) reduces dyspnoea and improves exercise tolerance in patients with chronic heart failure. Moreover the regression slope relating minute ventilation to CO₂ significantly decreases after dihydrocodeine administration.

(3) Nasal continuous positive airway pressure has been shown not only to reduce the Cheyne–Stokes respiratory pattern, but also to improve symptoms of fatigue and left ventricular ejection fraction in heart failure patients⁶². This device can also reverse humoral abnormalities such as atrial natriuretic peptide abnormally elevated in this syndrome⁶³.

(4) Theophylline supplementation has been shown to reduce the oscillatory respiratory pattern in heart failure⁶⁴; this effect may also be mediated by the antagonistic effect of theophylline, an adenosine, a potential mediator of receptor activation in this syndrome (e.g. ergoreceptors).

(5) The value of respiratory training (slow ‘yoga’ breathing) in improving patterns of breathing and oxygenation has been recently reported⁶⁵.

It is interesting to observe that many of the treatment options proven in heart failure have only an indirect relationship to improvement in cardiac output.

**Conclusions**

The autonomic and reflex associations of Cheyne–Stokes breathing may be amenable to therapeutic opportunities never envisaged by Cheyne and Stokes. Thus, in the days of molecular biology we should not overlook opportunities useful physiological observation can reveal.

**References**


