Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure

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Summary

Background In chronic heart failure (CHF), impaired pulmonary function can independently contribute to oxygen desaturation and reduced physical activity. We investigated the effect of breathing rate on oxygen saturation and other respiratory indices.

Methods Arterial oxygen saturation (SaO₂) and respiratory indices were recorded during spontaneous breathing (baseline) and during controlled breathing at 15, six, and three breaths per min in 50 patients with CHF and in 11 healthy volunteers (controls). 15 patients with CHF were randomly allocated 1 month of respiratory training to decrease their respiratory rate to six breaths per min. Respiratory indices were recorded before training, at the end of training, and 1 month after training.

Findings During spontaneous breathing, mean SaO₂ was lower in CHF patients than in controls (91·4±0·4 vs 95·4±0·2, p<0·001). Controlled breathing increased SaO₂ at all breathing rates in patients with CHF. Compared with baseline, minute ventilation increased at 15 breaths per min (+45·9% [9·8], p<0·01), did not change at six breaths per min, and decreased at three breaths per min (−40·3% [4·8], p<0·001). In the nine CHF patients who had 1 month of respiratory training, resting SaO₂ increased from 92·5±0·3 to 93·2±0·4 (p<0·05), their breathing rate per min decreased from 13·4 (1·5) to 7·6 (1·9) (p<0·001), peak oxygen consumption increased from 1157 ±83 to 1368 ±110 L/min (p<0·05), exercise time increased from 583 ±29 to 615 ±23 min/s (p<0·05), and perception of dyspnoea reduced from a score of 19·0 (0·4) to 17·3 (0·9) on the Borg scale (p<0·05). There were no changes in the respiratory indices in the patients who did not have respiratory training.

Interpretation Slowing respiratory rate reduces dyspnoea and improves both resting pulmonary gas exchange and exercise performance in patients with CHF.

Lancet 1998; 351: 1308–11

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Introduction

In chronic heart failure (CHF) the consequences of impaired cardiac and respiratory function may be additive, and independently contribute to reduce oxygen saturation and the ability to do physical work. Although previous studies of CHF have shown respiratory dysfunction, and the impact controlled breathing has on autonomic control and arterial oxygen saturation (SaO₂), the optimum breathing pattern is not known.

Our aim was to establish the optimum breathing rate on SaO₂ in patients with CHF and healthy controls, and then assess the effect the optimum rate had on respiratory indices and exercise capacity in CHF patients who were randomly allocated training to this optimum rate.

Methods

We enrolled 50 patients with stable CHF who had had no changes in their signs and symptoms in the 2 weeks before examination and 11 healthy volunteers (controls). The exclusion criteria were pulmonary disease and smoking in the 2 years before the start of the study. None of the controls were smokers and all had normal lung function. The study protocol was approved by the local ethics committee and all individuals gave informed consent to take part.

Controls and patients with CHF had simultaneous measurements of heart rate by electrocardiogram, instantaneous lung volume by inductance plethysmography (Respitrace, Ardley, NY, USA), non-invasive systolic and diastolic blood pressure (Finapres, Ohmeda, Englewood, CO, USA), and SaO₂ (Medlab, Karlsruhe, Germany). We did four breathing recordings: 10 min of spontaneous breathing; 4 min of controlled breathing at 15 breaths per min; 4 min at six breaths per min; and 4 min at three breaths per min. The recording of spontaneous breathing was always done first, and we did not tell patients and controls when recording began. All the recordings of controlled breathing were done in random order. No attempt was made to control the depth of breathing, so that each individual was able to maintain comfortable breathing. We also measured minute ventilation and estimated the ventilation to perfusion inequality (dead-space ventilation to tidal volume ratio) during spontaneous breathing and controlled breathing periods in 15 patients with CHF and in the controls.

Analogue signals of heart rate by electrocardiogram, blood pressure, instantaneous lung volume by Respitrace, and SaO₂ were simultaneously recorded on computer (mean [SD] values). We used spectral analysis to assess the rate of respiration during spontaneous breathing. Since the respiratory signal by Respitrace estimates tidal volume and minute ventilation in relative terms, values were expressed as % deviation from baseline (spontaneous breathing) for each individual. This limitation could not be avoided because we did not want to affect spontaneous respiration.

To test the hypothesis that patients with CHF could have unstable oxygen saturation as a result of irregular breathing, we characterised the respiratory instability by time-varying spectral analysis of respiration which provides an instantaneous description of respiratory rate and amplitude. Respiratory instability was characterised by two indices: the coefficient of variation of the power (CV-pw) of the instantaneous respiratory peak (to assess instability in tidal volume), and the coefficient of variation of the frequency (CV-Hz) at which the
instantaneous respiratory peak occurred (to assess instability in breathing rate).

After the results of this study were known, we did a preliminary study of respiratory training in 15 (14 men) new consecutive CHF patients (mean age 52±6.1 years). All the patients were in sinus rhythm, without angina pectoris as an exercise limiting factor (assessed by an exercise test done <3 weeks before inclusion), without obstructive or restrictive lung disease, clinically stable, and with no change in medical treatment for at least the previous 4 weeks. Patients were randomly allocated to receive either breathing training under the guidance of a physiotherapist or rest. The aims of training were to reduce the breathing rate and learn how to mobilise in sequence—ie, within the same breath—the diaphragm, the lower chest, and then the upper chest during inspiration, and the same sequence during expiration. This technique, known among practitioners of yoga as complete yoga breathing, produces slow, deep breathing usually at a frequency of about six breaths per min. Patients were asked to practice this respiration at home for 1 h (continuous or split into shorter periods) every day for 1 month. Motivation was assessed at the first study session and at the following study sessions on a scale from 0 (no motivation) to 10 (high motivation). The patients were assessed before the training, at completion of the training (1 month), and 1 month after completion. The six patients in the rest group had assessments at baseline and 1 month. All 15 patients had maximal, symptom-limited upright bicycle cardiopulmonary exercise testing with a ram-like protocol (increment of 2 Watts per 10 s after 3 min of steady 15 Watt load), with monitoring of gas exchange and ventilation done by an observer unaware of which group the patient had been assigned to. The patients exercised until severe fatigue or dyspnoea made them unable to continue. Two masked observers assessed the anaerobic threshold by the V-slope. Oxygen consumption per kg, time, and levels of exercise were measured at anaerobic threshold and peak exercise. The levels of perceived fatigue and dyspnoea were recorded according to the Borg scale.

We assessed differences in respiratory indices between spontaneous and controlled breathing and between controls and CHF patients by mixed-model analysis of variance (repeated measures on two independent groups). A p value of less than 0.05 was significant. When overall differences were significant, differences between controls and patients or between different breathing rates were evaluated by unpaired t test and Sheffe’s tests, respectively. We used linear regression analysis to test that association between SaO₂ and respiratory variables.

Results

Table 1 shows the baseline characteristics of the 50 patients with CHF. There were no substantial changes in mean respiratory rate interval, systolic and diastolic blood pressures in CHF patients and controls during the study. During spontaneous breathing, mean SaO₂ was lower in CHF patients than in controls, whereas SaO₂ instability (assessed by SaO₂ SD) was greater in patients with CHF than in controls (table 2), irrespective of Cheyne-Stokes respiration (recorded in 19 of the CHF patients). Mean SaO₂ and SaO₂ instability were inversely related (r=-0.48, p<0.001). In both groups, controlled breathing significantly increased mean SaO₂ at all breathing rates, even at three breaths per min (table 2). The increase in mean SaO₂ was inversely correlated, at each breathing rate, to resting SaO₂ levels (15 breaths per min r=-0.668; six breaths per min r=-0.639, three breaths per min r=-0.668; six breaths per min r=-0.639, three breaths per min r=-0.702, all p<0.0001). Of the 15 CHF patients with resting SaO₂ below 90%, only four,
and controls (15·6 [0·7] difference in respiratory rates between patients with CHF and became similar to that of controls at three breaths per min (table 2). CHF patients from spontaneous to controlled breathing, the increase in SaO2 show a correlation with the increase in ventilation (figure) and alveolar ventilation, without improvement in the ventilation to perfusion ratio, thus probably at the expense of an increase in ventilatory work.16 With the slowest breathing rate, three breaths per min; there were no between-group differences in this ratio (table 3).

Respiratory instability was similar in CHF patients and in controls; in both groups this index decreased significantly from spontaneous to controlled breathing (table 2). In patients with CHF, respiratory instability correlated with instability in SaO2 during spontaneous breathing (CV-Pw vs SaO2, SD r=0·565, p<0·0001; CV-Hz vs SaO2, SD r=0·608, p<0·0001). These correlations were independent of Cheyne-Stokes breathing pattern.

In the follow-up study, the nine CHF patients who had breathing training reported that slow breathing became easier with practice and a general reduction in the sensation of dyspnoea. Motivation to train increased from the start of training to completion (7·6 [0·3] vs 8·8 [0·5], p<0·05) and at 1 month follow-up (9·1 [0·2], p<0·01). After training, the spontaneous breathing rate decreased (13·4 [1·5] to 7·6 [1·9]) breaths per min, p<0·001), SaO2 increased (92·5 [0·3] to 93·2% [0·4], p<0·05), and exercise time increased (615 [23] to 583 s [29], p<0·05). During peak exercise, the load reached increased (92 [6] to 100 W [4], p=0·05), and oxygen consumption increased (13·9 to 15·9 [0·8] L min⁻¹ kg⁻¹ [0·8], p<0·05). The anaerobic threshold was reached at higher load after training than before (64·8 [4·3] vs 59·4 W [3·7], p<0·05) and after a longer time (422 [22] vs 396 s [18], p<0·05), though without a significant increase in oxygen consumption per kg (12·0 [0·7] vs 11·3 [0·4], p=0·21). Sensation of dyspnoea did not change at 25 W (11·5 [0·5] vs 11·1 [0·3], p=0·31), but decreased at 50 W (12·1 [0·5] vs 13·1 [0·3], p<0·05), 75 W (14·1 [0·6] vs 15·1 [0·4], p<0·05), and 90 W (17·3 [0·9] vs 19·4 [0·4], p<0·05). A significant reduction in the sensation of fatigue was observed at only 75 W load (13·7 [0·7] vs 15·0 [0·5], p<0·05). At the 1 month follow-up all values were higher than baseline, but only the sensation of dyspnoea at all workloads and sensation of fatigue at 50 W and 75 W were statistically significant compared with baseline (p<0·05). The rest group showed no significant changes in any index either at rest or in response to exercise.

Discussion

Our results confirm that although SaO2 can be normal in CHF,1,13 many patients have reduced SaO2 at rest.13,15 Reduced SaO2 is associated with an instability in oxygen saturation, which, in turn, is associated with an instability in breathing frequency and amplitude. The controls also had irregularities in respiratory patterns, but because they had a normal cardiac function they had higher SaO2.
minute, despite a 40% decrease in ventilation, $\mathrm{SaO}_2$ increased with a substantial improvement in the ventilation to perfusion ratio. However, because this slow rate is difficult to maintain, it was not suitable for long periods. At six breaths per min, the increase in $\mathrm{SaO}_2$ could be obtained without changes in minute ventilation, but with a significant increase in alveolar ventilation and improvement in the ventilation to perfusion ratio, suggesting that this rate of breathing was more effective in terms of gas exchange as Cotes has suggested for slower breathing rates. The importance of the increase in $\mathrm{SaO}_2$ is not easily appreciated when data from all CHF patients are considered, because the patients with $\mathrm{SaO}_2$ during spontaneous breathing had a limited increase in $\mathrm{SaO}_2$, whereas the patients with the lowest $\mathrm{SaO}_2$ values showed the greatest improvement.

Deeper and slower respiration usually involves a greater use of the diaphragm and our results suggest that this is beneficial during low rates of breathing and probably does not increase respiratory workload. 6 breaths per min seems to be an ideal compromise since it was not difficult to achieve and sustain in the long-term.

The effects of arterial desaturation in heart failure are important because they may impair skeletal muscle and metabolic function, and lead to muscle atrophy and exercise intolerance. Our findings, therefore, have a potential clinical application and accord with previous reports of the beneficial effects of increases and improvements in respiratory muscles and function in CHF.\

Could the spontaneous pattern of breathing be changed by appropriate training? Stanescu and colleagues reported that individuals who practised regular respiratory exercises (hata yoga) have resting respiratory rates of about six breaths per min, a lower rate than controls; these findings were explained as the chronic effect of manipulating breathing. During meditation, the respiratory rate decreases spontaneously to a similar value.

In this study, the nine patients with CHF who had a yoga-derived breathing training reduced their spontaneous breathing rate and sensation of dyspnoea, and increased their resting oxygen saturation and exercise performance. The sensation of dyspnoea was reduced to a greater extent than the sensation of fatigue, suggesting that the improvement was mainly due to mobilisation of respiratory muscle. We cannot exclude the possibility that awareness of the aim of the study could have affected the spontaneous breathing pattern of the participants. Nevertheless, the changes we observed in the response to exercise and the increased motivation of the patients to continue the training after the requested period suggest that the benefits of this simple practice were maintained, irrespective of whether the breathing pattern was permanently modified. Although the increase in exercise performance was lower compared with home-based physical training, this result was obtained with an independent procedure that did not involve any other additional type of physical training. Our findings support previous studies that report beneficial effects of training respiratory muscles and decreasing respiratory work in CHF, or physical training in general, and suggest that the effects of slow breathing could be additive to other forms of treatment.

Contributors
Luciano Bernardi was responsible for the overall design of the study. All the investigators contributed to the study design, collection of data, interpretation of the results, and writing of the paper.

Acknowledgments
We thank the physiotherapy team at Herz-Zentrum (Bad Krozingen, Germany), and Gabriella Cella, from the Suria-Chandra Marga Yoga Institute (Piacenza, Italy) for their professional skills and invaluable collaboration.

References
activity, were demonstrated in vitro in 1976, so the resistance to cephalosporins was predictable. Information of this kind should be taken into account in drug development and licensing.

The committee sensibly goes to some length to address methods for prevention of cross-infection and surveillance of antibiotic-resistant bacteria. The UK has a strong history of good control-of-infection practices in hospitals. Nevertheless, the striking rise in reports of infection caused not only by meticillin-resistant but also by meticillin-sensitive _S aureus_ in the UK suggests that some changes in medical and administrative practice have created conditions for the nosocomial spread of this bacterium. Effective cross-infection control relies on accurate and also rapid identification of antibiotic-resistant bacteria. Hope was expressed that good methods for identification of such bacteria will be developed, but technical and financial constraints mean they are unlikely to be available in the near future.

Meanwhile, quality-controlled routine antibiotic-sensitivity testing of clinical specimens in the UK’s National Health Service and Public Health Laboratory Service laboratories is generating much potentially useful information on antibiotic resistance and cause of infectious diseases. However, adequate information-technology resources are required to integrate the data from these two sources. In addition, the statutory reporting of infectious diseases by disease, rather than by organism, is archaic, and microbiological data, if available, must be incorporated.

The provision of those data and future research and development activities rely on the existence of well-funded departments of clinical microbiology. Here the committee highlights the failure to direct resources, both human and financial, to correct the poor state of clinical academic microbiology.

Antibiotic-resistant bacteria have no respect for geographical boundaries, as illustrated by the importation, on several occasions, into the UK from Pakistan and India of _Escherichia coli_ resistant to all β-lactam antibiotics other than carbapenems. The committee asks the UK government to continue its support of the WHO Antimicrobial Resistance Monitoring programme and endorses the resolution to be considered at the forthcoming World Health Assembly to put the programme on a firmer financial footing. The creation of a global monitoring scheme is fundamental to the reduction of antimicrobial resistance.

Rates of resistance are lower in the UK than in many other countries. Nevertheless, the committee was not convinced that Ministers, the public, or the veterinary and agricultural community have grasped the importance of action in the short term. The health-care profession may have a better understanding of the problem, but is not provided with the resources to take action. The committee draws attention to the fact that the Swann Committee recommended the establishment of a multidisciplinary interdepartmental committee to oversee policy and research relating to antibiotic use. That was 30 years ago. We cannot afford to delay any longer the setting up of this committee.

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**Teaching heart-failure patients how to breathe**

*See page 1308*

The pathophysiology of heart failure used to seem easy. In heart failure dyspnoea was caused by wet lungs and muscle fatigue by reduced cardiac output. The only way to make the patient better was to improve the function of the heart. Research over the past two decades has shown these tenets to be misleading. The pathophysiology underlying the symptoms of chronic heart failure is complex and poorly understood.

The metabolite that stimulates the drive to breathe during exercise is not known. Potassium, lactate, adenosine, and carbon dioxide have each been proposed as the major stimulus. Given this complexity it is not surprising that treatments to relieve dyspnoea in heart failure are not uniformly effective, and that substantial limitation of everyday activities remains despite maximum modern pharmacological therapy. Treatments that do not take into account the important pathophysiological changes in the syndrome of chronic heart failure are unlikely fully to rehabilitate the heart-failure patient back to a good symptom-free quality of life. Treatments that correct the haemodynamics of heart failure do not reliably increase exercise tolerance or reduce the severity of dyspnoea because changes in endothelial, skeletal, and respiratory musculature, in lung and respiratory control mechanisms, and in whole-body metabolic and anabolic/catabolic balance may have become the factors limiting exercise capacity.

The study by Luciano Bernardi and colleagues in _The Lancet_ today addresses the importance of abnormalities of the pattern of respiration in patients with heart failure. Unstable ventilatory control has long been known to occur sometimes in heart failure, and to lead commonly to...
Effects on exercise tolerance in stable chronic heart failure

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<td>Positive inotropic drugs</td>
<td>Usually unchanged</td>
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<td>Heart transplantation</td>
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<td><strong>“Lung” treatments</strong></td>
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<td>Diuretics</td>
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<td>Reducing ventilatory work</td>
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ACE=angiotensin-converting enzyme; NO=nitric oxide.
*With the exception of digoxin this effect is seen only at the expense of increased mortality.
‡Only if patient was severely limited at time of operation and if patient underwent exercise rehabilitation after procedure.
§Only if patient was initially congested.

Cheyne-Stokes respiration and sleep-disordered breathing. 1, 2 Surges of chemoreceptor-driven ventilatory efforts, with their concomitant sympatho-excitation occurring simultaneously with dips of hypoxaemia, are a potential hazard in patients susceptible to ventricular arrhythmia. 3 Apart from this there is the wasted metabolic costs of inefficient ventilation during exercise and the harmful effects of intermittent hypoxaemia on organ function. Bernardi and colleagues investigated two important questions: first, whether in patients with heart failure instability of breathing pattern contributed to reduced arterial oxygen saturation at rest; and, second, whether short-term or medium-term alterations in breathing pattern could improve oxygen saturation and exercise tolerance.

They studied 50 patients with stable chronic heart failure and 11 controls and identified a reduction in mean arterial oxygen saturation at rest. This reduction correlated with the degree of instability of respiratory pattern, which suggested a causal link. This finding is to be expected; arterial oxygen saturation is asymmetrically distributed around its mean value, and it can dip substantially below its mean value during periods of low ventilation, but it cannot go above 100% during periods of increased ventilation. In a novel twist on the known beneficial effects of conventional exercise training or respiratory-muscle training in chronic heart failure, the investigators trained nine patients with heart failure to adopt the most appropriate respiratory pattern, that of slow regular breathing, by use of coordinated diaphragmatic and chest breathing. They applied yoga breathing techniques that had been shown to be adopted by healthy people adept at yoga. 5 Average oxygenation not only improved over the short term but also was maintained for the month of “training” and for a month after the end of the programme. A control group of six heart-failure patients showed no such change. The yoga training techniques led to a small but useful increase in exercise tolerance and peak oxygen uptake, with a reduced sensation of dyspnoea during exercise.

Bernardi’s study raises interesting possibilities. It adds another treatment option to the list of those that can increase exercise tolerance in heart failure. Surprisingly, many of the treatment options so proven (panel) have only an indirect relation to improvement of cardiac output. It appears that in terms of symptoms and exercise tolerance in the short term, the non-cardiac physiological changes need to be addressed as well as the heart itself. The second issue is whether patients with heart failure could master these techniques in more routine clinical settings. Respiratory-pattern training may play a part in selected patients and it could be a useful addition to other rehabilitative measures in a wider group of patients. How practical this approach will prove for wider groups of patients, how will they adhere to the techniques, and whether the training effects persist in the longer term are all questions to be answered. The value of this study is probably more in the general than in the specifics. It teaches us there are more ways to improve symptoms than stimulation of the failing organ, and that the progress of disease in human beings is complex and multifactorial and offers multiple approaches to amelioration.

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Biomarkers of asthma
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The recognition that asthma is primarily an inflammatory disorder of the Airways orchestrated by T lymphocytes, with release of many mediators, underpins guidelines for asthma management. Symptom diary cards and measurements of peak expiratory flow have been invaluable in guiding therapy in self-management plans, but these records reflect the downstream consequences of the prevention or control of airway inflammation rather than events relating to the inflammatory response itself. Hence there has been a search for new “biomarkers” of airway inflammation in asthma that predict changes in airway dysfunction and therefore improve disease management.

A fundamental abnormality in asthma is that the Airways contract too much and too easily, a state referred to as bronchial hyper-responsiveness (BHR). Although useful in helping to confirm a diagnosis of asthma, repeated measurement of BHR by use of standard bronchial provocation tests with histamine or methacholine has proved disappointing and impracticable for reflecting day-to-day variation in the disease. Although

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**COMMENTARY**

1300 THE LANCET • Vol 351 • May 2, 1998