Induction of oscillatory ventilation pattern using dynamic modulation of heart rate through a pacemaker

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Submitted 29 January 2008; accepted in final form 1 May 2008

Manisty CH, Willson K, Davies JE, Whinnett ZI, Baruah R, Mebrate Y, Kanagaratnam P, Peters NS, Hughes AD, Mayet J, Francis DP. Induction of oscillatory ventilation pattern using dynamic modulation of heart rate through a pacemaker. Am J Physiol Regul Integr Comp Physiol 295: R219–R227, 2008. First published May 7, 2008; doi:10.1152/ajpregu.00064.2008.—For disease states characterized by oscillatory ventilation, an ideal dynamic therapy would apply a counteracting oscillation in ventilation. Modulating respiratory gas transport through the circulation might allow this. We explore the ability of repetitive alternations in heart rate, using a cardiac pacemaker, to elicit oscillations in respiratory variables and discuss the potential for therapeutic exploitation. By incorporating acute cardiac output manipulations into an integrated mathematical model, we observed that a rise in cardiac output should yield a gradual rise in end-tidal CO2 and, subsequently, ventilation. An alternating pattern of cardiac output might, therefore, create oscillations in CO2 and ventilation. We studied the effect of repeated alternations in heart rate of 30 beats/min with periodicity of 60 s, on cardiac output, respiratory gases, and ventilation in 22 subjects with implanted cardiac pacemakers and stable breathing patterns. End-tidal CO2 and ventilation developed consistent oscillations with a period of 60 s during the heart rate alternations, with mean peak-to-trough relative excursions of 8.4 ± 5.0% (P < 0.0001) and 24.4 ± 18.8% (P < 0.0001), respectively. Furthermore, we verified the mathematical prediction that the amplitude of these oscillations would depend on those cardiac output (r = 0.59, P = 0.001). Repetitive alternations in heart rate can elicit reproducible oscillations in end-tidal CO2 and ventilation. The size of this effect depends on the magnitude of the cardiac output response. Harnessed and timed appropriately, this cardiorespiratory mechanism might be exploited to create an active dynamic responsive pacing algorithm to counteract spontaneous respiratory oscillations, such as those causing apneic breathing disorders.

periodic breathing; physiology; pacing; reflex

There are clinical conditions characterized by oscillatory ventilation patterns, for example periodic breathing in heart failure patients. In these subjects, cardiorespiratory control is unstable, and they suffer significant morbidity and a poor prognosis (9, 23, 25, 35). If a simple and clinically acceptable intervention were available that could add an oscillatory increment to ventilation, of a desired predictable size and timing, this could be developed into a treatment to attenuate the respiratory instability seen in these patients.

Cardiovascular function is critical to respiratory gas exchange, and there is a well-observed increase in ventilation at the start of exercise. The mechanism behind this remains controversial (3), although a “cardiodynamic hyperpnea” has been described, linking increased cardiac output to the rise in ventilation at the onset of exercise (43, 45). This was initially demonstrated by pharmacological manipulation of cardiac output using vasoactive drugs: when cardiac output was increased, there was an accompanying increase in ventilation. It was thought that the function of this “cardiodynamic” reflex was to maintain end-tidal CO2 (ETCO2) within narrow limits by increasing ventilation as CO2 production and transport to the lungs increased, although the mechanism was unclear. Further investigations using pacemakers showed that when heart rate was reprogrammed to a higher rate, there was a rise in ventilation. However this was only after a delay of ~30 s, during which period end-tidal gases changed in a direction that would be expected to stimulate ventilation (21).

If the effect of cardiac output on delivering respiratory gases to the lung is incorporated into a conventional mathematical model, it becomes apparent that an acute increase in cardiac output might be expected to produce a transient rise in ETCO2. Subsequently, ventilation will be expected to rise, via the chemoreflex. In brief, when cardiac output is greater than average, CO2 delivery to the lungs (via the bloodstream) exceeds that removed by exhalation; therefore, ETCO2 concentrations rise. Conversely, when cardiac output is less than average, net CO2 balance is negative, so lung concentrations fall. We show a simple example of such a mathematical model in the appendix.

A significant proportion of heart failure patients have implanted cardiac devices, such as biventricular pacemakers, allowing manipulation of heart rate and hence cardiac output at will. This heart failure population is also at risk of apneic disorders, including periodic breathing (11, 13, 26, 34, 35, 42), and, therefore, a pacing algorithm could potentially be used to deliver oscillatory ventilatory increments to counteract the spontaneous oscillations in ventilation found in periodic breathing.

The first step in determining whether pacemaker manipulation might have therapeutic potential for such diseases is to determine whether cyclical respiratory fluctuations of an appropriate frequency (typically one cycle/min for periodic breathing diseases) can be elicited at will by a sequence of programmed pacemaker manipulations.

We hypothesized that, through a protocol of alternating cardiac output between two values using a dynamic pacing
ETCO2 levels and ventilation in clinical subjects.

We hypothesized that this would then produce detectable phasic oscillations in ventilation at a frequency of potentially practical interest.

METHODS

The initial stage to our study involved applying an acute change in cardiac output to a fundamental model of cardiorespiratory control. We then proceeded to a clinical study using dynamic alternating changes in cardiac output via preimplanted cardiac pacemakers, to try to produce measurable respiratory oscillations.

Part 1: The Cardiorespiratory Model

We modified a standard model of cardiorespiratory physiology to accommodate a cardiac output that changes with time (APPENDIX). We used this to examine the expected behavior of ETCO2 levels for the short period of time after cardiac output undergoes an acute change.

Part 2: Clinical Study

We examined the acute effects of cardiac output manipulation on ETCO2 levels and ventilation in clinical subjects.

Study population. We recruited consecutive patients with implanted cardiac pacemakers (and/or defibrillators) from our general pacemaker clinic and our specialist heart failure clinic. All subjects were screened to exclude periodic breathing during daytime assessment in the clinic. Patients were monitored for 30 min while recumbent for oscillations of ~1 min in ventilation and oxygen saturation recordings. If oscillations in respiratory variables were detected, then patients were excluded from the study. No changes had been made to any of the patients’ medication or their pacemaker settings for a minimum of 6 wk before entering the study.

Exclusion criteria were the presence of periodic breathing, a resting native heart rate >90 beats/min, implantable cardiac defibrillators with antitachycardia therapy set at an unusually low rate (<120 beats/min), and atrial fibrillation with a poorly controlled ventricular response. These patient groups were excluded to ensure that we were able to safely alternate the demand pacing rate between two values 30 beats/min apart.

All patients gave informed consent for this study, which was approved by the St. Mary’s Hospital local research ethics committee. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Measurements. Patients lay on a comfortable couch, with the head section tilted upwards at an angle of ~45°, and the lower section horizontal. Their state of wakefulness was documented by visual confirmation that their eyes were open. They breathed through a calibrated pneumotachograph attached to a metabolic cart (MedGraphics Cardio CP2, Medical Graphics, MN) measuring ventilation and inspiratory and expiratory respiratory gases.

An ECG signal was recorded using the Hewlett-Packard 78351A, from which we derived the heart rate. Blood pressure and cardiac output were measured noninvasively using a photoplethysmograph device (Finometer, Finapres Medical Systems). This uses a cuff that is placed around the finger, a built-in photo-electric plethysmograph, and a volume-clamp circuit that dynamically follows arterial pressure. The device yields a continuous beat-to-beat arterial pressure waveform and incorporates the “model flow” algorithm (44), which tracks changes in cardiac output by relating pressure changes to changes in a nonlinear, three-element aortic impedance model. We entered the patients’ age, sex, height, and weight, and these were used to estimate the three elements of the aortic impedance model (based on population averages) (24). The Finometer has been extensively validated against invasive measurements for absolute noninvasive measurement of changes in cardiac output (18, 32, 39, 41). We also performed noninvasive validation of the Finometer against echocardiography for measuring changes in cardiac output during reprogramming pacemaker atriовentricular delay. We found the Finometer to be significantly more reproducible than echocardiography at measuring cardiac output changes: in 12 patients, the Bland-Altman difference for two successive measurements of cardiac output change using the Finometer across all patients was 0.17 l/min, SD 0.12 l/min, compared with 0.73 ± 0.37 l/min for cardiac output measured using echocardiography (P = 0.0004).

Pacemaker reprogramming was performed via a pacemaker telemetry head positioned on the subjects’ skin over their implanted device, to enable the heart rate to be changed according to protocol.

Protocol. To enable us to control the heart rate during the study, all subjects whose clinical pacing configuration and underlying disease gave them atrial sensing at rest had their devices reprogrammed with a lower pacing rate 5 beats/min above their native rate. This ensured that all subjects were paced throughout the study session.

The patients were monitored at this fixed baseline heart rate for 30 min with measurements of ECG, blood pressure, cardiac output, ventilation, ETCO2, and end-tidal O2 (ETO2) recorded to confirm stable baseline respiratory control with no evidence of respiratory oscillations suggestive of periodic breathing.

We continued to monitor cardiorespiratory variables while alternating the pacing rate (via the pacemaker telemetry head) between baseline and 30 beats/min above baseline, with a cycle time of 1 min. This cycle of repeated square-wave heart rate alternations was repeated five times, and a signal-averaged single cycle was then calculated.

To assess the effect of differing magnitudes of heart rate increment, in a subset of five patients, we assessed repeated alternations in heart rate of 10, 20, 30, 40, 50, and 60 beats/min in size.

Data acquisition. The data were sampled at 1,000 Hz and read into our unit’s custom data-acquisition system: an analog-to-digital card (DAQCard 6062E, National Instruments, Austin, TX) with a workstation running custom software written in Labview instrument control language (version 7.0, National Instruments). This system enables data to be collected simultaneously from different devices.

The data were later analyzed offline using custom software based on a foundation of Matlab (Natick, MA), which our laboratory has developed and validated (8, 10). Heart rate, blood pressure, cardiac output, end-tidal gas concentrations, and ventilation were digitally interpolated and resampled to obtain signals at 1 Hz for subsequent analysis. The reason for the lower sampling rate for data analysis is that our laboratory uses a standard acquisition rate of 1,000 Hz, which allows QRS complexes to be timed to 1 ms, giving a precise measurement of heart rate. The end-tidal measures are only obtained at the end of each breath, and we judged, therefore, that a practical fixed-frequency sampling rate at which to display the results would be 1 Hz, higher than the actual information rate of end-tidal and ventilation signals and reasonable for the reader to interpret. Interpolation was done between breaths so that a value was available each second to be averaged across all cycles.

Measurement of hemodynamic and respiratory oscillations. The amplitude of the hemodynamic and respiratory oscillations in response to the heart rate alternation was quantified using signal averaging. Data from each of the five individual 60-s alternations was time aligned using the transition point as a fiducial marker, and then the mean and SE at each point in time were calculated. The amplitude and timing of the oscillations were calculated using Fourier analysis at a frequency of 1/60 Hz, corresponding to the stimulus cycle time of 1 min.

We were able to calculate an index of each subject’s ventilatory sensitivity to CO2 by calculating the ratio between the amplitudes of oscillation in ventilation and ETCO2. For simplicity, we have described this as a notional integrated “pseudo-chemoreflex gain.” This is not the conventional use of the term chemoreflex gain, which usually represents the response to a change in a single gas concen-
tation (rather than to concomitant changes in both ETCO₂ and ETO₂).

RESULTS

Results of the Mathematical Analysis

As shown in the appendix, the mathematical analysis suggested that a step change in cardiac output would produce, over the following few seconds, a gradual change in lung gas concentrations. When cardiac output is acutely increased, there is an exponential increase in the rate of delivery of CO₂-rich venous blood to the lungs. In the short term, this raises lung PₐCO₂ levels and hence arterial CO₂ levels, which will, in turn, via the chemoreflex, result in increased ventilation.

Results of the Clinical Study

Subject characteristics. Of 32 patients screened, 3 were excluded because of atrial fibrillation, 3 because of baseline periodic breathing, and 4 because their native heart rate exceeded 80 beats/min. The 22 remaining subjects (14 with heart failure and 8 with normal systolic function) were enrolled (Table 1).

Of the subjects with heart failure, eight had biventricular pacemakers, and the remainder dual-chamber devices. Indications for implantation of dual-chamber devices included atrioventricular block, sick sinus syndrome, and sinus node disease.

None of the patients with normal systolic function were taking cardiac medication, and all were free of cardiac symptoms. At the time of study, four of the heart failure patients were in New York Heart Association (NYHA) class I, six were in NYHA II, and four were in NYHA III. All were prescribed maximal medical therapy: 12 were taking β-blocker medication, bisoprolol or carvedilol, 10 were taking angiotensin-converting enzyme inhibitors, 4 were taking angiotensin-II receptor antagonists, 8 were taking spironolactone, 9 were taking a diuretic (loop or thiazide), and 3 were taking digoxin.

Effect of alternation in heart rate on respiratory parameters. Alternating heart rate every 30 s by 30 beats/min produced oscillations in cardiorespiratory parameters in all subjects. The mean amplitude of oscillations in cardiac output was 0.72 ± 0.43 l/min, with a tendency toward higher values in subjects with normal systolic function than in heart failure subjects (0.91 vs. 0.62 l/min, P = 0.06). Following the increase in paced heart rate, ETCO₂ rose, and then, after a delay, ventilation increased (Fig. 1). Correspondingly, when the paced heart rate was restored, there was initially a decrease in ETCO₂, followed by a fall in ventilation.

Table 1. Baseline subject characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-Heart Failure Subjects</th>
<th>Heart Failure Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>7/1</td>
<td>13/1</td>
<td>0.90</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>68.7±8.4</td>
<td>32.4±10.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63.6±14.6</td>
<td>73.9±7.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>55±12.0</td>
<td>60±10.2</td>
<td>0.30</td>
</tr>
<tr>
<td>Baseline mean arterial blood pressure, mmHg</td>
<td>97.2±26.4</td>
<td>88.6±24.5</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Values are means ± SD.

The pattern of repeated alternations in paced heart rate, therefore, elicited oscillations in ETCO₂, ETO₂, and ventilation (Figs. 1 and 2). Each of the alternations were then signal averaged, allowing accurate measurement of amplitudes and timings of the peaks of the oscillations (Fig. 3).

In all subjects, the rise in ETCO₂ occurred shortly after the rise in cardiac output and preceded the increase in ventilation (average time delay from peak cardiac output to peak ETCO₂ was 4.9 ± 7.4 s, and mean delay from peak cardiac output to peak ventilation was 33.7 ± 10.5 s). The average delay between peak ETCO₂ and peak ventilation was 21.3 ± 4.7 s.

Figure 2 shows an example of data from one subject with heart failure showing baseline measurements of ETCO₂ and ventilation (Fig. 2). The pattern of oscillations in ETCO₂ was then signal averaged, allowing accurate measurement of amplitudes and timings of the peaks of the oscillations (Fig. 3).
of 2.6 \pm 1.5\%). The magnitude of oscillations in ventilation was 1.08 \pm 0.84 l/min (relative amplitude 12.2 \pm 9.4\%).

There was good reproducibility in the response to repeated heart rate alternations within individual subjects (the SE for the ETCO\(_2\) response averaged 0.073 kPa, and for ventilation averaged 0.59 l/min). Between different subjects, the same 30 beats/min oscillation in heart rate produced different sizes of oscillations in respiratory parameters (Fig. 4).

The relationship between cardiac output oscillations and oscillations in respiratory variables. The mathematical model (APPENDIX) predicts that the relative size of oscillations in ETCO\(_2\) should be directly proportional to the relative size of oscillations in cardiac output (\(\Delta C/C_0 \propto \Delta Q/Q_0\)) (see APPENDIX for definition of terms in equation).

This was verified in the clinical data: there was a strong relationship within individual patients between these variables.
We have demonstrated a direct cardiorespiratory reflex whereby oscillations in the respiratory system can be induced using a purely cardiac intervention. We found that serially changing a subject’s heart rate (and thereby cardiac output) by dynamic pacemaker reprogramming can modulate ventilation.

Heart rate alternations of depth of 30 beats/min at a frequency of one cycle/min (similar to that found physiologically in periodic breathing and other apneic disorders) caused consistent oscillations in ETCO$_2$, ETO$_2$, and ventilation of reproducible magnitude and phase within individuals. Different individuals had different ventilatory responses to the heart rate alternation, and this was dependent on the cardiac output increment induced and the individual subject’s ventilatory sensitivity to CO$_2$.

The concept of such an interaction between the cardiac and respiratory systems was raised by Wasserman’s group as a potential mechanism for early exercise hyperpnea (43, 45): the process received the name “cardiodynamic reflex” because of its perceived relevance to exercise. Newer studies, using spinal cord transaction patients, have excluded a prominent role for this in the genesis of early exercise hyperpnea (3, 28). Yet the process does exist, and the present study shows how it can be readily elicited in phasic form. Instead of thinking of this as a failed candidate mechanism for early exercise hyperpnea, we propose that it should be considered a potential candidate mechanism for dynamic intervention on the respiratory system using a cardiac pacemaker, and, accordingly, we propose it be given a more appropriately descriptive term, such as “cardiopacnic”.

Using manipulation of programmed cardiac pacemaker parameters, we were able to deliver an acute step change in heart rate, making determination of the chronology of the changes easier. In addition, the acute timeframe over which we were measuring the respiratory effects of the cardiac output change (30 s posttransition) and the likelihood that there will be less sympathetic activation following a pacemaker-induced cardiac output change than an exercise-induced one mean that we should have minimized neurohumoral effects in our study.

Several observations support a causative role for cardiac output in the changes to ventilation. First, there is only a short delay between the increase in heart rate and the rise in ETCO$_2$ (~5 s), followed by a delay of ~20 s before ventilation increased [a value similar to published chemoreflex delays (13, 412 vs. 387 l·min$^{-1}$·kPa$^{-1}$, P = 0.04). This thus measure of chemoreflex gain, albeit unconventional, gives values broadly similar to those obtained by conventional methods (4, 13, 19, 40).

**DISCUSSION**

In all five patients who underwent heart rate alternations of different magnitudes, the relative size of oscillations in cardiac output and ETCO$_2$ was strongly correlated (mean of within-patient correlation coefficients was 0.83 ± 0.10, P < 0.0001 in all cases, Fig. 5). Because ETCO$_2$ and ventilation are closely related via the chemoreflex (average individual correlation coefficient 0.78 ± 0.1), the relative amplitude of oscillations in ventilation was also correlated with the relative amplitude of oscillations in cardiac output within an individual subject (mean within-patient r = 0.48, P = 0.006).

Across the entire study group, the relationship between the relative size of oscillations in ETCO$_2$ and the relative size of oscillations in cardiac output was still significant (r = 0.59, P = 0.01; Fig. 4).

Ventilatory sensitivity to changes in respiratory gases (“pseudo-chemoreflex gain”). This measure of pseudo-chemoreflex gain was inversely correlated with ejection fraction (r = −0.47, P = 0.03). Pseudo-chemoreflex gain was significantly higher in subjects with heart failure than in those subjects without heart failure (716 ± 412 vs. 387 ± 122 l·min$^{-1}$·kPa$^{-1}$, P = 0.04). Thus this measure of chemoreflex gain, albeit unconventional, gives values broadly similar to those obtained by conventional methods (4, 13, 19, 40).

Fig. 4. Relationship between oscillations in ETCO$_2$ and cardiac output across the patient group. The magnitude of the ETCO$_2$ oscillations was closely related to the magnitude of cardiac output oscillations during heart rate alternation, throughout the group of subjects.

Fig. 5. Relationship between cardiac and respiratory parameters in response to different amplitudes of heart rate alternations, in a subset of 5 subjects. Although, in each individual subject, there is a different slope in the relationship between the increment in cardiac output and the relative amplitude of oscillations in CO$_2$ when heart rate is alternated, each subject has a linear relationship between the amplitude of oscillations in these two variables.
In the same direction as the effect of the concomitant CO2 fluctuation, the magnitude of the ventilation oscillations is at least partly due to an improvement of ventilation-perfusion matching with the increased cardiac output. In our data, ventilation increased following the increase in ETCO2, which contradicts this. If the increased cardiac output improved perfusion of ventilated lung fields, more CO2 would be removed from the venous blood. This would result in lower CO2 levels in the arterial blood reaching the chemoreceptors, and therefore a fall in ventilation after the chemoreflex delay.

Additionally, we were able to measure beat-to-beat changes in cardiac output using the Finometer. These data strongly support the changes in ETCO2 and ventilation being related to the increase in cardiac output. Within individual subjects, the relationship was extremely strongly correlated across a wide range of cardiac outputs.

There was a significantly lower cardiac output response to the programmed heart rate change in the heart failure subjects than the non-heart failure subjects, which was to be expected. Previous evidence has shown that heart failure subjects have decreasing cardiac index with increasing heart rate (15), and in vitro studies have shown abnormalities in the force-frequency relation in heart failure subjects (17, 30). However, because of their enhanced ventilatory sensitivity to respiratory gas fluctuations, the magnitude of the ventilation oscillations was similar in the two groups.

Although our model described explicitly only the CO2 response to dynamic changes in cardiac output, there are also small oscillations in ETCO2 in almost exact antiphase to the oscillations in ETCO2 (12). Cardiac output, in addition to determining the rate of delivery of CO2-rich venous blood to the lungs, also determines the rate of delivery of oxygen-depleted venous blood to the lungs for oxygenation. The immediate consequence of a step rise in cardiac output will, therefore, be a gradual decline in ETCO2 levels in the lungs. The effect of this on ventilation may well be very small, but will be in the same direction as the effect of the concomitant CO2 change.

We were able to calculate an index for an individual subject’s ventilatory sensitivity to CO2 because the heart rate alternations produced oscillations in CO2, which produced oscillations in ventilation via the chemoreflex. Although the small oscillations in oxygen may also have stimulated ventilation, and this is neither the conventional separated central or peripheral chemoreflex gains, it allows some measure of ventilatory sensitivity. It also refers preferentially to the processes with a frequency of once per minute (1/60 Hz) relevant to periodic breathing and correlates with ejection fraction.

Comparison with Other Studies

One group of investigators showed, using isolated step changes in heart rate in patients with pacemakers, that it is possible to increase ventilation in resting patients, and that this was likely to be via the chemoreflex (21). They did not measure cardiac output directly, but instead extrapolated the immediate changes in end-tidal Po2 after the heart rate change to conclude that oxygen consumption was changing. By assuming that there was little change in arterial and mixed-venous oxygen contents, they, therefore, could use changes in oxygen consumption as a proxy for changes in pulmonary blood flow and cardiac output.

Our results add to their findings by demonstrating the ability to induce oscillations in respiratory parameters (using repeated heart rate alternations). We also showed the predictability of the ventilatory response and also the dependence on the cardiac output increment and the individual subject’s ventilatory sensitivity to CO2.

There may also be a role for the carotid baroreflex in the interaction between the cardiac and respiratory systems, as large changes in ventilation are likely to affect cardiac filling and hence blood pressure and cardiac output (33, 38).

Clinical Implications

Interaction between the cardiovascular and respiratory systems in heart failure has long been recognized, but little clinical work has been directed at utilizing this complex interaction therapeutically. In particular, the effect of dynamic alternations in cardiac parameters on respiratory variables (including ventilation and CO2) has not been studied in detail.

A large proportion of patients with left ventricular dysfunction have unstable respiratory control, which manifests as periodic breathing with cyclical hypopneas and hyperpneas, driven by oscillations in blood gases (20, 36). Patients with periodic breathing have significant symptomatology (including sleep disruption with daytime fatigue), and a worse prognosis than subjects with similar cardiac function but stable cardio-respiratory control (9, 25).

Attempts to stabilize breathing have focused on improving overall cardiac function [for example, through drugs (22)] or cardiac resynchronization therapy using biventricular pacing (14, 37)] or respiratory devices (5), which are poorly tolerated and nonportable (e.g., continuous positive airways pressure). Most of these currently available treatments for periodic breathing are essentially static, providing continuous treatment throughout the periodic breathing cycle, rather than applying phasic treatment to address the underlying pathophysiological oscillations. The proportion of heart failure patients with implanted cardiac devices (biventricular pacemakers and/or defibrillators) is rapidly expanding due to the growing body of evidence for both their prognostic and symptomatic benefits (1, 2, 6, 7, 29).

We have shown that intentional changes in cardiac output can dynamically control ventilation. If this could be combined with currently available ventilation monitoring pacemaker technology (27), an algorithm of variable dynamic changes in cardiac output might be created to counteract the respiratory gas oscillations that sustain periodic breathing. This would offer patients a therapy for periodic breathing without the need for compliance with external devices that many patients find unacceptably uncomfortable or inconvenient. This newly reported process for active phasic control of respiratory variables via acute cardiac modulation could be used to dynamically stabilize breathing in patients who have cardiac pacemakers or defibrillators in situ.

Pacemaker-induced changes to cardiac output produce predictable amplitude and timings of ventilatory responses within an individual due to the good reproducibility. If this method of
influencing ventilation were to be incorporated into a therapy for periodic breathing, this information would be very helpful. As a patient with periodic breathing can have varying amplitudes of oscillations in ventilation, the reasonably linear correlation with amplitude of cardiac output would allow an algorithm to produce a ventilatory effect of the desired size to counteract the spontaneous oscillations.

Study Limitations

We performed this study noninvasively, measuring end-tidal gas concentrations and a noninvasive beat-to-beat index of cardiac output. To minimize trauma to the subjects for this proof of concept study, we did not insert intra-arterial catheters for sampling of blood gases, nor for cardiac output quantification. However, we obtained good time resolution with our expired gas analysis, which would have been difficult to obtain invasively, even with an arterial line and very frequent sampling of arterial gas concentrations. We believe that end-tidal and arterial gases parallel each other to a reasonable degree within individual patients (46) over durations as short as this study. Other methods for noninvasive measurement of gases, such as transcutaneous assessment using the TINA device, have been shown to be accurate at tracking changes over chronic time scales, but pilot efforts at our institution found that its time resolution could not match that of end-tidal monitoring. We were also unable to investigate the specific part that the carotid baroreflex plays in cardiorespiratory interaction in a study of this design, and further experiments would be required to elucidate these mechanisms.

The gold standard measure of cardiac output is invasively measured thermodilution, but this does not easily lend itself to tracking acute changes over such a short cycle time, with good time resolution. The ability of modifications in peripheral pulse waveforms to faithfully reflect modulation of hemodynamic parameters might be questioned, and we, therefore, performed validation of the model flow method for measurement of cardiac output against a reference method, Doppler echocardiography. We performed these studies in the context of this experimental method for tracking changes in cardiac output induced by pacemaker reprogramming, and found the Flowmeter to be more sensitive and reproducible.

We only screened patients for periodic breathing during daytime assessments in the clinic. It is possible that some of the patients with impaired systolic function would have features of periodic breathing, if they were assessed with sleep studies, but all patients had stable baseline respiration before the onset of pacemaker reprogramming.

Perspective and Significance

In this study, we demonstrate the ability to elicit oscillations in respiratory variables by alternating heart rate and cardiac output. Both the amplitude and phase of respiratory oscillations produced are predictable and reproducible. This technique has potential translational clinical application for the stabilization of periodic breathing in heart failure. However, this would require further technical developments for the detection of the amplitude and phase of periodic breathing, and a method for conveying this information to a system that can dynamically reprogram a pacemaker in real time. Such automated technology is not currently available, but in principle could be developed.

Conclusion

Respiratory oscillations can be produced at will by dynamic modulation of heart rate using a cardiac pacemaker. The mechanism of this appears to be dynamic alteration of the rate of cardiac output and thereby CO₂ transport from the systemic tissues to the lungs. This might be developed into a potential therapeutic modality for the treatment of dynamic breathing disorders, such as periodic breathing.

APPENDIX: THE CARDIORESPIRATORY MODEL

In our model, ventilation (V) is considered to be controlled by a chemoreflex response to changes in CO₂. For simplicity, we directly modeled this with only a single variable for CO₂ (ETCO₂), with C representing its concentration at time t. Physiologically, the rate of change of lung CO₂ C is determined by the difference between the rate of CO₂ delivery to the pulmonary circulation, and the rate of its removal from the lungs by V and arterial blood. Blood entering the pulmonary circulation has two components, the first of which is the CO₂ originally in the blood (C₀) when it first left the pulmonary circulation at time t – δ. The second component is the CO₂ gained when flowing through tissues at a rate Qε (at time t – δ) as a product of metabolism (whose rate of production is VCO₂).

CO₂ is removed from the lungs by alveolar V and diffusion into the bloodstream. Both the rate of delivery of CO₂ in the venous blood, and the rate of removal of CO₂ in the arterial blood are influenced by cardiac output (Q). The simplest form of the fundamental equation that determines dC/dt, the rate of change of lung CO₂ C, is:

\[
\frac{dC}{dt} = V_L \left( C_{\infty} + \frac{V_{CO_2}}{\beta Q_{\infty}} \right) - (\beta Q + V_C) \tag{A1}
\]

where V_L is lung volume.

If Q is increased in this theoretical cardiorespiratory control system, there will be three principal consecutive effects on CO₂. J) The rate of delivery of CO₂ from the peripheries to the lungs will increase.

Fig. 6. Mathematical model of cardiorespiratory control. Left: the concentration of alveolar CO₂ at any give time is dependent of the amount of CO₂ added to the blood by metabolism t – δ ago, the amount of CO₂ in the blood leaving the lungs t – δ ago, and the amount of CO₂ removed from the lungs by ventilation and diffusion back into the blood at that time. Right: a step increase in cardiac output is predicted to result initially in an exponential rise in ETCO₂ toward an asymptote. See APPENDIX for definition of terms used in equations.
2) The CO₂ added to the circulation by the body’s metabolic stores falls, as the peripheral tissue stores of CO₂ become depleted. 3) The C of CO₂ in the blood leaving the lungs will increase, as lung CO₂ levels rise.

For simplicity, we have, therefore, divided the circulation into three phases, with three locations of interest (see Fig. 6), which occur at different time points with reference to current time t. The circulation time (time delay between blood leaving the lungs and returning again) is δ seconds. 1) CO₂-depleted blood leaves the lungs t – δ seconds before returning to the lungs. 2) CO₂ is added to the blood by metabolism in the body, approximately halfway around the circulatory cycle of blood traveling from and returning to the lungs. This occurs at (t – ε) seconds before returning to the lungs. 3) CO₂-rich blood returns to the lungs at time t.

We, therefore, make two simplifications about the effect on lung CO₂ (C₀), when Q is changed from Q₀ to Q₁. First, until time t + δ, C₀(t – δ) is equivalent to the C of CO₂ in the lungs before the Q change (C₀). Second, until time t + ε, Q₁(t – ε) is equivalent to Q₀ (the Q before the increase in cycle rate). After time t + ε but before time t + δ, Q₀(t – ε) is Q₁ (the new Q). Using these assumptions, we can predict that the time course of lung CO₂ under these conditions will initially be an exponential approach to another value, of the general form C₁ = C₀ + k₁ (1 – exp –k₁t).

Specifically, the expected behavior is:

\[ C = C₀ + \frac{C₀V}{Q₀ + V} \left( Q₀ - Q₀ \right) \left( 1 - \exp \left( \frac{\beta Q₀ + V}{\delta L} t \right) \right) \]  
(A2)

This means that the predicted initial effect of a rise in Q is that lung CO₂ will increase according to an exponential trajectory toward an asymptote (Fig. 6B).

GRANTS

C. H. Manisty was supported by a Research Training Fellowship from the Wellcome Trust (077049/Z/01/SZ) and the Coronary Flow trust. D. P. Francis (FS/04/079), Z. I. Whinnett (FS/05/068), and J. E. Davies (FS/05/006) were supported by the British Heart Foundation. K. Williams received support from the Foundation for Circulatory Health.

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