Novel Use of Cardiac Pacemakers in Heart Failure to Dynamically Manipulate the Respiratory System Through Algorithmic Changes in Cardiac Output

Resham Baruah, MBBS, BSc, MRCP; Charlotte H. Manisty, MBBS, MRCP; Alberto Giannoni, MD; Keith Willson, MSc, FIPEM; Yoseph Mebrate, MSc; A. John Baksi, MBBS, BSc, MRCP; Beth Unsworth, BSc; Nearchos Hadjiloizou, MBBS, BSc, MRCP; Richard Sutton, DSc, FRCP; Jamil Mayet, MD, MBA, FRCP; Darrel P. Francis, MA, MD, FRCP

Background—Alternation of heart rate between 2 values using a pacemaker generates oscillations in end-tidal CO2 (et-CO2). This study examined (a) whether modulating atrioventricular delay can also do this, and (b) whether more gradual variation of cardiac output can achieve comparable changes in et-CO2 with less-sudden changes in blood pressure.

Methods and Results—We applied pacemaker fluctuations by adjusting heart rate (by 30 bpm) or atrioventricular delay (between optimal and nonoptimal values) or both, with period of 60 s in 19 heart failure patients (age 73 ± 11, EF 29 ± 12%). The changes in cardiac output, by either heart rate or atrioventricular delay or both, were made either as a step (“square wave”) or more gradually (“sine wave”). We obtained changes in cardiac output sufficient to engender comparable oscillations in et-CO2 (PNS) in all 19 patients either by manipulation of heart rate (14), or by atrioventricular delay (2) or both (3). The square wave produced 191% larger and 250% more sudden changes in blood pressure than the sine wave alternations (22.4 ± 11.7 versus 13.6 ± 4.5 mm Hg, P < 0.01 and 19.8 ± 10.0 versus 7.9 ± 3.2 mm Hg over 5 s, P < 0.01), but peak-to-trough et-CO2 elicited was only 45% higher (0.45 ± 0.18 versus 0.31 ± 0.13 kPa, P = 0.01).

Conclusion—This study shows that cardiac output is the key to dynamically manipulating the respiratory system with pacing sequences. When manipulating respiration by this route, a sine wave pattern may be preferable to a square wave, because it minimizes sudden blood pressure fluctuations. (Circ Heart Fail. 2009;2:166-174.)

Key Words: respiration ■ hemodynamics ■ reflex ■ pacemakers ■ heart failure

The recent finding that manipulations of heart rate (HR) by a cardiac pacemaker produces fluctuations in end-tidal carbon dioxide (CO2),1 might be developed therapeutically for conditions common in heart failure such as periodic breathing which are characterized by spontaneous oscillations in end-tidal CO2.2

Clinical Perspective on p 174

However, embarking on such a development pathway requires certain challenges to be overcome. First, there may not always be scope to alter HR to make changes in CO2 of potentially useful magnitude, for example either because of a high resting rate or because of the underlying rhythm. This might be resolved if the mechanism were not dependent on HR per se, but rather on cardiac output, because it is possible to alter cardiac output by changing stroke volume without changing HR, for example, by changing atrioventricular (AV) delay.

Second, dynamic manipulation of cardiac output necessarily induces fluctuation in blood pressure (BP), which may be undesirable. Such sizeable changes in BP have been observed with the step changes in HR used to demonstrate this mechanism.1 It would be preferable to build algorithms from elements that minimize rapid BP changes while still achieving substantial CO2 manipulations.

In this study of heart failure patients, we tested whether adding the option to manipulate AV delay (instead of only HR) allows us to produce CO2 oscillations in all patients. We further aimed to determine whether a more gradual “sine wave” pattern of cardiac output manipulation could still elicit fluctuations in CO2, as achieved by the sudden step of the “square wave” pattern, while avoiding such sudden BP changes.
Methods

Subjects
A distinct set of 19 patients with cardiac pacemakers and a clinical diagnosis of heart failure were recruited from the outpatient cardiac service of our hospital. The diagnosis of heart failure was based on a history of clinical symptoms, appropriate clinical signs at the time of diagnosis, and original echocardiographic evidence of abnormal systolic function. Exclusion criteria were atrial fibrillation, an intrinsic ventricular rate of greater than 80 beats per minute, and implantable cardiac defibrillators with antiarrhythmia therapy set at an unusually low rate (<120 beats per minute), because it would limit the ability to vary the HR during the experiment. The only exclusion criteria were significant respiratory disease (FEV₁ <50% predicted), any condition precluding lying comfortably on a bed for 90 minutes, a recent deterioration in condition i.e., admission in previous 6 weeks, a brittle condition and renal failure requiring dialysis.

Patients were screened to confirm the absence of daytime periodic breathing during daytime assessment in clinic. On the day of the study, they were further monitored for 30 minutes while recumbent to exclude the presence of any form of apnea with a pause of respiration for 10 s or more, either with or without respiratory effort.3 Periodic breathing was defined as an oscillatory breathing pattern characterized by cyclic rises and falls in ventilation without true periods of apnea4–6 and any patients showing such stereotypical oscillations, with a period of around the order of 60 s in end-tidal CO₂, end-tidal O₂ ventilation, were not enrolled in the study. In total, 25 patients were assessed. Four patients were excluded because they demonstrated periodic breathing, one of whom also had atrial fibrillation. A further 2 patients were excluded because of atrial fibrillation. All patients gave informed consent for the study which was approved by the local Research Ethics Committee. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Measurements
Patients relaxed, recumbent on a couch, while breathing through a calibrated pneumotachograph attached to a Multicap (Datex Instrumentarium, Helsinki, Finland) measuring ventilation, inspiratory, and expiratory respiratory gases. An ECG signal was recorded using a Hewlett-Packard 78351A, from which HR was derived. Beat-by-beat BP and cardiac output were measured noninvasively using a photoplethysmograph device (Finometer, Finapres Medical Systems, The Netherlands). 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 BP and cardiac output were measured noninvasively using 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 which tracks changes in cardiac output by relating pressure changes to changes in a nonlinear 3-element aortic impedance model7 and has been extensively validated against invasive measurements for noninvasive measurement of changes in cardiac output.8–13

Pacemaker Protocol
Pacemaker reprogramming was performed via a pacemaker telemetry head positioned on the subjects’ skin over their implanted device, to enable the HR to be changed according to protocol. Initially, the HR was varied by 30 beats from the resting value, and the effect on cardiac output was measured. This process was repeated for a range of baseline HRs, from the resting rate up to a baseline of 80 beats per minute. We then selected the baseline HR which allowed the greatest increment in cardiac output from the 30-bpm HR elevation. In those patients in whom the cardiac output failed sufficiently to engender oscillations in ventilatory gases with any of the 30-bpm HR steps, we used alteration in AV delay between 30 and 120 ms instead of alternation of HR. If cardiac output still failed to change appreciably, we combined changing HR and AV delay simultaneously (Figure 1 depicts the protocol).

To enable us to control the HR during the study, all subjects whose clinical pacing configuration and underlying disease gave them atrial or ventricular sensing at rest had their devices reprogrammed with a lower pacing rate 5 beats per minute above their intrinsic rate. This ensured that all subjects were paced throughout the study session.

Data Acquisition
The data were sampled at 1000 Hz using a custom data acquisition system consisting of an analogue-to-digital rd (DAQCard 6062E, National Instruments, Austin, Tex) and a workstation running software written in Labview instrument control language (v7.0, National Instruments). This system allowed data to be collected simultaneously from all the devices. The data were later analyzed off-line using software14,15 written in Matlab (Natick, Mass). HR, BP, cardiac output, end-tidal gas concentrations, and ventilation were digitally interpolated and resampled to obtain signals at 1 Hz for subsequent analysis. Interpolation was done between beats so that a value was available at each 1-s time-point to allow averaging across multiple cycles.

Data Analysis
The amplitude of the hemodynamic and respiratory oscillations in response to the cardiac output alteration were quantified using signal averaging. Data from each of the individual 60-s cycles were
time-aligned, and then the mean and standard error at each point in time were calculated. A signal-averaged single cycle was produced for each patient, for each shape. 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 minute. An example of this is shown in Figure 3. The peak-to-trough excursion for each parameter was defined as the difference between the maximum and minimum value. The peak rate of change of BP was defined as the maximum rate of BP change over any 5 s of the cycle, as determined by linear regression.

Statistical Analysis
Continuous values are expressed as the mean±standard deviation. Paired t-tests were performed to compare square wave alternations with sinusoidal alternations within individuals. Patient subgroups were compared in a posthoc analysis by ANOVA. A value of P<0.05 was considered statistically significant. The sample size was designed for the principal question namely looking for a difference between square and sine wave. On the basis that the peak to trough BP would be of the order of 20 mm Hg in the square wave intervention, from previous experience, and the standard deviation approximately 5 mm Hg, to detect a change in peak to trough pressure of 5 mm Hg between the square wave and the new sine wave intervention, with 90% power at the 2-tailed 5% significance level, we would need 12 patients for the paired comparison.

Statement of Responsibility
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Subject Characteristics
Nineteen consecutive patients (7 women, 12 men) met the eligibility criteria and were enrolled. Table 3 shows the baseline characteristics. Sixteen patients had undergone biventricular pacemaker implantation for relief of heart failure symptoms in accordance with national guidelines. The remaining 3 patients had undergone conventional dual chamber pacemaker implantation, 2 for heart block, and 1 for sick sinus syndrome.

Modulating Ventilation Via Cardiac Output
In each patient, the purpose of the initial evaluation was to select a mechanism by which cardiac output would be altered in that individual in the main study: HR alone, AV delay alone or both (Figure 1). In all patients, the initial evaluation successfully identified a means of producing oscillations in end-tidal CO₂ and ventilation. In 14 of the 19 patients, the initial evaluation showed that alternation of HR by 30 beats per minute produced distinct changes in cardiac output on the Finometer. In a further 2 patients a greater change in cardiac output was elicited by instead altering AV delay from 30 to 120 ms: in them the AV delay alternation was used. In the remaining 3 patients, cardiac output failed to change appreciably using either HR or AV delay alone and therefore both HR and AV delay were altered together.

In a posthoc analysis, we found that the average size of oscillations in cardiac output and end-tidal CO₂ achieved by
the individually-selected pacing intervention, were comparable among patients in whom HR, AV delay or both were selected (cardiac output: 2.7±0.3 versus 1.3±0.4 versus 2.3±1.2 L/min, P=NS by ANOVA; end-tidal CO₂: 0.40±0.30 versus 0.36±0.30 versus 0.30±0.17 kPa, P=NS by ANOVA). Thus, if HR alone fails to elicit cardiac output changes in a particular individual, it may still be possible to achieve an appreciable effect using an alternative mechanism.

Shape of the Cardiac Output Waveform Elicited

Application of square wave changes in pacing configuration achieved fluctuations in cardiac output as previously described1 (Figure 3). Application of the sine wave pattern in pacing configuration, by sequential manual programming under guidance from real-time computer software, also yielded fluctuations in cardiac output (Figure 4). The shape of the fluctuation in cardiac output produced by sine wave intervention fitted well to a sine wave (r²=0.73, P<0.01, Figure 4). The peak-to-trough difference in cardiac output was similar in both square wave alternations and sine wave alternations (2.8±1.6 versus 2.2±1.2 L/min, P=0.2).

Effect of Alternation of Cardiac Output on Sequence of Respiratory Parameters

Sine wave fluctuations in cardiac output produced sinusoidal oscillations in end-tidal CO₂ (fit to sine wave r²=0.80 P<0.01). Interestingly, even with square wave intervention the shape of fluctuation in CO₂ produced still fitted fairly well to a sine wave (r²=0.77, P<0.01) and indeed better than it did to a square wave shape (r²=0.22, P=0.04; Figure 3). This smoothing effect suggests that the temporal response of the end-tidal CO₂ is a gradual process of moving from one steady state value to another, which takes in the order of 30 s, so that the waveform produced is gently curved rather than a sharp square wave pattern.

The sequence of events was first an increase in the cardiac output followed by a rise in end-tidal CO₂ and then, after a delay, an increase in ventilation as shown in Figures 5 and 6. The delay between the waveform of cardiac output and the waveform of end-tidal CO₂ was the same regardless of whether pacing intervention shape was square wave or as a sine wave (12.2±11.7 versus 13.0±12.1 s, P=0.84). The chemoreflex delay (measured as the time difference from peak end-tidal CO₂

Table 3. Baseline Characteristics

<table>
<thead>
<tr>
<th>Heart Failure Patients (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>NYHA III-IV, %</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
</tr>
<tr>
<td>ACE inhibitor/angiotensin II receptor blocker, %</td>
</tr>
<tr>
<td>Beta blocker, %</td>
</tr>
<tr>
<td>Diuretic, %</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
</tr>
<tr>
<td>Biventricular pacemaker/dual chamber, %</td>
</tr>
</tbody>
</table>

Figure 3. An example of the variables recorded in one subject after 4 cycles of square wave HR manipulation (left panel) and the resultant signal-averaged cycle (right panel). Each individual cycle on the left is represented by a different color (blue, red, black, and green) and the resultant signal-averaged cycle on the right is depicted in red. Square wave changes in cardiac output can be seen to elicit, rapid and sizeable blood pressure oscillations (MAP) and sinusoidal fluctuations in end-tidal CO₂ and O₂.

The individually-selected pacing intervention, were comparable among patients in whom HR, AV delay or both were selected (cardiac output: 2.7±3.0 versus 1.3±0.4 versus 2.3±1.2 L/min P=NS by ANOVA; end-tidal CO₂: 0.40±0.30 versus 0.36±0.30 versus 0.30±0.17 kPa, P=NS by ANOVA). Thus, if HR alone fails to elicit cardiac output changes in a particular individual, it may still be possible to achieve an appreciable effect using an alternative mechanism.

Shape of the Cardiac Output Waveform Elicited

Application of square wave changes in pacing configuration achieved fluctuations in cardiac output as previously described1 (Figure 3). Application of the sine wave pattern in pacing configuration, by sequential manual programming under guidance from real-time computer software, also yielded fluctuations in cardiac output (Figure 4). The shape of the fluctuation in cardiac output produced by sine wave intervention fitted well to a sine wave (r²=0.73, P<0.01, Figure 4). The peak-to-trough difference in cardiac output was similar in both square wave alternations and sine wave alternations (2.8±1.6 versus 2.2±1.2 L/min, P=0.2).

Effect of Alternation of Cardiac Output on Sequence of Respiratory Parameters

Sine wave fluctuations in cardiac output produced sinusoidal oscillations in end-tidal CO₂ (fit to sine wave r²=0.80 P<0.01). Interestingly, even with square wave intervention the shape of fluctuation in CO₂ produced still fitted fairly well to a sine wave (r²=0.77, P<0.01) and indeed better than it did to a square wave shape (r²=0.22, P=0.04; Figure 3). This smoothing effect suggests that the temporal response of the end-tidal CO₂ is a gradual process of moving from one steady state value to another, which takes in the order of 30 s, so that the waveform produced is gently curved rather than a sharp square wave pattern.

The sequence of events was first an increase in the cardiac output followed by a rise in end-tidal CO₂ and then, after a delay, an increase in ventilation as shown in Figures 5 and 6. The delay between the waveform of cardiac output and the waveform of end-tidal CO₂ was the same regardless of whether pacing intervention shape was square wave or as a sine wave (12.2±11.7 versus 13.0±12.1 s, P=0.84). The chemoreflex delay (measured as the time difference from peak end-tidal CO₂

Figure 3. An example of the variables recorded in one subject after 4 cycles of square wave HR manipulation (left panel) and the resultant signal-averaged cycle (right panel). Each individual cycle on the left is represented by a different color (blue, red, black, and green) and the resultant signal-averaged cycle on the right is depicted in red. Square wave changes in cardiac output can be seen to elicit, rapid and sizeable blood pressure oscillations (MAP) and sinusoidal fluctuations in end-tidal CO₂ and O₂.

The individually-selected pacing intervention, were comparable among patients in whom HR, AV delay or both were selected (cardiac output: 2.7±3.0 versus 1.3±0.4 versus 2.3±1.2 L/min P=NS by ANOVA; end-tidal CO₂: 0.40±0.30 versus 0.36±0.30 versus 0.30±0.17 kPa, P=NS by ANOVA). Thus, if HR alone fails to elicit cardiac output changes in a particular individual, it may still be possible to achieve an appreciable effect using an alternative mechanism.

Shape of the Cardiac Output Waveform Elicited

Application of square wave changes in pacing configuration achieved fluctuations in cardiac output as previously described1 (Figure 3). Application of the sine wave pattern in pacing configuration, by sequential manual programming under guidance from real-time computer software, also yielded fluctuations in cardiac output (Figure 4). The shape of the fluctuation in cardiac output produced by sine wave intervention fitted well to a sine wave (r²=0.73, P<0.01, Figure 4). The peak-to-trough difference in cardiac output was similar in both square wave alternations and sine wave alternations (2.8±1.6 versus 2.2±1.2 L/min, P=0.2).

Effect of Alternation of Cardiac Output on Sequence of Respiratory Parameters

Sine wave fluctuations in cardiac output produced sinusoidal oscillations in end-tidal CO₂ (fit to sine wave r²=0.80 P<0.01). Interestingly, even with square wave intervention the shape of fluctuation in CO₂ produced still fitted fairly well to a sine wave (r²=0.77, P<0.01) and indeed better than it did to a square wave shape (r²=0.22, P=0.04; Figure 3). This smoothing effect suggests that the temporal response of the end-tidal CO₂ is a gradual process of moving from one steady state value to another, which takes in the order of 30 s, so that the waveform produced is gently curved rather than a sharp square wave pattern.

The sequence of events was first an increase in the cardiac output followed by a rise in end-tidal CO₂ and then, after a delay, an increase in ventilation as shown in Figures 5 and 6. The delay between the waveform of cardiac output and the waveform of end-tidal CO₂ was the same regardless of whether pacing intervention shape was square wave or as a sine wave (12.2±11.7 versus 13.0±12.1 s, P=0.84). The chemoreflex delay (measured as the time difference from peak end-tidal CO₂

Figure 3. An example of the variables recorded in one subject after 4 cycles of square wave HR manipulation (left panel) and the resultant signal-averaged cycle (right panel). Each individual cycle on the left is represented by a different color (blue, red, black, and green) and the resultant signal-averaged cycle on the right is depicted in red. Square wave changes in cardiac output can be seen to elicit, rapid and sizeable blood pressure oscillations (MAP) and sinusoidal fluctuations in end-tidal CO₂ and O₂.
to peak ventilation) was also the same regardless of the shape of modulation of cardiac output, with a mean of 23.4±7.7 s for square wave and 24.9±9.6 s for sine wave (P=0.59).

**Differences in Peak-to-Trough BP, End-Tidal CO₂, and Ventilation Between Square Wave and Sine Wave**

The BP oscillations induced were more dramatic with square wave interventions than sinusoidal interventions: peak-to-trough BP swing was almost twice as large with squarewave than with sinusoidal (22.4±11.7 versus 13.6±4.45 mm Hg, P<0.01; Figure 7).

The rapidity of BP rise, measured as the fastest 5-s slope, during the cycle, was 250% steeper with square wave oscillation than sinusoidal (19.8±10.0 versus 7.9±3.2 mm Hg over 5 s, P<0.01; Figure 8).

The change in the peak-to-trough end-tidal carbon dioxide produced, was also higher with square wave alternations than sinusoidal, but only by 45% (0.45±0.18 versus 0.31±0.13 kPa, P=0.01, Figure 7). Peak-to-trough ventilation showed only a nonsignificant trend to being larger with square wave alternations than sine wave alternations (square: 0.05±0.03 L/s, sine: 0.04±0.02 L/s, P=0.24) as shown in Figure 7.

**Figure 4.** An example of the variables recorded in one subject after 4 cycles of sine wave HR manipulations (left panel) and the resultant signal-averaged cycle (right panel). Again, each individual cycle on the left is represented by a different color (blue, red, black, and green) and the resultant signal-averaged cycle on the right is depicted in red. The HR manipulation resembles a sine wave and the resultant cardiac output change elicits less rapid BP (MAP) changes but nevertheless achieves comparable oscillations in ventilatory gases.

**Figure 5.** A single alternation of HR (preceded by 30 s of free breathing without any pacemaker manipulation) demonstrates a rise in HR (top panel), is first followed by a rise in end-tidal CO₂ (middle panel) and then a rise in ventilation (bottom panel).
Discussion

This study shows that in patients with heart failure and a cardiac pacemaker, it is possible to use an algorithm of repetitive manipulations of HR, AV delay or both, to produce fluctuations in end-tidal CO₂ and consequently ventilation. Manipulations of this nature, if carefully timed, might be harnessed to counteract the spontaneous oscillations in CO₂ that drive daytime periodic breathing in patients with heart failure. If such an algorithm were to incorporate gradual changes in cardiac output, based on sine waves, then changes in end-tidal CO₂ could be elicited without necessarily incurring sudden changes in BP.

A previous study has demonstrated that repetitive alternations in HR via cardiac pacemaker produce ventilatory oscillations. This study demonstrates, for the first time, that changes in ventilation are the result of cardiac output changes rather than related to HR per se. Moreover, this study introduces a new alternative to the square wave method of alternating HR and shows that gradual alterations in cardiac output produce comparable ventilatory changes as step changes in cardiac output while simultaneously minimizing any rapid BP changes.

Ventilatory Disorders in Heart Failure

A substantial proportion of patients with heart failure suffer from respiratory disorders such as periodic breathing. Periodic breathing is associated with increased mortality in heart failure. During sleep, there are mechanical interventions which can alleviate ventilatory instability, reduce daytime fatigue and somnolence and markers of neuroendocrine activation. However, these mechanical interventions, including CPAP, BiPAP, and AutosetCS, generally require a firmly-held mask so that they can deliver the altered pressure to the lung. As a result, some patients find the treatment uncomfortable. Whereas patients with obstructive sleep apnea experience often marked symptomatic relief from CPAP and therefore find it highly acceptable, the symptomatic relief is not always as marked in central sleep apnea in heart failure and therefore compliance ranges from good to moder-
There may still, therefore, be a role for exploring opportunities to develop treatments for periodic breathing that might have a higher acceptability to patients with central apneas.

The concept of using pacing to attenuate sleep apnea is not new. Atrial overdrive pacing has previously been mooted as a potential tool for the attenuation of sleep disordered breathing but studies failed to consistently demonstrate its efficacy. Cardiac resynchronization therapy using biventricular cardiac pacemakers is increasingly being used in heart failure and has been demonstrated to have a beneficial effect on mortality. Moreover, biventricular pacemakers have been demonstrated to reduce the apnea-hypopnea index and can improve sleep quality in central sleep apnea, making them a useful adjuvant to other therapies. Nevertheless, implantation of a biventricular pacemaker does not uniformly extinguish periodic breathing.

Static carbon dioxide administration has previously been used and demonstrated to be effective at attenuating the severity of periodic breathing. However, this supplementary administration has been associated with adverse consequences such as an overall increase in mean ventilation and adrenergic activation. An optimal oscillatory cardiac pacemaker algorithm that delivers a dynamic counteraction to an intrinsic tendency to ventilatory oscillations allows the “redistribution” of carbon dioxide within the body at the correct times with no additional carbon dioxide being added to the system. Moreover, this intervention could be achieved without a closely-fitting mask and therefore might conceivably be used in situations other than sleep. Because an increasing proportion of patients with heart failure are receiving pacemaker devices it may be possible to have such an algorithm programmed within a device being implanted anyway, with the intention of additionally attenuating daytime periodic breathing beyond the benefits already recognized from biventricular pacemaker implantation itself.

**Mechanism: Pacemaker Manipulation of CO₂ fluxes**

This study has demonstrated that manipulations of HR, or AV delay or both can elicit changes in end-tidal CO₂ followed by ventilation. This is the first time that this effect has been demonstrated using AV delay rather than HR. This finding suggests the effect is secondary to a change in cardiac output, rather than being some direct result of HR variation.

From our study, we cannot be certain whether the mechanism by which cardiac output changes lead to the changes in carbon dioxide and ventilation is the result of a primary effect on carbon dioxide (leading to a change in ventilation) or ventilation (leading to a change in carbon dioxide) because ventilation and carbon dioxide affect each other mutually. Significantly more invasive experimentation, especially if carried out in animals, might be able to establish whether the change in cardiac output induced by pacemaker manipulation affects pulmonary vagal irritant receptors sufficiently to affect ventilation. Within the protocol for this study, we do have a small amount of information to guide us (Figure 5) that suggests that after cardiac output increases, end-tidal CO₂ seems to rise first, after which ventilation rises.

By increasing the cardiac output, either suddenly as a square wave or more gradually as a sine wave, one possible mechanism for this effect is that a greater quantity of CO₂-rich blood is delivered via the systemic veins to the lungs. The greater quantity of CO₂ delivered to the pulmonary capillaries shifts the
dynamic equilibrium so that the alveolar CO2 levels gradually rise: this is detectable as a rise in end-tidal CO2. Blood draining from the pulmonary capillaries, which has been in equilibrium with the alveolar gases, correspondingly rises in CO2 concentration. This higher arterial CO2 concentration (and the parallel lower arterial O2 content) is soon sensed by chemoreceptors, which elicit a ventilatory response: an increase in ventilation. The chemoreflex gain is the degree of cardiorespiratory response of the system to dynamic changes in respiratory gases. Hence, dependent on the individual’s chemoreflex gain, there will be a corresponding change in ventilation.

An alternative mechanism may be that an increase in cardiac output may produce a fall in pulmonary capillary wedge pressure which produces a rise in ventilation. Invasive studies would be required to discriminate with total confidence between these 2 possibilities.

Sine Wave or Square Wave Oscillations of Cardiac Output
If this was to be developed into a means of manipulating ventilation, it would be preferable to achieve this while minimizing any induced sudden changes in BP. Square wave changes in cardiac output are easy to program manually but are associated with large sudden changes in BP. We found that by manipulating cardiac output in a gradual, approximately sinusoidal configuration, changes in end-tidal CO2 and ventilation can still be elicited with comparable efficiency as if a step change were used. Importantly, the very sudden surges in BP are greatly reduced.

Potential Clinical Impact
A system for treating unstable ventilatory control in heart failure patients that used cardiac pacemakers might be completely implantable within the patient and need not impose any potentially uncomfortable equipment in the face or nose area. Devices such as biventricular pacemakers that are already in situ or that are going to be implanted on current clinical grounds could be opportunistically used.

In most patients altering HR alone is likely to be sufficient to bring about changes in ventilation, although AV delay is a potential tool in patients who are paced using a dual chamber pacemaker.

Study Limitations
This study deliberately only included patients with heart failure, as this is the population likely to gain maximum benefit from this form of therapeutic manipulation of ventilation, and we aimed to assess the size of the effects attainable in them. Therefore, the effects of different algorithms for changing cardiac output, on BP and end-tidal CO2 in a nonheart-failure population remains untested. The comparision between those patients who had HR manipulated alone, those who had HR and AV delay manipulated and those who had AV delay manipulated alone was not a planned analysis and therefore is likely to have been underpowered to detect any true differences.

In this study, we have focused on measuring the effects of a fixed sequence of cardiac output alterations of a defined frequency and amplitude with fixed patterns (square or sine wave). In reality, for practical clinical benefit it would be necessary to have a real-time algorithm which monitors either blood composition or ventilation or both, to appropriately adjust the pacemaker configuration multiple times per minute. It will need the ability to adjust the timing of therapy to the timing of the underlying oscillations, and may also need the ability to vary the intensity of therapy (duration and/or amplitude) to suit the severity of the underlying oscillations. Although this technology is not yet available, this study suggests that it may be worthwhile to explore.

The sine wave modulations of cardiac output were approximations that were limited by both individual pacemaker programmers and the speed at which changes could practically and safely be made. Despite this, changes in HR or AV delay produced changes in cardiac output that were a good approximation to a sine wave. The study protocol allowed a standardized gradual change in cardiac output to be compared to a standardized sudden change in cardiac output. An eventual therapeutic system would have to be designed to have much finer changes in HR or AV delay, so that sudden BP changes would be even further attenuated.

Conclusion
It is possible to use a cardiac pacemaker to alter end-tidal CO2 and ventilation dynamically by altering cardiac output either by changing HR or AV delay or both. The respiratory and hemodynamic changes elicited are consistent regardless of the mechanism by which cardiac output is altered.

In the therapeutic application of modulating ventilation via a cardiac pacemaker, altering the cardiac output sinusoidally has the advantage of minimizing sudden changes in BP seen with square wave oscillations in cardiac output. This information might be helpful in developing novel technologies to treat awake patients with heart failure and periodic breathing.

Acknowledgments
We acknowledge the National Institute for Health Research Biomedical Research Centre that has utterly transformed the administrative concomitances associated with clinical research in the United Kingdom.

Sources of Funding
R.B. (PG/07/065), D.P.F. (FS/04/079), N.H. (FS/05/034), and B.U. (PG/07/066) were supported by the British Heart Foundation. C.M. was supported by the Wellcome Trust (077049/Z/05/ZDHHP_01707.01). A.G. was supported by a European Society of Cardiology research grant. K.W. (ICCH/05/5004) and A.J.B. received support from the Foundation for Circulatory Health.

Disclosures
The authors’ institution has filed a patent on some of the technologies described in this manuscript.

References
Periodic breathing is a common condition in heart failure, associated with increased mortality. It is characterized by oscillations in ventilation and in ventilatory gas measurements. Our group has recently shown it is possible to manipulate and deliberately oscillate these parameters using a cardiac pacemaker by alternating heart rate. Therefore, it is theoretically possible to counter any ventilatory oscillations seen in periodic breathing by using a cardiac pacemaker. Biventricular pacemakers are increasingly being used in the management of heart failure, reducing morbidity and mortality, making algorithms for attenuating periodic breathing that opportunistically use pacemakers a particularly attractive and convenient therapeutic option. To do this, it is important to understand how to manipulate the pacemaker to achieve therapeutic effects. In this study, we consider whether this reflex is the result of a change in heart rate per se or cardiac output. We go on to consider whether alternating the heart rate and cardiac output more gradually than the step changes previously used produces similar oscillations in ventilation while minimizing the rapid fluctuations in blood pressure previously seen.
Novel Use of Cardiac Pacemakers in Heart Failure to Dynamically Manipulate the Respiratory System Through Algorithmic Changes in Cardiac Output
Resham Baruah, Charlotte H. Manisty, Alberto Giannoni, Keith Willson, Yoseph Mebrate, A. John Baksi, Beth Unsworth, Nearchos Hadjiloizou, Richard Sutton, Jamil Mayet and Darrel P. Francis

Circ Heart Fail. 2009;2:166-174; originally published online March 23, 2009;
doi: 10.1161/CIRCHEARTFAILURE.108.806588

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/2/3/166

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/