Novel use of cardiac pacemakers in heart failure to dynamically manipulate the respiratory system through algorithmic changes in cardiac output

Baruah, Pacemaker Manipulation of Respiratory System

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Keywords: respiration, hemodynamics, reflex, pacemakers, heart failure
Abstract

Background

Alternation of heart rate (HR) between two values using a pacemaker generates oscillations in end-tidal CO\textsubscript{2} (et-CO\textsubscript{2}).

This study examined (a) whether modulating AV delay can also do this, and (b) whether more gradual variation of cardiac output can achieve comparable changes in et-CO\textsubscript{2} with less-sudden changes in blood pressure (BP).

Methods and Results

We applied pacemaker fluctuations by adjusting HR (by 30 bpm) or atrioventricular (AV) delay (between optimal and non-optimal values) or both, with period of 60 seconds in 19 heart failure patients (age 73±11, EF 29%±12%). The changes in cardiac output, by either HR or AV 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-CO\textsubscript{2} (p=NS) in all 19 patients either by manipulation of HR (14), or by AV delay (2) or both (3). The square wave produced 191% larger and 250% more sudden changes in BP than the sine wave alternations (22.4±11.7 versus 13.6±4.5 mmHg, p<0.01 and 19.8±10.0 versus 7.9±3.2 mmHg over 5s, p<0.01), but peak-to-trough et-CO\textsubscript{2} 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 BP fluctuations.

Keywords: respiration, hemodynamics, reflex, pacemakers, heart failure


**Introduction**

The recent finding that manipulations of heart rate 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 characterised by spontaneous oscillations in end-tidal CO₂².

However, embarking on such a development pathway requires certain challenges to be overcome. First, there may not always be scope to alter heart rate 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 heart rate per se, but rather on cardiac output, because it is possible to alter cardiac output by changing stroke volume without changing heart rate, for example, by changing atrioventricular (AV) delay.

Second, dynamic manipulation of cardiac output necessarily induces fluctuation in blood pressure, which may be undesirable. Such sizeable changes in blood pressure have been observed with the step changes in heart rate used to demonstrate this mechanism¹. It would be preferable to build algorithms from elements that minimise rapid blood pressure changes whilst 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 heart rate) 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, whilst avoiding such sudden blood pressure changes.

**Methods**

**Subjects**

A distinct set of nineteen 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 then 80 beats per minute, and implantable cardiac defibrillators with anti-tachycardia therapy set at an unusually low rate (<120 beats per minute), because it would limit the ability to vary the heart rate during the experiment. The other 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 six 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 whilst recumbent to exclude the presence of any form of apnoea with a pause of respiration for ten seconds or more, either with or without respiratory effort. Periodic breathing was defined as an oscillatory breathing pattern characterized by cyclical rises and falls in ventilation without true periods of apnoea and any patients showing such stereotypical oscillations, with a period of around the order of 60 seconds in end-tidal CO₂, end-tidal O₂ or 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
two 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, whilst breathing through a calibrated
pneumotachograph attached to a Multicap (Datex Instrumentarium, Helsinki, Finland)
measuring ventilation, inspiratory and expiratory respiratory gases. An
electrocardiogram signal was recorded using a Hewlett-Packard 78351A, from which
heart rate was derived. Beat-by-beat blood pressure and cardiac output were measured
non-invasively using a photoplethysmograph device (Finometer, Finapres Medical
Systems, 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-to-beat arterial pressure
waveform and incorporates the ‘Modelflow’ algorithm which tracks changes in
cardiac output by relating pressure changes to changes in a non-linear three-element
aortic impedance model and has been extensively validated against invasive
measurements for non-invasive measurement of changes in cardiac
output.

**Pacemaker Protocol**

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. Initially the heart rate 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 heart rates, from the resting rate up to a baseline of 80 beats per minute. We then selected the baseline heart rate which allowed the greatest increment in cardiac output from the 30-bpm heart rate elevation.

In those patients in whom the cardiac output failed sufficiently to engender oscillations in ventilatory gases with any of the 30-bpm heart rate steps, we used alteration in AV delay between 30 and 120 ms instead of alternation of heart rate. If cardiac output still failed to change appreciably, we combined changing heart rate and AV delay simultaneously (Figure 1 depicts the protocol).

In order to enable us to control the heart rate 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.

In all patients, the cardiac output changes (whether it was by heart rate alone or AV delay or both) were made as a step alternation (or square wave) and as a gradual alternation (based on a sine wave).

To achieve an approximation of a sinusoidal pattern of pacing, we calculated a sequence of pacing configurations and times based on a sine wave pattern using custom written software written in Matlab (Natick, MA, USA). This software determined the closest programmable actual values of heart rate and AV delay, taking into account that these values cannot be varied continuously but rather only to a set of values specific to each model of pacemaker (Figure 2 shows an example of this and of
the step change. The software allowed the magnitude of change in heart rate or AV delay and the possible values that could be programmed (e.g. multiples of 10) to be tailored to the individual patient as well as the period of the cycle desired e.g. 60 seconds. Examples of this for heart rate and AV delay are shown in Tables 1 and 2 respectively.

We monitored cardiorespiratory variables whilst alternating the pacing rate and or AV delay (via the pacemaker telemetry head) as a square wave for five cycles of 60-seconds and as a sine wave, also for five 60-second cycles. Each pattern used the same range of heart rates (and/or AV delay), for example in an individual patient the square wave might consist of altering heart rate between 60 and 90 bpm and the sine wave consisted of a series of gradual changes between 60 and 90 bpm. The order in which this was done was allocated randomly for each patient with at least a five minute washout period between the square wave and sine wave protocols.

**Data Acquisition**

The data were sampled at 1000 Hz using a custom data acquisition system consisting of an analogue-to-digital card (DAQCard 6062E, National Instruments, Austin, TX, USA) 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 was later analysed off-line using software written in Matlab (Natick, MA, USA). Heart rate, blood pressure, cardiac output, end-tidal gas concentrations and ventilation were digitally interpolated and re-sampled to obtain signals at 1 Hz for subsequent analysis. Interpolation was done between breaths so that a value was available at each 1-second time-point to allow averaging across multiple cycles.
Data Analysis

The amplitude of the haemodynamic and respiratory oscillations in response to the cardiac output alternation were quantified using signal averaging. Data from each of the individual 60-second 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 one 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 blood pressure was defined as the maximum rate of blood pressure change over any 5 seconds 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 sub-groups were compared in a post-hoc 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 blood pressure would be of the order of 20mmHg in the square wave intervention, from previous experience, and the standard deviation approximately 5mmHg, in order to detect a change in peak to trough pressure of 5mmHg 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 female, 12 male) 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 three patients had undergone conventional dual chamber pacemaker implantation, two for heart block and one 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: heart rate 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 heart rate 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 ms to 120 ms: in them the AV delay alternation was used. In the remaining 3 patients, cardiac output failed to change appreciably using either heart rate or AV delay alone and therefore both heart rate and AV delay were altered together.

In a post-hoc 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±3.0 versus 1.3±0.4 versus 2.3±1.2 L/min p=NS by ANOVA; end-tidal
CO$_2$: 0.40±0.30 versus 0.36±0.30 versus 0.30±0.17 kPa, p=NS by ANOVA). Thus if heart rate 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 described$^1$ (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 ($r^2=0.73$, 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 CO$_2$ (fit to sine wave $r^2=0.80$ p<0.01). Interestingly, even with square wave intervention the shape of fluctuation in CO$_2$ produced still fitted fairly well to a sine wave ($r^2=0.77$, p<0.01) and indeed better than it did to a square wave shape ($r^2=0.22$, p=0.04; Figure 3). This smoothing effect suggests that the temporal response of the end-tidal CO$_2$ is a gradual process of moving from one steady state value to another, which takes in the order of 30 seconds, 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 CO$_2$ 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 seconds, p = 0.84). The chemoreflex delay (measured as the time difference from peak end-tidal CO₂ 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 blood pressure, end-tidal CO₂ and ventilation between square wave and sine wave**

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

The rapidity of blood pressure rise, measured as the fastest 5-second slope, during the cycle, was 250% steeper with square wave oscillation than sinusoidal (19.8±10.0 versus 7.9±3.2 mmHg over 5s, 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 and 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 non-significant 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.
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 heart rate, 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 upon sine waves, then changes in end-tidal CO₂ could be elicited without necessarily incurring sudden changes in blood pressure.

A previous study has demonstrated that repetitive alternations in heart rate via cardiac pacemaker produce ventilatory oscillations⁴. This study demonstrates, for the first time, that changes in ventilation are the result of cardiac output changes rather than related to heart rate per se. Moreover, this study introduces a new alternative to the square wave method of alternating heart rate and shows that gradual alterations in cardiac output produce comparable ventilatory changes as step changes in cardiac output whilst simultaneously minimising any rapid blood pressure changes.

Ventilatory disorders in Heart Failure

A substantial proportion of patients with heart failure suffer from respiratory disorders such as periodic breathing⁶,¹⁶. Periodic breathing is associated with increased mortality in heart failure¹⁷,¹⁸. During sleep, there are mechanical interventions which can alleviate ventilatory instability, reduce daytime fatigue and somnolence and markers of neuroendocrine activation¹⁹. 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 apnoea (OSA) experience often marked symptomatic relief from CPAP and therefore find it highly acceptable, the symptomatic relief is not always as marked in central sleep apnoea (CSA) in heart failure and therefore the compliance ranges from good to moderate. 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 apnoeas.

The concept of using pacing to attenuate sleep apnoea is not new, atrial overdrive pacing has previously been muted as a potential tool for the attenuation of sleep disordered breathing but studies failed to consistently demonstrate its efficacy. Cardiac resynchronisation 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 apnoea, 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 utilised in situations other than sleep. Since 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 heart rate, 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 heart rate. This finding suggests the effect is secondary to a change in cardiac output, rather than being some direct result of heart rate 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) since 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) which suggests that after cardiac output increases, end-tidal CO₂ appears 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 two 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 minimising any induced sudden changes in blood pressure. Square wave changes in cardiac output are easy to program manually but are associated with large sudden changes in blood pressure. 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 blood pressure are greatly reduced.

**Potential Clinical Impact**

A system for treating unstable ventilatory control in heart failure patients that utilized 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 heart rate 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 blood pressure and end-tidal CO₂ in a non-heart-failure population remains untested. The comparison between those patients who had heart rate manipulated alone, those who had heart rate 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 alternations 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, in order 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. While 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 heart rate or AV delay produced changes in cardiac output that were a good approximation to a sine wave. The study protocol allowed a standardised gradual change in cardiac output to be compared to a standardised sudden change in cardiac output. An eventual therapeutic system would have to be designed to have much finer changes in heart rate or AV delay, so that sudden blood pressure 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 heart rate or atrioventricular delay or both. The respiratory and haemodynamic 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 minimising sudden changes in blood pressure 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.

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Conflict of Interests Disclosures

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

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DPF has received a grant from the British Heart Foundation in excess of $10,000.
References


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patients with chronic heart failure: relationship to baroreflex sensitivity.


**Figure Legends**

**Figure 1:** Protocol for deciding how to alter cardiac output. In each algorithm (HR alone, AV delay alone and both), both square wave and sine wave changes were made in each subject. Changes in cardiac output were deemed “sufficient” if a clear change in end-tidal CO₂ and ventilation could be seen following the alternation in cardiac output.

**Figure 2:** Upper panel: an example of a square wave alternation of heart rate. Lower panel: an example of a sine wave alternation with ‘ideal’ sine wave (red) and programmable heart rates (blue). Alternations of AV delay and AV delay and heart rate were made in a similar way.

**Figure 3:** An example of the variables recorded in one subject after four cycles of square wave heart rate manipulation (left panel) and the resultant signal-averaged cycle (right panel). Each individual cycle on the left is represented by a different colour (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.

**Figure 4:** An example of the variables recorded in one subject after four cycles of sine wave heart rate manipulations (left panel) and the resultant signal-averaged cycle (right panel). Again, each individual cycle on the left is represented by a different
colour (blue, red, black and green) and the resultant signal-averaged cycle on the right is depicted in red.

The heart rate manipulation resembles a sine wave and the resultant cardiac output change elicits less rapid blood pressure (MAP) changes but nevertheless achieves comparable oscillations in ventilatory gases.

**Figure 5:** A single alternation of heart rate (preceded by 30 seconds of free breathing without any pacemaker manipulation) demonstrates a rise in heart rate (top panel), is first followed by a rise in end-tidal CO$_2$ (middle panel) and then a rise in ventilation (bottom panel).

**Figure 6:** Recording from one subject, in whom alternations in cardiac output were established, demonstrating sinusoidal manipulations of cardiac output (upper panel) were followed by end-tidal carbon dioxide oscillations (middle panel) and then fluctuations in ventilation (bottom panel).

**Figure 7:** Comparison of peak-to-trough blood pressure, end-tidal CO$_2$ and ventilation elicited via (i) sine wave alternations and (ii) square wave alternations in all patients.

**Figure 8:** An example of five 60-second averaged ventilatory cycles from one patient of square wave changes of heart rate (upper left) and resultant change in blood
pressure with marked upstroke and down-stroke (middle left) and change in end-tidal CO₂.

Right-hand panel demonstrates sinusoidal heart rate change (upper right) in the same patient and resultant more gradual change in blood pressure (middle right) and comparable oscillation of CO₂.
Tables

Table 1: An example of the times at which the pacemaker should be reprogrammed to produce an approximation of a sine wave from a heart rate of 50 beats per minute (bpm) up to 80 bpm in 10 bpm steps, with period 60 seconds.

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Table 2: An example of the times at which the pacemaker should be reprogrammed to produce an approximation of a sine wave from an AV delay of 40 ms up to 120 ms in 10 ms steps, with period 60 seconds.

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Table 3: Baseline Characteristics

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Change Heart Rate

Sufficient Change in Cardiac Output?  

Yes → Use Heart Rate

No → Change AV delay

Sufficient Change in Cardiac Output?  

Yes → Use AV delay

No → Change AV delay and Heart Rate

Sufficient Change in Cardiac Output?  

Yes → Use Heart Rate and AV delay

No → Exclude from further participation
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Raw Data</th>
<th>Signal-averaged data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td><img src="image" alt="Heart rate" /></td>
<td><img src="image" alt="Heart rate" /></td>
</tr>
<tr>
<td>End-tidal CO₂ (kPa)</td>
<td><img src="image" alt="End-tidal CO₂" /></td>
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</tr>
<tr>
<td>Ventilation (L/s)</td>
<td><img src="image" alt="Ventilation" /></td>
<td><img src="image" alt="Ventilation" /></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
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<td><img src="image" alt="MAP" /></td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td><img src="image" alt="Cardiac Output" /></td>
<td><img src="image" alt="Cardiac Output" /></td>
</tr>
</tbody>
</table>
Novel use of cardiac pacemakers in heart failure to dynamically manipulate the respiratory system through algorithmic changes in cardiac output

Resham Baruah, Charlotte Harriet Manisty, Alberto Giannoni, Keith Willson, Yoseph Mebrate, John Arun Baksi, Beth Unsworth, Nearchos Hadjiloizou, Richard Sutton, Jamil Mayet and Darrel Parthipan Francis

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