Inspiratory timing during anaesthesia: a model of cardioventilatory coupling

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We describe a simple model of cardioventilatory coupling in which a hypothetical inspiratory pacemaker is stimulated by a signal related to cardiac action. At suitable values for the control variables (cardiac signal magnitude, heart rate, inspiratory pacemaker rate and inspiratory rate variability), the model was found to: (1) replicate all clinically described patterns of coupling; (2) predict variations in these described patterns and new patterns which were subsequently found in clinical time series; (3) simulate variations in clinically observed breathing frequency variations associated with each coupling pattern; (4) simulate the clinically observed distribution of coupling patterns between heart rate and breathing frequency; (5) explain the invariability of coupling below a critical heart rate/breathing frequency ratio; and (6) simulate the changes in breathing frequency and transitions between coupling patterns from the heart rate time series of human subjects. Although cardioventilatory coupling causes complex breathing rate irregularities during anaesthesia, these are readily explained by three variables, heart rate, intrinsic breathing frequency, and the strength of their interaction. This simple model, along with clinical observations of cardioventilatory coupling may provide a useful non-invasive method to study the respiratory central pattern generator.

Keywords: model, cardioventilatory coupling; heart, heart rate; ventilation, pattern

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**Method**

*The model*

We assume the presence of a spontaneous intrinsic inspiratory pacemaker, the instantaneous state of which can be represented by the function (Φ(I)). This function increases linearly from a basal level immediately following a previous inspiratory onset. When Φ(I) reaches a specific threshold (the inspiratory firing threshold), inspiration is triggered; Φ(I) is then reset to a basal level (Fig. 1). The intrinsic ventilatory period (the interval between consecutive inspiratory onsets) is governed by the (Φ(I)) slope. The breathing frequency generated by Φ(I) alone we term the *intrinsic* breathing frequency (fi).

An afferent signal of cardiovascular origin reaches the brain stem soon after the onset of cardiac systole. With each cardiovascular afferent signal, a burst stimulus (MBC) transiently augments the Φ(I). Because the interval between R wave and inspiratory onset, during human coupling, is approximately 0.5 s, and allowing for a delay in detecting the actual onset of inspiration, we will assume the R wave of cardiac systole and the onset of the cardiac related signal are separated by a constant interval of 0.4 s. The cardiac signal was empirically set to a square wave burst of duration 0.1 s.

With cardiac related bursts transiently augmenting Φ(I), inspiration will occur if either (a) the intrinsic Φ(I) or (b) the cardiac burst transiently augmented Φ(I) exceeds the inspiratory firing threshold. The slope of the Φ(I) can, therefore, be divided into alternating sections of exposed intrinsic slope and sections which are in the ‘shadow’ of a cardiac burst (Fig. 1). The relative size of these sections and, therefore, the likelihood of cardiac versus intrinsic triggering, varies according to the slope of Φ(I), HR and the cardiac burst magnitude. Although the intrinsic breathing frequency is constant, given a constant Φ(I) slope, the addition of cardiac bursts causes the ventilatory period to vary if the mechanism of inspiratory triggering changes from one breath to the next. In the presence of coupling therefore, the resulting observed ventilatory frequency (fo) may differ from the intrinsic frequency (fi); it is important to note that fo will always be equal to or greater than fi as a triggered breath will always occur before the expected time of a non-coupled intrinsic breath.

For simplicity, the cardiac pacemaker activity at the sinus node was regarded as equivalent to Φ(I), with a linear cardiac pacemaker function, Φ(C), rising to a cardiac firing threshold at which cardiac systole is initiated and Φ(C) is reset to a baseline value.

Noise can be expected in any biological system and variability is assumed to occur in burst magnitude, Φ(I) slope and HR. To avoid undue complexity, we incorporated variability into our model by varying the value of Φ(I) using a Gaussian distributed random variation. The standard deviation of this Gaussian distribution we will term the Φ(I) slope variability.

Respiratory sinus arrhythmia (RSA) was not examined in any detail in this preliminary description. However in order to determine whether RSA causes major instability in the model we crudely incorporated RSA by transiently reducing cardiac firing threshold following inspiratory onset. In those simulations, which included RSA, we reduced linearly, the cardiac threshold for firing from 1.0, at inspiratory onset to 0.8, 1.5 s following inspiratory onset. In those firing threshold, linearly, to 1.0 by the following inspiratory onset.

*Input variables*

The following variables and parameters define the behaviour of the model.

(a) Inspiratory and cardiac firing thresholds; regarded as constant values=1.0.
(b) Φ(I) slope.
(c) Φ(C) slope.
(d) R wave to cardiac burst interval=0.4 s.
(e) Cardiac burst magnitude, MBC.
(f) Cardiac burst duration=0.1 s.
(g) The magnitude and time course of the cardiac firing threshold lowering by RSA.
(h) Φ(I) slope variability.
Simulation

A computer simulation was written using LabView 5 on a Macintosh PowerBook 1400cs and iterated in time steps of 0.01 s.

Coupling interval (RI) pattern

From simulated time series, we determined the timing of consecutive R waves and inspiratory onsets. Within each breathing cycle (from inspiration to inspiration) we determined the time from each enclosed R wave to the following inspiratory onset. Coupling patterns are observed when these RI intervals are plotted as a time series (the RI plot). Within each breath there will be a number of RI intervals (equal to the entrainment ratio), the shortest of which (RI–1) will generally correspond to the coupling interval, although this may vary according to coupling pattern and heart rate.\(^1\)\(^5\)

Model behaviour

Simulation was performed using a range of cardiac burst magnitudes, and for HR/fi values over the general distribution determined for intra-operative anaesthetized, spontaneously breathing subjects.\(^5\) Simulations were also performed with variations in Φ(I) slope and with RSA. Φ(I) slope variations were examined in the region 0–0.02.

In examining the model behaviour we determined (1) the range of coupling interval patterns generated, (2) the regions of the HR/fi plot associated with each coupling pattern, (3) the difference between intrinsic and observed breathing frequency, and (4) the specific pattern of ventilatory variation associated with each coupling pattern.

Simulation of human time series

Data were taken for study from material used in previous papers on cardioventilatory coupling.\(^5\) from subjects showing clear pattern I, II, III, IV, or uncoupled RI interval plots or transitions between coupling patterns. Simulations were performed by using the patient’s own heart rate time series and adding values for fi and burst magnitude into the model. To remove the effect of RSA the real heart rate time series was first filtered using a simple n beat, boxcar moving averager, where n is the closest integer to mean HR/fo ratio. From this filtered time series, a Φ(C) slope time series was calculated (Φ(C) slope=60/HR) and this was used to vary heart rate during simulation. For these simulations, we therefore knew both HR and fo, but burst magnitude and fi were unknown. Once we understood the relationship between fi, fo, burst magnitude and the specific coupling pattern (see results below), it was comparatively simple to determine approximate burst magnitude and fi values.

Nomenclature

The plot of HR/fi can be divided into a series of radiating areas between lines of integer relationship. To describe the distribution of coupling patterns on this plot, we term the area between any pair of consecutive integer ratio lines as the ‘domain’ of the lower integer ratio. Coupling pattern regions within each domain will be termed ‘zones’, indicated by an appropriate superscript. Thus, the area between 2:1 and 3:1 integer ratio lines is the 2:1 domain and a zone within this domain in which pattern I is generated is denoted I\(^2\).

Results

Coupling patterns

Coupling patterns I, III, and IV were readily reproduced and were the most commonly observed patterns over a wide range of burst magnitude, HR and fi values. In Figure 2, we illustrate the simulated coupling patterns alongside comparable clinical recordings. In Figure 3 we show the distribution of these patterns over a map relating burst magnitude against the ratio HR/fo. Within each domain the relationship between coupling pattern, burst magnitude and HR/fo is qualitatively similar, although the range of burst magnitudes at which the various patterns occur differs with domain.

In addition to pattern I, III and IV, three zones of differing coupling type were also observed, two large areas A, B, and a smaller area C. Patterns A and B were similar to pattern III in that they exhibited multiple horizontal bands in the RI plot. However, unlike pattern III they were more complex, with a greater number of bands and these changed in appearance with small changes in HR, M\(_{bc}\) or fi. In comparing these simulated patterns A and B, with real epochs of data, brief periods of similar pattern were observed although generally were transient. In the rabbit, we have previously described, and illustrated, stable periods of such patterns with eight bands in the 2:1 domain.\(^2\) If noise was applied to fi by adding Φ(I) slope variability, the rapid changes in patterns A and B gave the appearance of their being entirely uncoupled.

The smaller zone, C, was observed sandwiched between the zones for pattern III and I. Retrospectively examining epochs of human data, this pattern was found in a number of human time series. Two examples are shown in Figures 2 and 7.

Within each domain, there are two pattern IV zones, which we term IV\(_{hi}\) and IV\(_{lo}\). Corresponding to the patterns seen in clinical time series, the RL–1 interval progression for pattern IV\(_{hi}\) is downgoing and IV\(_{lo}\) upgoing (Fig. 2).

In Figure 4, we show the RI interval plots for a range of cardiac burst magnitudes and HR/fi ratios. For burst magnitudes in the range 0–0.2, patterns III and IV will occur commonly in the lower domains (between 2:1 and 4:1 HR/fi) but with increasing HR/fi, these patterns occur less commonly. For any particular burst magnitude there is a ‘critical domain’ or HR/fi ratio, in which patterns III and IV are no longer apparent and above which only pattern I will
occur. The domain in which this occurs will vary directly with burst magnitude.

If burst magnitude is held constant and the ratio HR/fi is allowed to progress through a domain, from the higher to lower integer relationship line, a sequence of pattern zones will be encountered which will differ according to both domain and burst magnitude. Thus, in the 3:1 domain at a burst magnitude of 0.075, HR/fi progresses through zones IVhi, A3, III3, B3, IVlo, and I3, whereas for a burst of 0.15, the progression is IVlo, III3, C3 and I3.

These pattern zones may also be represented on the map of HR versus fi. Figure 5A shows the zones as radiations on the HR/fi map for the burst magnitude 0.15. The width and presence of these radiations will vary according to burst magnitude.
Intrinsic versus observed breathing frequency

Because cardiac triggered breaths occur earlier than intrinsic breaths, coupling makes the mean observed breathing frequency greater than the intrinsic rate and causes the observed breathing frequency to vary from breath to breath depending upon the pattern of coupling. To illustrate how observed frequency varies, we show, in Figure 5, the effect of allowing the HR to decrease from 75 to 50 beats min⁻¹ while \( f_i \) remains constant at 25 bpm. The HR/\( f_i \) relationship moves from the 3:1 to 2:1 integer relationship line, through the 2:1 domain, passing through a sequence of pattern zones. The exact sequence of zones will vary, according to burst magnitude. If burst magnitude is 0.15 the sequence is \( IV_{hi}^2 \), \( A^2 \), \( III^2 \), \( C^2 \), and \( I^2 \). If burst magnitude is 0.05 the sequence is \( IV_{hi}^2 \), \( A^2 \), \( III^2 \), \( B^2 \), \( IV_{lo}^2 \), and \( I^2 \). As HR/\( f_i \) moves between these zones, the coupling pattern changes, as also does the pattern of inspiratory timing (\( f_o \)).

Starting from the 3:1 integer relationship line, where \( f_o = f_i \), the HR/\( f_i \) relationship moves across the zone. During its passage, the value of \( f_o \) jumps to and fro between \( f_i \) and a greater value, with \( f_o \) increasingly taking on the greater value as HR falls. Mean \( f_o \) therefore becomes increasingly greater than the starting \( f_i \) value. The fluctuation in breathing frequency in Figure 5 is seen to be less than the horizontal interval between integer ratio lines. As this horizontal distance corresponds to a variation in ventilatory period of one heart period, pattern \( IV_{hi}^2 \) ventilatory period variability is associated with variations of less than one heart period. It can be seen in Figure 5 that the maximum magnitude of these ventilatory variations are equal to the horizontal width of the pattern \( I^2 \) zone where the HR/\( f_i \) will later cut the transition between \( IV_{hi}^2 \) and \( I^2 \). The variation in breathing frequency will therefore be proportional to burst magnitude (which determines the width of the pattern I zone). Thus, the breathing frequency variation for \( M_{Bc}=0.15 \) is considerably greater than that for 0.05. In general, the mean breathing frequency during a pattern \( IV_{hi}^2 \) epoch will vary within an area of the 2:1 domain on the HR/\( f_o \) map, a little below the 3:1 integer ratio line.

Passing through \( A^2 \), where breathing variation diminishes from that in \( IV_{hi}^2 \), HR/\( f_i \) moves into the pattern \( III^2 \) zone, where breathing rate begins to alternate with consecutive breaths, again with a jump in ventilatory period of less than one heart period. Initially the quantal variability is of similar magnitude to that in the preceding pattern \( IV_{hi}^2 \) zone but decreases as HR falls. When the HR/\( f_i \) ratio falls to an exact half integer, the breathing rate variation of pattern \( III^2 \) is zero. On the HR/\( f_o \) map, the observed breathing frequency variation for pattern \( III^2 \) is now occupying the central region of the 2:1 domain.

From the pattern \( III^2 \) zone the HR/\( f_i \) passes via \( B^2 \) into pattern \( IV_{lo}^2 \) if \( M_{Bc}=0.05 \) or directly into \( C^2 \) if \( M_{Bc}=0.15 \). The maximum \( f_o \) variability in \( B^2 \), \( IV_{lo}^2 \) and \( C^2 \) are of similar magnitude to that in the \( IV_{hi}^2 \) zone although the specific pattern of variability differs between coupling patterns. In both \( C^2 \) and \( IV_{lo}^2 \), \( f_o \) increasingly takes on the maximum value. On the HR/\( f_o \) map, the observed breathing frequency variation is now occupying the lowermost region of the 2:1 domain.

As the HR/\( f_i \) passes into the pattern \( I^2 \) region, \( f_o \) is ‘captured’ by the 2:1 integer relationship line. The \( f_o \) initially takes on a value equal to the maximum which was observed in the \( IV_{hi}^2 \) and \( IV_{lo}^2 \) zones. The displacement of \( f_o \) from \( f_i \) is greatest at this transition and can be seen to be proportional to burst magnitude. Remaining on the integer

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**Fig 3** Pattern zones on the map of HR/\( f_i \) vs \( M_{Bc} \) for (A) 3:1 domain and (B) between the 7:1 and 2:1 domains.
Fig 4 RI interval plots with constant HR=60 beats min⁻¹ and \( \beta \) increasing from 10 to 30 bpm. (A) The effect of increasing MBc on coupling pattern for values of MBc between 0 and 0.20. Note that as MBc increases the region occupied by pattern I coupling increases, and that this increase is more marked in higher domains. (B) The effect of adding RSA, although HR has changed there is little qualitative difference in RI plot. (C) Effect of adding \( \nu_{(l)}=0.02 \) to \( \Phi(l) \), showing the generation of pattern II in the 5:1 and 4:1 domains.

Fig 5 (A) HR\( /\beta \) map for MBc=0.15. With simulation at \( \beta=25 \) bpm, heart rate is decreased from 75 (3:1 IRL) to 50 beats min⁻¹ (2:1 IRL) indicated by the vertical bar. The sequence of pattern zones encountered is IVLo, A, III, and I. The resulting observed breathing frequency, \( f_o \), is shown in (B). With the same simulation re-run for MBc=0.05 the sequence of pattern zones is IVLo, A, III, B, IVLo and I. The resulting observed breathing frequency and corresponding RI plot are shown in (C) and (D) respectively.
relationship line the value of $f_o$ continues to smoothly decrease as HR falls until HR/$f_i$ intersects the 2:1 integer relationship line at which time $f_o$ will once again equal $f_i$. Thereafter a sequence of pattern zones in the first domain would be encountered.

From these observations, we can compare the coupling pattern distribution on the maps of HR/$f_i$ and HR/$f_o$. The HR/$f_i$ map shows radiations corresponding to the four pattern zones, but because $f_o$ is altered by the coupling pattern, the pattern distribution on the HR/$f_o$ map is different. Pattern I occupies only the integer relationship lines, pattern III occupies the central regions of these domains and pattern IV_{hi} and IV_{lo} occupy regions adjacent to the integer relationship lines. The simulated pattern distribution of the HR/$f_o$ map is therefore qualitatively similar to that which is observed in the anaesthetised human subject (Fig. 6).

**Pattern II**

In clinical samples, pattern II coupling is seen primarily from the 4:1 domain upwards and from 6:1 it is the only pattern observed. In human epochs of pattern II, all breaths are initiated by cardiac related activity (as $R_{I-1}$ is constant) and because entrainment ratio varies in an apparently random manner, consecutive breaths may show a sequence of, for example 5,7,5,6,7,5 entrainment. This form of coupling implies, in our model, that inspiratory onset is always cardiac burst related but may be initiated after a different number of cardiac bursts from breath to breath. In simulation, we observed that when a small random variation was applied to the $\Phi(I)$ slope at low ventilatory rates (i.e. higher domains), pattern II coupling was readily produced (Figs 2 and 4). Thus variability of $\Phi(I)$ and probably also HR or burst magnitude, causes variation in the specific cardiac burst which achieves threshold crossing. Because of the steeper $\Phi(I)$ slope, similar degrees of variation at higher breathing rates generally did not disrupt the I, III, and IV patterns to any great extent. Thus above the critical domain at which pattern I is invariable, noise in the system changes these invariable pattern I domains into pattern II. We conclude therefore that pattern II can be accounted for by (a) the invariability of a cardiac burst initiating the threshold crossing when $\Phi(I)$ slope is low together with (b) small variations in $\Phi(I)$ slope, HR or burst magnitude.

As seen in clinical samples, the breathing frequency variability during pattern II coupling was observed in simulation to be characterised by quantal jumps in ventilatory period corresponding to changes in entrainment ratio. Thus, changes in ventilatory period occurred in multiples of the heart period. The distribution of coupling types seen in the HR/$f_o$ map of anaesthetised subjects (Fig. 6) can therefore be entirely explained by our model. Pattern II is invariably present above a critical boundary domain, below which patterns I, III, and IV occur in radiating zones.

**Respiratory sinus arrhythmia**

Other than the associated increase in HR caused by reducing the cardiac threshold, the addition of RSA had no major qualitative effect on the HR/$f_i$ distribution of coupling patterns or $f_o$ variability (Fig. 4).

**Simulation of human time series**

Although the qualitative behaviour of our model is similar to that observed in human subjects, it would be of considerable interest to demonstrate whether the model can simulate clinical observations exactly. Unfortunately, in clinical data we observe $f_o$, HR and the RI interval variation, but the two variables $f_i$ and burst magnitude are unknown. To simulate the patterns of coupling and $f_o$ variability from real data we, therefore, need to choose suitable values for $f_i$
and burst magnitude. From the foregoing observations, several pointers are available to guide our choice of values:

**Burst magnitude**

1. If there were no sudden transitions in heart rate or ventilatory frequency we could assume that the HR/\(f_i\) relationship would wander smoothly through regions of the HR/\(f_i\) versus burst magnitude map. A crude guide to burst magnitude could, therefore, be obtained if some transitions between patterns only occur in certain burst magnitude ranges. Thus, IV\(_{2}\) only occurs at low burst magnitudes and a rapid transition between IV\(_{2}\) and I\(_2^2\) via pattern C\(_2\), will only occur at high burst magnitudes.

2. Burst magnitude could be inferred from the magnitude of the maximum breathing frequency variation during pattern IV.

3. The bands in the pattern III RI plot are evenly separated when burst magnitude is small but more closely grouped into pairs as burst magnitude increases. Close groupings therefore suggest a high burst magnitude.

**Intrinsic breathing frequency**

The longest ventilatory period will correspond to that preceding an intrinsic \(\Phi(1)\) triggered breath. For those patterns where the mechanism of inspiratory triggering varies between breaths (patterns III, IV, A, B, and C), the lowest breathing frequency will, therefore, correspond to \(f_i\). Unfortunately a pure pattern I (or II) epoch gives no obvious clues as to its control variables as all breaths are cardiac triggered and any combination of burst magnitude and \(f_i\) falling within a pattern I zone gives the same HR/\(f_o\).

Using these observations, we could recreate the observed breathing patterns and RI plots of human subjects using the subject’s own heart rate time series and inferred \(f_i\) and burst magnitude values. In all clinical time series, which we have examined, agreement between the real and simulated RI

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**Fig 7** Comparison of a human and simulated RI interval plot and breathing frequency time series. A hypothetical explanation for this epoch was given by Galletly and Larsen. The time series is for an anaesthetised subject given fentanyl at time 720 s. (A) Human observed breathing frequency time series and estimated input values for intrinsic breathing frequency used for simulation. (B) The associated human RI interval time series showing progression through patterns I\(_4\), III\(_3\), I\(_1\), IV\(_{2}\) \(_{hi}\) and C\(_3\). In Galletly and Larsen, the C\(_3\) segment was classified originally as pattern II, but is almost certainly associated with the pattern C zone. Input variables for simulation were \(f_i\) as in (A), \(M_{bc}=0.175\) increasing to 0.2 at 720 s and filtered HR time series (E). The resulting simulated breathing frequency time series (C) and simulated RI interval plot (D) bear a remarkable similarity to the human data. In (F) we show the same simulation but in the absence of cardiac bursts (i.e. \(M_{bc}=0\)).
In our hypothetical model, inspiration occurs when the activity of an intrinsic pacemaker function reaches an inspiratory firing threshold. The likelihood of this function crossing the firing threshold increases in response to a signal of cardiac origin, and therefore, the exact timing of inspiratory onset will vary according to whether the intrinsic pacemaker function crosses the threshold or whether an earlier cardiac signal causes threshold crossing. Depending upon the ratio of HR to \( f_i \), and the magnitude of the afferent cardiac signal, the sequence of consecutive threshold crossings (cardiac triggered versus intrinsic) will vary, and these variations are seen as the observed coupling patterns and corresponding breathing rate irregularities.

### Pattern I
Consecutive inspirations are all initiated by the cardiac stimulus and the same number of heart beats occur within each ventilatory period (i.e. the entrainment ratio is constant). Pattern I occurs when HR/\( f_i \) is in the range where consecutive leading edges of the cardiac burst cause inspiratory threshold crossing. If the magnitude of the cardiac stimulus is low, pattern I coupling only occurs when the HR/\( f_i \) ratio is equal to, or a little over an integer value. However, as the cardiac stimulus intensity increases, pattern I occurs over a wider range of HR/\( f_i \) values within a domain. The critical HR/\( f_i \) above which pattern I is invariable (or because of ‘noise’ pattern II) occurs, in our model, when the tip of one cardiac burst exceeds the base of the following cardiac burst (Fig. 1). It can be shown from simple geometry that in a simple linear model, this critical boundary occurs at HR/\( f_i \)=1/burst magnitude. Breathing frequency variability during pattern I coupling is negligible because entrainment ratio is constant and ventilatory period equals the interval between burst related crossings of the inspiratory threshold.

### Pattern II
Pattern II is a variant of pattern I in which small variations in \( \Phi(I) \) slope (and/or HR and burst magnitude) cause variation in the entrainment ratio. The effect of \( \Phi(I) \) slope variation is greatest when \( \Phi(I) \) slope is least and hence pattern II is most common at high HR/\( f_i \) ratios or low breathing rates. Varying entrainment ratios cause quantal variation in breathing frequency corresponding to one or more multiples of the heart period.

### Pattern III
Consecutive inspirations alternate between intrinsic and cardiac triggering. Ventilatory period also alternates with this variation; the alternate ventilatory periods are (i) from the cardiac burst crossing to intrinsic crossing and (ii) from the intrinsic crossing to cardiac burst crossing. The ventilatory period between a cardiac triggered breath and a following intrinsic breath will correspond to \( f_i \), whereas

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**Discussion**

This model of cardioventilatory coupling is consistent with observations of coupling and ventilatory variability during spontaneous breathing general anaesthesia. The model explains observed patterns of coupling and predicted variations of these patterns, which were subsequently found in clinical time series. The model satisfactorily explains why coupling is invariable above a critical boundary region, and the distribution of coupling patterns on the map of HR/\( f_o \) for clinical data. The simulation is consistent with clinically observed breathing variation associated with each coupling pattern and allows reproduction of both RI plots and ventilatory variability from the heart rate time series of human subjects.

From our clinical observations and from the clinically consistent behaviour of the model we can, therefore, elaborate on the preliminary hypothesis put forward for the generation of coupling, coupling patterns and intra-operative breathing irregularity.

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**Fig 8** An RI plot transition between pattern I and what appears to be uncoupled. Using the patients’ own heart rate time series and an MBc of 0.05 the simulated RI plot shows a transition between pattern IV and the more complex pattern B. This suggests that epochs which appear uncoupled may at times represent patterns A or B with added ‘noise’.

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**Clinical recording**

![Clinical recording diagram](image)

**Simulated**

![Simulated diagram](image)
the interval from an intrinsically triggered inspiration to one that is cardiac triggered will be shorter. The magnitude of this variation from breath to breath is less than one heart period. It follows from this that the slowest observed frequency seen during pattern III variation will correspond to the intrinsic breathing frequency \( f_0 \).

**Pattern IV**

Cyclical periods of intrinsic inspiratory triggering follow periods of cardiac burst related triggering. Breathing rate varies according to the phase of this cycle although the largest variation will occur when a cardiac burst related breath changes to an intrinsic triggered breath. The minimum \( f_0 \) during a period of pattern IV coupling will occur during the phase of consecutive intrinsic crossings. Thus, as with pattern III, the intrinsic breathing frequency will correspond to the slowest observed frequency. The magnitude of the breathing frequency variation will be directly proportional to the magnitude of the afferent cardiac signal.

‘Uncoupled’

Apparently uncoupled patterns are generated under two circumstances. (i) If burst magnitude is small and the majority of breaths are initiated by the intrinsic \( \Phi(I) \). Small degrees of breathing frequency variability under this circumstance may occur because of ‘noise’ and occasional cardiac burst related triggerings. (ii) At higher burst magnitudes apparently uncoupled time series may be generated during complex patterns A and B which have been disrupted by small variations in HR, burst magnitude, \( f_1 \) and coupling interval.

The described model structure is remarkably similar to that proposed over 20 yr ago by Cohen and Feldman\(^6\) in order to explain the effects of electrical stimulation of certain brain regions on inspiratory timing. In their model, the slope of a hypothetical inspiratory function (also \( \Phi \)) was increased or decreased by electrical stimulation of the rostral or ventral part of the nucleus parabigeminalis, respectively. Delay or shortening of the expiratory—inspiratory phase switch could be achieved by such stimulation. Within the framework of Cohen’s model, cardioventilatory coupling might be viewed as an example of pulse synchronous rostral stimulation. It may therefore be relevant that the nucleus parabigeminalis is the main relay for visceral traffic from the nucleus tractus solitarius to forebrain structures.\(^7\) As the nucleus tractus solitarius is the main site of termination of afferent cardiovascular receptors it is conceivable that this region could mediate coupling related cardiovascular stimulus.

An important component of our model is the presence of an intrinsic inspiratory pacemaker. A pacemaker such as this is well recognized, with spontaneous pacemaker activity being measured in isolated brain stem regions associated with respiratory activity. However, it is also known that the frequency of this pacemaker is slower than that in intact animal preparations. The pre-Botzinger complex of the isolated rat brain stem has an intrinsic frequency approximately one third that of the normal breathing rate and, in intact preparations, brain stem de-afferentation reduces breathing frequency.\(^8\) If, as many authors believe, the pre-Botzinger complex pacemaker is the origin of the breathing rhythm, a mechanism must exist which augments the intrinsic activity and increases the frequency of the core oscillator. A key feature of our model is the shortening of intrinsic ventilatory period by the cardiac afferent stimulus and therefore this might, in part, explain a mechanism for this augmentation. Furthermore, both somatic stimulation and locomotor activity are also capable of entraining the respiratory rhythm.\(^9\)\(^–\)\(^11\) Perhaps therefore cardioventilatory coupling simply represents one aspect of a general mechanism whereby an intrinsic respiratory pacemaker is augmented by a number of afferent inputs. Such a mechanism could relate to a variety of clinical observations including the ventilatory responses to stimulation and exercise.

Although ample evidence suggests the presence of an intrinsic respiratory pacemaker, and the presence of coupling suggests some form of interacting cardiovascular signal, we stress that the described model need not have exact neuroanatomical or electrophysiological correlates. The model is one that behaves in a similar manner to that of the intact anaesthetized human inspiratory timing mechanism, and as such, may be useful for predicting behaviour. It should be used with caution, however, for understanding the detailed underlying mechanisms. The quantity ‘cardiac burst magnitude’ represents a process whereby the value of \( \Phi(I) \) and the inspiratory firing threshold are transiently brought closer together. This process could also have been brought about by other means with no change in the overall behaviour. Thus, the afferent cardiac signal could equally reduce inspiratory threshold instead of cardiac bursts augmenting \( \Phi(I) \). Each variant does not differ in its overall behaviour and hence could equally be considered as models of inspiratory timing. However, certain features of the model are invariant, that is, present irrespective of how the model is constructed. Perhaps the most important of these is the central idea that a cardiac triggered breath will always be shorter than the intrinsic breath, which would have occurred if the cardiac signal had not been present. The effect of coupling in the model is always to increase the mean observed frequency over the intrinsic. This property has the potential for two clinical implications.

**Cardioventilatory ‘overdrive’**

In some regions of the HR/\( f_1 \) map (especially at high \( f_1 \), high burst magnitude and at the boundary of patterns IV\(_{lo}\) and I), \( f_0 \) may be ‘driven’ at rates well in excess of \( f_1 \). From our
analysis, as $HR/f_i$ crosses from a IV$_{lo}$ to I zone, the $HR/f_o$ will be forced, at the same heart rate onto the next lowest integer relationship line. Thus, at $HR=80$ and $f_i=30$, the $HR/f_i$ ratio is 2.66. If cardiac bursts are of sufficient magnitude to place this $HR/f_i$ ratio into a pattern I zone the resulting $HR/f_o$ would equal int2.66=2. As $HR$ remains at 80 and $HR/f_o=2$, the breathing frequency will increase from 30 to 40 bpm. Unexpectedly high breathing rates such as these are occasionally seen in anaesthetized subjects in the absence of opioids and may in part be a result of this cardioventilatory ‘overdrive’. It might be expected that if breathing frequency is driven in this manner for any length of time, with constant tidal volume, there will be a chemoreceptor mediated adjustment of minute ventilation to a lower value. Whether a resetting of intrinsic breathing frequency occurs or whether tidal volume falls in response to a sustained coupling related frequency overdrive, needs to be determined experimentally. However, if a resetting of intrinsic frequency occurred it would be expected that pattern I could not be sustained for long periods as the $f_i$ resetting will cause the $HR/f_i$ to move back into the IV$_{lo}$ zone and hence reduce mean breathing frequency. In our clinical time series, some subjects were observed to remain in pattern I, locked onto the integer relationship line for periods of 5 min or longer suggesting that minute ventilation is being adjusted in these subjects by changes in tidal volume, rather than through adjustment in $f_i$.

**Cardioventilatory ‘support’**

The potential for excessively high breathing frequencies can be contrasted to the effect of coupling at low intrinsic breathing frequency. At low simulated breathing rates, the $\Phi(I)$ slope is comparatively flat, and because all breaths at rates less than 10–12 bpm are cardiac burst initiated, coupling is invariably present (as pattern I or II). It follows therefore that at low breathing rates the mean observed breathing frequency will always be greater than the intrinsic frequency. Figure 7 demonstrates this supporting effect of coupling in a human time series. After the administration of fentanyl, the opioid, presumably by an effect on the inspiratory pacemaker, has reduced $f_i$ to approximately 15.5 bpm (we can infer $f_i$ because, as noted above, the minimum $f_o$ will correspond to $f_i$ in patterns III, IV, A, B, C). The cardiac triggered breaths however are of higher breathing frequency and, as the breathing frequency jumps between cardiac and intrinsic triggered breaths the mean breathing frequency is increased to approximately 19 bpm. During opioid mediated depression of the intrinsic inspiratory pacemaker, therefore, cardiac afferent activity supports breathing frequency at values greater than that of the intrinsic pacemaker. Whether such support is clinically relevant remains to be determined. As noted above, the regulation of breathing involves the control of minute ventilation by alteration of both rate and tidal volume. However, a mechanism that is relevant to the control of frequency should be of clinical interest as central apnoea is a failure of frequency control. Because cardioventilatory coupling provides a simple non-invasive indicator of frequency control which is not otherwise accessible, we suggest that observations of coupling (cardiac, somatic and locomotor) in subjects with abnormal control of respiratory frequency may be helpful.

In previous papers, we have attempted to quantify coupling in terms of the constancy of the $RL_1$ interval (the interval between the inspiration and the preceding R wave). This constancy was measured as the proportional Shannon entropy of the $RL_1$ interval ($H_{RL_1}$). This quantity varies according to coupling pattern, with the most disordered RI plots (i.e. those that are uncoupled) having higher $H_{RL_1}$ values than those that are perfectly ordered (pattern I). $H_{RL_1}$ varies with pattern according to the order: $I = II < III < IV <$ uncoupled. Although intuitively $H_{RL_1}$ may be considered a measure of ‘strength of coupling’ our model clearly indicates that the true strength of coupling must be burst magnitude and that this cannot be directly equivalent to $H_{RL_1}$. Thus, two individuals may have identical burst magnitudes and very similar $HR/f_i$ ratios but if one falls into a pattern I zone the $H_{RL_1}$ will be low whereas the other, with a fractionally different $HR/f_i$, may fall into a pattern III or IV zone and hence the $H_{RL_1}$ will be high. As the burst magnitude is identical in these subjects, the underlying strength of interaction between the cardiac afferent and the respiratory pacemaker is the same. Measures based on the RI interval variation such as $H_{RL_1}$, should be distinguished from the true strength of signal interaction (cardiac burst magnitude). Differences in coupling pattern (and hence $H_{RL_1}$) may be caused by minute changes in $HR/f_i$ and not by the changes in the strength of interaction between the cardiac afferent and the intrinsic pacemaker. To observe a true alteration in the strength of cardiac afferent/respiratory interaction, or to infer an intrinsic disorder of coupling, demands the observation of altered burst magnitude rather than a simple comparison of coupling pattern or RI plot. We describe several strategies for determining the magnitude of the cardiac afferent signal.

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