

CLINICAL INVESTIGATIONS

Ventilatory frequency variability in spontaneously breathing anaesthetized subjects

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During spontaneous breathing general anaesthesia, inspiration is generally started by a signal related to preceding cardiovascular activity. This phenomenon, 'cardioventilatory coupling', contributes to the variation in ventilatory frequency. However, the detailed, breath-to-breath timing relationship between heart beat and inspiratory onset is complex, with at least four distinct patterns (designated patterns I–IV). These coupling patterns are defined according to the particular breath-to-breath change in: (a) entrainment ratio and (b) coupling interval, the interval between inspiratory onset and the preceding initiating heart beat. We have examined the relationship between coupling and timing of breathing in adult subjects breathing spontaneously during general anaesthesia. The heart rate–ventilatory frequency interaction was explored by identifying the distribution of different coupling patterns in a plot of heart rate vs ventilatory frequency (the HR/*f* plot) and analysing the variation in breathing frequency during each coupling pattern by differentiating between changes in entrainment ratio from changes in coupling interval. We observed that: (i) coupling patterns are distributed within specific regions of the HR/*f* plot; (ii) specific patterns of variation in breathing are associated with each coupling pattern; (iii) this variation is a consequence of the balance between changes in entrainment ratio and coupling interval; (iv) coupling was invariably present at low breathing frequencies; and (v) the inverse non-linear relationship between ventilatory frequency and variation is largely a consequence of changing coupling pattern with ventilatory frequency. Coupling explains much of the breath-to-breath variability of ventilatory frequency during anaesthesia, and may be relevant to the phenomena of hypoventilation, central apnoea and ventilatory arrhythmia. A hypothesis concerning the generation of coupling patterns is presented.

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The complex relationship between respiratory and cardiac timing involves two major physiological interactions. The best known is respiratory sinus arrhythmia, vagal modulation of the heart period secondary to breathing activity.¹ The second has been variously termed cardioventilatory 'entrainment',² 'synchronization',³ 'co-ordination'⁴ or 'coupling'.⁵ Cardioventilatory coupling is almost the converse of sinus arrhythmia in that whereas sinus arrhythmia is modulation of heart rate (HR) by breathing, coupling is modulation of ventilatory timing by a cardiovascular signal.⁶ Instead of a simple modulation of frequency however, as in sinus arrhythmia, coupling appears to be a triggering of inspiratory onset by the preceding cardiovascular activity.⁷

Initiation of inspiration by cardiac action is probably mediated via one or more afferent pressoreceptor pathways to the brainstem.

Coupling can be shown in heart rate–ventilatory frequency time series by showing a constant time relationship between consecutive inspirations and preceding heart beats. Practically, the ECG R wave is used as the cardiac signal, although it is important to stress that this does not assume that the trigger for inspiration is related specifically to the R wave or even cardiac systole. The interval between each ECG R wave and the immediately following inspiration (RI interval) is determined and these RI intervals are plotted as a time series (the RI plot). Coupling is seen in these

plots as horizontal banding, in which R waves maintain constant temporal relationship with the inspiration.⁵ In coupled intraoperative time series however, we have observed several complex patterns of RI plot, heart beat–inspiratory alignment.⁵ An individual subject may show a single stable pattern or multiple apparently random transitions between patterns. We have classified these RI plot patterns as I, II, III and IV, in addition to uncoupled (see Fig. 4 for representative examples). The reason for the stability or transitional behaviour of these patterns is unknown. However, these patterns can be differentiated by two major features: (a) the number of heart periods elapsing before each inspiration is initiated (the entrainment ratio) and (b) variations in the interval between inspiratory onset and the preceding (presumably triggering) heart beat, which we term the coupling interval (Figs 4, 7).⁵ Both of these variables influence the duration of the breathing cycle. Thus in anaesthetized subjects, variation in the timing of the breathing cycle may depend to a large extent on the specific coupling pattern present.

Although heart rate variability, and specifically sinus arrhythmia, has been the subject of considerable research interest in anaesthetized subjects,^{8–11} a smaller number of articles have examined breath-to-breath variations in ventilatory period and fewer still have suggested a relationship between this variability and cardioventilatory coupling. In 1995, Goodman reported an apparent bimodality of breathing frequency in spontaneously breathing anaesthetized subjects.¹² We later demonstrated that quantal variations in ventilatory period were seen during cardioventilatory coupling and occurred when the entrainment ratio between heart and breathing rhythms varied from one breath to the next.⁵ In one breath, for example, an inspiration might be initiated after 4 heart beats, and in the following breath, after 5. The change in ventilatory period between these breaths approximates to one heart period. This process is analogous to the rapid quantal variation in heart period seen in unstable atrial flutter with rapidly varying degrees of atrioventricular block. This quantal variation was seen particularly in the coupling pattern which we have classified as pattern II.

Although quantal variation in ventilatory period clearly demonstrates the relevance of coupling in the genesis of ventilatory variability, this specific pattern occurred clearly only in some ventilatory epochs and, in many instances, the apparent quantal variation in ventilatory period was less, and in some cases considerably less, than one heart period. As coupling involves triggering of inspiration, is common in anaesthetized subjects and is observed in time series which do not demonstrate quantal ventilatory fluctuations, it is reasonable to assume that during anaesthesia, significant ventilatory variability may be caused by coupling in the absence of quantal, one heart period, variation.

In this article, we have explored the relationship between coupling pattern, ventilatory timing and heart rate. We begin

by examining the factors which influence coupling pattern and then explore why specific coupling patterns are associated with characteristic patterns of breathing variation. We show that: (a) breath cycle variation is determined to a large extent by cardioventilatory coupling, (b) this variation differs according to the specific pattern of coupling and (c) although it is caused by comparatively simple cardiorespiratory interactions, the result is complex and non-linear.

Patients and methods

Ethics Committee approval was obtained for data collection, and consent was obtained from all patients. Data were obtained from 98 ASA I adult subjects during elective procedures who met the following criteria: spontaneous ventilation during general anaesthesia; no medications known to influence autonomic function; no evidence of cardiorespiratory disease; and normal sinus rhythm.

Anaesthesia was induced in all subjects with propofol 1.5–2.5 mg kg⁻¹, and maintained by spontaneous inhalation of isoflurane and 66% nitrous oxide in oxygen. Morphine, fentanyl or alfentanil was given according to surgical indications and at the discretion of the anaesthetist. After induction of anaesthesia, a laryngeal mask airway was inserted and assisted ventilation or increased $F_{I_{O_2}}$ were provided as necessary to maintain arterial oxygen saturation $\geq 96\%$ at all times. Data recording began only after resumption of spontaneous ventilation. In all subjects, we monitored routinely arterial oxygen saturation Sp_{O_2} , end-tidal carbon dioxide partial pressure and non-invasive arterial pressure (all Datex AS3).

The electrocardiogram was derived from a CM₅ lead (Corometrics Neo-Trak 502) and the timing of the breathing cycle was determined using a non-return valve within the breathing system. The valve was modified by addition of a photodetector and light beam across the path of the valve shuttle. The photodetector generated a 1.5-V square wave signal while the valve was open (i.e. from the start of inspiration to end inspiration). Continuous recordings of ECG and ventilatory timing were made using a Macintosh IIcx computer with 16-bit ADC board (National Instruments MIO-16) and a sampling rate of 500 Hz.

Data analysis

Qualitative graphical determination of cardioventilatory coupling

A method for demonstration of cardioventilatory coupling has been described previously.⁵ From the ECG and breathing signals, we determined the timing of consecutive R waves and the start of each inspiration. From these time series we determined the interval between each R wave and the immediately following inspiratory onset (RI intervals). RI intervals were then plotted as a time series (RI interval plot). In the RI interval plot, horizontal banding indicates the presence of cardioventilatory coupling where R waves fall in constant timing relationship with inspiratory onset.

The heart beat which immediately precedes inspiration is given a negative subscript (R_{-1}) and the RI_{-1} interval is regarded as equivalent to the coupling interval (Ci), the normal value of which is approximately 0.5 s. However, we recognize that at high heart rates (>100 – 120 beat min^{-1}) and in atrial fibrillation, some RR intervals may be so short that R_{-2} may be the triggering beat and hence the true coupling interval may be better approximated by RI_{-2} .¹³ In this study, the rhythm was sinus and heart rates were generally less than 100 beat min^{-1} ; therefore, RI_{-1} is used with this proviso, synonymously with Ci.

Quantitative measurement of cardioventilatory coupling

As a quantitative measure of cardioventilatory coupling, we used a measure of dispersion within the distribution of RI_{-1} intervals—Shannon entropy (SH). This measure is also used in the biological sciences as a measure of diversity where it is known as the Shannon–Weaver diversity index (see Larsen, Trent and Galletly,⁶ and Zar,¹⁴ for a worked example). Coupling is associated with a constant RI_{-1} interval and absent coupling with an RI_{-1} interval which changes from breath to breath. A series of identical RI_{-1} intervals (associated with strong cardioventilatory coupling) would contain no diversity and $SH=0$. A series of RI_{-1} intervals that were all different (i.e. where cardioventilatory coupling is absent) would contain a high degree of diversity and SH would approach a maximum finite value (SHmax). A simple measure of coupling is therefore the ratio SH/SH_{α} which we term the proportional Shannon entropy— SH_{α} . Therefore, the degree of coupling ranges between $SH_{\alpha}=1$ (absent coupling) to $SH_{\alpha}=0$ (perfectly coupled).

To calculate SH_{α} we examined 10 successive RI_{-1} intervals and placed each of these into a 10-bin histogram, the outer limits of which ranged between 0 and the mean RR interval which spans the corresponding 10 inspiratory onsets. SH_{α} was calculated from the distribution of bin contents within this histogram:

$$SH = -\sum_{b=1}^N P_b \cdot \log(P_b)$$

$$SH_{\max} = -\log(1/N)$$

$$SH_{\alpha} = SH/SH_{\max}$$

where P =observed histogram bin probability, b =bin number and N =number of histogram bins. SH_{α} was calculated for successive moving windows of 10 RI_{-1} intervals over the data epoch and the median value calculated as our measure of coupling. From a series of simulated random number time series, we determined that the probability of a random time series attaining a median SH_{α} value of less than 0.72 was less than 0.001. The scale of SH_{α} is non-linear and therefore its analysis is non-parametric.

Selection of coupling pattern epochs

Each RI plot was examined for coupling pattern, classified visually as patterns I–IV or uncoupled (see Fig. 4 for

example). Specific criteria for inclusion of coupling pattern epochs were then applied as follows.

Pattern I. An epoch length of at least 15 consecutive breaths with at least 95% of breaths containing the same number of heart beats (i.e. identical entrainment ratio) and $SH_{\alpha} < 0.7$.

Pattern II. An epoch length of at least 15 consecutive breaths in which no more than 50% of breath cycles have the same entrainment ratio and $SH_{\alpha} < 0.7$.

Pattern III. An epoch length of at least 15 consecutive breaths in which: (a) the RI_{-1} interval and the entrainment ratio alternated between two values from breath to breath; and (b) the RI_{-1} interval for one breath was similar to that two breaths later.

Pattern IV. An epoch in which RI_{-1} interval increased (or decreased) progressively from breath to breath until, within a narrow RI_{-1} window, the interval remained reasonably constant before continuing to increase (or decrease). This pattern was repeated on at least three successive occasions for a total of at least 15 breaths.

Uncoupled. An epoch length of at least 15 consecutive breaths with no discernible pattern of RI_{-1} alignment and $SH_{\alpha} > 0.75$.

We selected periods from the RI time series (without reference to heart rate or ventilatory frequency time series) meeting the above criteria. Between one and three epochs were extracted from each subject but no two identical coupling patterns were selected from any one subject.

Heart period, breath cycle period and coupling interval characteristics for each coupling pattern

For each coupling pattern epoch, we calculated the following variables: (a) mean RR interval (\overline{RR}); (b) mean absolute value of the consecutive difference between RR intervals ($|\overline{CDRR}|$); (c) mean breath cycle period, measured from consecutive inspiratory onsets (\overline{II}); (d) mean absolute value of the consecutive difference between breath cycle periods ($|\overline{CDI-I}|$); (e) mean and SD of the heart rate–ventilation frequency ratio ($\overline{HR/f}$, SD ($\overline{HR/f}$), f) mean RI_{-1} ($\overline{RI_{-1}}$); (g) mean absolute value of the consecutive difference of the RI_{-1} interval ($|\overline{CDRI_{-1}}|$); and (h) SH_{α} (Table 1).

Plotting the HR/f relationship

To study the relationship between coupling pattern and the specific heart rate–ventilatory frequency relationship, we plotted values of heart rate against ventilatory rate according to coupling type. From the heart rate (HR) and ventilatory frequency (f) time series of each subject, we determined the value of HR and f at 10-s intervals. Breathing frequency was calculated from the breath period (inspiration to inspiration) which spanned consecutive 10-s markers (at low f (<6 bpm), duplicate ventilatory periods were ignored). Heart rate was calculated as the mean RR interval from the R wave which followed the initial inspiration to the R wave which followed the next inspiratory onset. For each coupling pattern, we plotted HR and f values at consecutive 10-s intervals, superimposing data for separate subjects. We then

constructed a frequency histogram of individual HR/*f* ratios for each coupling pattern.

*Transitional behaviour and movement within the HR/*f* plot*

The preceding HR/*f* plot shows values of HR and *f*, superimposed for each subject, and allows the distribution of coupling patterns according to HR/*f* to be determined. We were also interested in the movement of the HR/*f* relationship over time for each coupling pattern. For each subject and for every breath, we plotted mean HR against breath-to-breath values of *f*. For these plots, *f* was determined from each I-I interval and HR was determined as for the HR/*f* plot (above). The ‘routes’ taken by the HR/*f* relationship during the course of anaesthesia were examined visually and related to changes in coupling pattern.

Components of breath cycle variation according to coupling pattern

To examine the relationship between coupling pattern and breath cycle variation, we divided the components of the cycle period into that related to: (a) variations in coupling interval and (b) variations in entrainment ratio. Figure 1 shows schematically three consecutive ventilatory onsets,

I₁, I₂ and I₃. Each inspiration has been triggered by heart beats, T₁, T₂ and T₃ which precede and are separated from the inspiratory onset by the coupling intervals Ci₁, Ci₂ and Ci₃. After each triggering heart beat there is an interval until the next triggering heart beat (S₁, S₂). The two breath cycle periods I-I_{1/2} and I-I_{2/3} have a duration:

$$I-I_{1/2} = S_1 - Ci_1 + Ci_2$$

$$I-I_{2/3} = S_2 - Ci_2 + Ci_3$$

The change from one breath cycle duration to the next is therefore:

$$I-I_{2/3} - I-I_{1/2} = S_2 - S_1 + (Ci_3 - Ci_2) + (Ci_1 - Ci_2)$$

The intervals S₁ and S₂ equal the product of the number of heart periods (n₁, n₂) making up that interval (equal to the entrainment ratio) and the mean RR interval of those heart periods (\overline{RR}_1 , \overline{RR}_2).

$$I-I_{2/3} - I-I_{1/2} = \Delta I - I = n_2(\overline{RR}_2) - n_1(\overline{RR}_1) + (Ci_3 - Ci_2) + (Ci_1 - Ci_2) \\ = n_2(\overline{RR}_2) - n_1(\overline{RR}_1) + \Delta Ci_{3/2} + \Delta Ci_{1/2} \dots (1)$$

Using RL₁ as equivalent to Ci, for each coupling pattern epoch, we plotted, as time series, the two variables (n₂(\overline{RR}_2) - n₁(\overline{RR}_1)), the entrainment effect, and (ΔCi_{3/2} + ΔCi_{1/2}), the coupling interval effect, comparing the relative change in each component of ventilatory variability for each pattern.

In addition to the above data extraction, we calculated time, frequency and non-linear domain measures from the HR series; these will be the subject of a separate article focusing on the effect of coupling on heart period variability.

All data manipulation was performed using purpose written software in LabView 2 and statistical analysis using Statview 5.

Results

We studied 42 male and 56 females, mean age 39.1 yr. A total of 169 pattern epochs were obtained from these subjects (pattern I, 37; pattern II, 49; pattern III, 16; pattern

Table 1 Abbreviations used in the text

CD	Consecutive difference
$ \overline{CDI-I} $	Mean absolute value of the consecutive difference between ventilatory periods
$ \overline{CDRL_1} $	Mean absolute value of the consecutive difference of the RL ₁ interval
$ \overline{CDRR} $	Mean absolute consecutive difference between RR intervals
Ci	Coupling interval, interval between inspiratory onset and the R wave associated with the preceding triggering heart beat (assumed to approximate to RL ₁)
<i>f</i>	Ventilatory frequency
HR	Heart rate
$\overline{HR/f}$	Mean heart rate-ventilatory frequency ratio
I-I	Ventilatory period measured from inspiration to inspiration
$\overline{I-I}$	Mean ventilatory period
ΔI-I	Difference between consecutive ventilatory periods
RL ₁	Interval between inspiration and the preceding R wave
RR	Interval between consecutive R waves
SD	Standard deviation
SH _α	Proportional Shannon entropy (a measure of coupling)

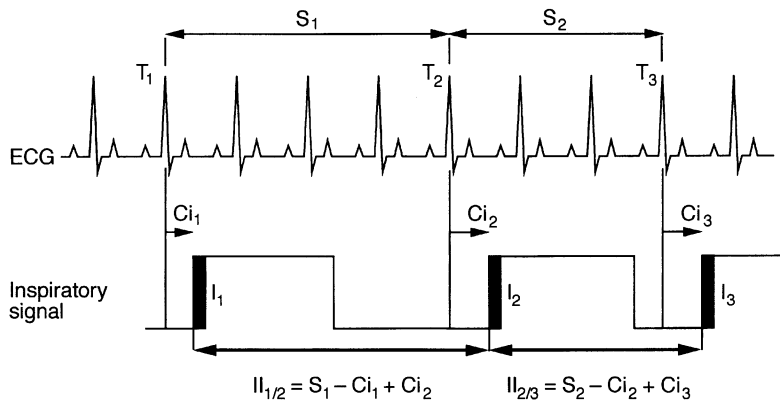


Fig 1 Schematic representation of three inspiratory onsets (I₁, I₂, I₃), triggered by preceding heart beats (T₁, T₂ and T₃). The intervals between triggering heart beats are denoted S₁ and S₂. The coupling intervals (Ci₁, Ci₂ and Ci₃) are equal to the corresponding RL₁ intervals. Consecutive ventilatory periods (I-I_{1/2}, I-I_{2/3}) are calculated from S and Ci.

IV, 29; uncoupled, 38). There was no significant relationship between coupling pattern and sex or age of the subjects.

The HR/f plot

A plot of HR against f , for all subjects and all data epochs, is shown in Figure 2A. Although HR correlated positively with f overall ($P < 0.0001$), the distribution was non-homogenous with preference for distribution along lines of integer relationship. A histogram of corresponding HR/ f ratios, showing integer relationships from 3 up to 9 and perhaps 11, is shown in Figure 2B.

Distribution of coupling patterns on the HR/f plot

Plotting HR against f for each coupling pattern demonstrated that coupling patterns were associated with specific regions of the HR/ f plot (Fig. 3).

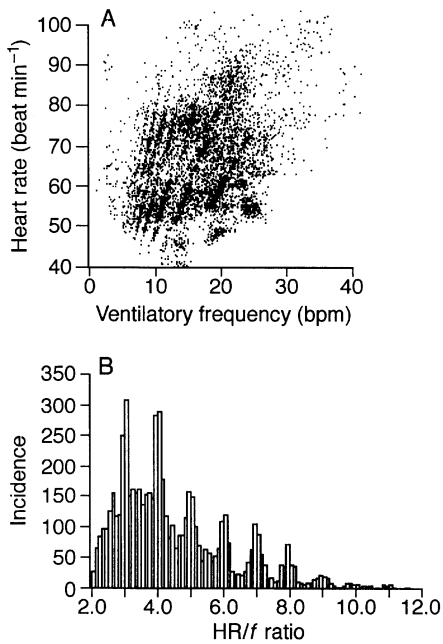


Fig 2 A: Heart rate vs ventilatory frequency (HR/ f plot) for all subjects, measured at 10-s intervals. B: Frequency histogram of HR/ f ratios.

Pattern I

By definition, pattern I is seen when HR/ f is in integer ratio and hence these epochs were associated with values of HR and f distributed along integer ratio lines. Ventilatory frequency for these pattern I epochs was greater than approximately 10 bpm. Entrainment ratios 3, 4 and 5:1 were prominent, although 6:1 was also represented. No stable pattern I coupling of greater than 6:1 entrainment was observed.

Pattern II

The pattern II distribution was seen along lines of integer ratio generally at lower respiratory frequencies than pattern I and overlapping the lower range of f values for other coupling patterns and also uncoupled epochs. Thus coupling was present in all epochs where ventilatory frequency was less than approximately 10–12 bpm and at these frequencies the coupling pattern was invariably pattern II. Within the pattern II distribution, HR/ f ratios of up to 11:1 were apparent.

Pattern III

Pattern III coupling is associated with alternating entrainment ratio. The HR/ f distribution for pattern III was seen only at non-integer HR/ f values in the spaces between adjacent integer ratio lines, primarily between 2/3:1 and 3/4:1.

Pattern IV

Pattern IV coupling was seen for HR/ f values close to whole number ratio. In Figure 3, these epochs are seen as points distributed alongside integer ratio lines, primarily in association with 3:1 and 4:1 integer ratio lines.

Uncoupled

Uncoupled epochs had HR/ f ratios distributed in a similar region to patterns I, III and IV coupling at ventilatory frequencies greater than 10 bpm. Although the distribution appeared unrelated to integer ratio lines, the histogram of HR/ f ratios clearly showed minima at integer ratios.

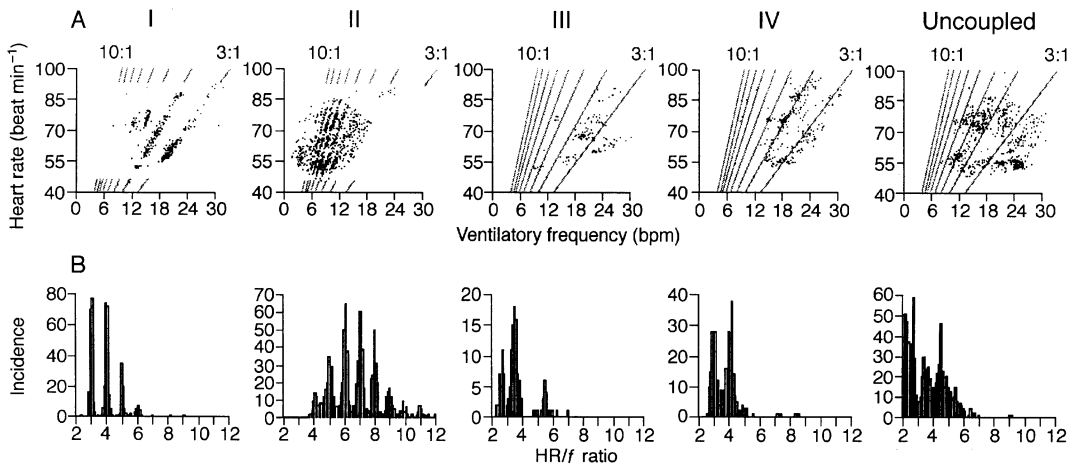


Fig 3 For each coupling pattern, plots of heart rate vs ventilatory frequency (HR/ f plot) with superimposed integer relationship lines (A) and frequency histograms of HR/ f ratio (B).

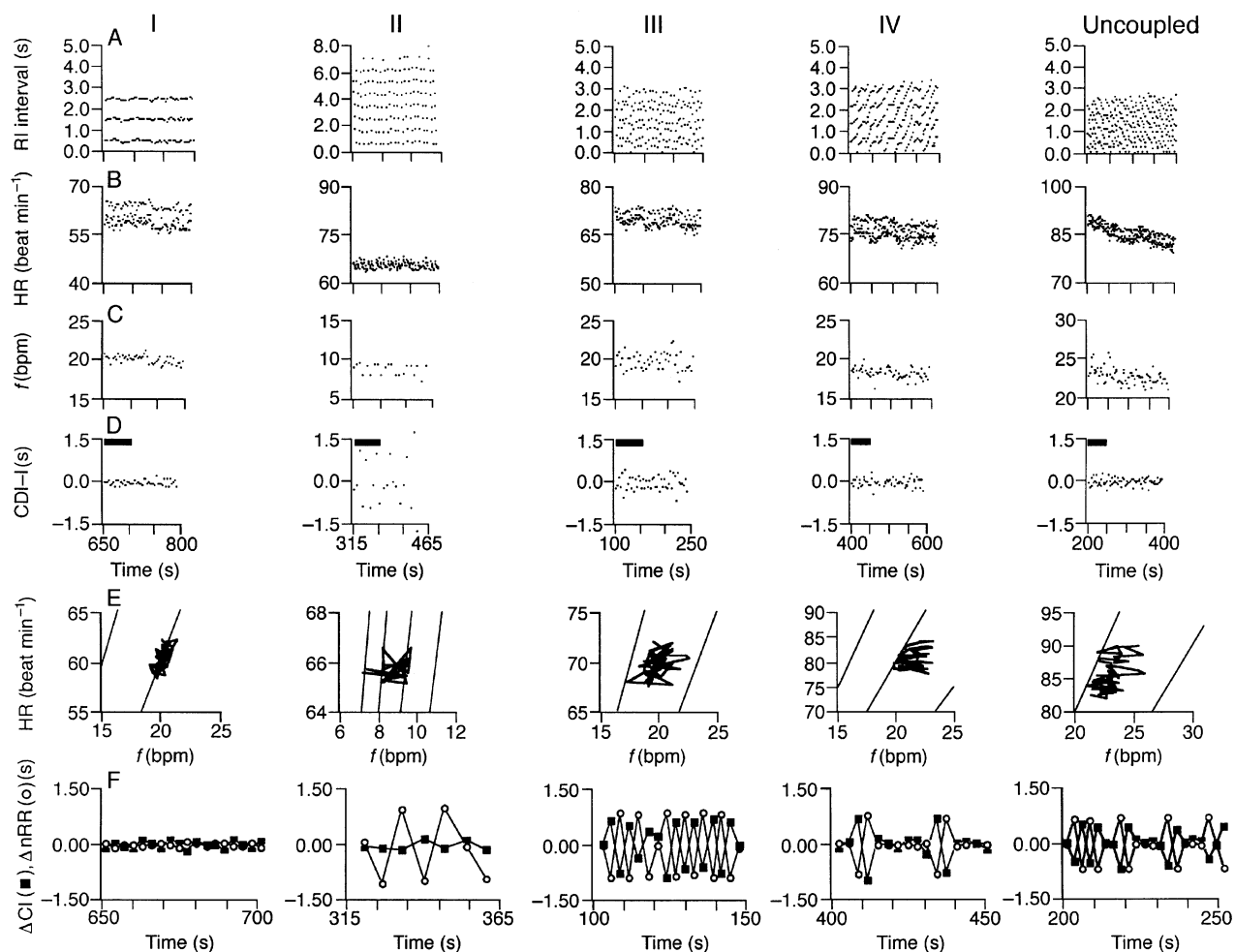


Fig 4 Heart rate and ventilatory variability according to coupling pattern. RI interval plots (A), heart rate time series (B), ventilatory frequency (f) (C), consecutive difference of the I-I time series (ventilatory period between consecutive inspiratory onsets (CDI-I) (D), pattern of variation on the HR/ f plot (E) and enlarged portion of the epoch corresponding to the horizontal bar in the CDI-I plot, showing the entrainment (ΔnRR) and coupling interval (ΔCI) components of ventilatory variability (F) (see text for explanation).

Examining individual RI time series we observed that patterns which did not fit exactly into one of the four classified coupling patterns could often be seen to be associated with HR and f values at the boundary of the two coupling patterns, with the RI time series pattern resembling a combination of each.

Having ascertained the above coupling pattern distributions, we went back to the raw data for each subject and, taking smaller epochs, irrespective of the number from each subject, determined the dominant extent of these distributions.

'Routes' taken by the HR/ f relationship

Plots of breath-to-breath change in HR and f , during the intraoperative period, showed a variety of behaviours. Although for some subjects routes were unrelated to integer ratio lines, for the majority a clear relationship was observed. At least four patterns of HR/ f movement were noted, each occurring in association with one of the four coupling patterns (Fig. 4).

- Movements along the integer ratio lines, seen in pattern I coupling.
- Jumps between integer ratio lines, seen in pattern II coupling.
- Oscillations in the space between integer ratio lines, seen in pattern III coupling.
- Small jumps back and forth between an integer ratio line and adjacent areas, seen in pattern IV coupling.
- No clear relationship to integer ratio lines, seen in uncoupled epochs.

The movement along integer ratio lines in pattern I was associated with small changes in both heart rate and breathing frequency. For patterns II, III and IV, the changes were primarily in respiratory frequency.

From these observations it was apparent that variation in breath cycle duration was different for each coupling pattern. Because a jump between two adjacent integer ratio lines corresponds to a change in breath duration of one heart period, we concluded that jumps of one heart period occur for pattern II, and for patterns III and IV the duration of

Table 2 Coupling interval (RI_{-1}), Shannon entropy, heart period, ventilatory frequency and measures of their variability according to coupling pattern. Measures are mean (SD) of the following variables, except for SH_{α} which is median (10th–90th percentiles). Mean RR interval (\overline{RR}); mean absolute value of the consecutive difference between RR intervals ($|\overline{CDRR}|$); mean ventilatory frequency (f); mean absolute value of the consecutive difference between ventilatory periods ($|\overline{CDI-I}|$); mean (SD) heart rate–ventilation frequency ratio ($\overline{HR/f}$, SD (HR/f)); mean RI_{-1} ($\overline{RI_{-1}}$); mean absolute value of the consecutive difference of the RI_{-1} interval ($|\overline{CDRI_{-1}}|$); and proportional Shannon entropy of the RI_{-1} intervals (SH_{α}). P values are for ANOVA, except for SH_{α} where P values are for Kruskal–Wallis. Comparisons between coupling patterns were made with t tests if ANOVA was significant and the Mann–Whitney U test where the Kruskal–Wallis test was significant. †Significantly different from pattern I; *significantly different from pattern II; ‡significantly different from pattern III; §significantly different from pattern IV

	Coupling type				Uncoupled	P
	I	II	III	IV		
n	37	49	16	29	38	
f	18.8 (4.0)*	10.6 (3.7)	20.4 (5.18)*	21.2 (4.87)*	19.68 (5.25)*	0.0001
$ \overline{CDI-I} $	0.12 (0.07)*	0.76 (0.621)	0.22 (0.14)*†	0.14 (0.08)*	0.20 (0.15)*†	0.0001
$\overline{HR/f}$	3.69 (0.85)*	6.12 (1.28)	3.62 (1.02)*	3.54 (0.66)*	3.83 (1.2)*	0.0001
SD (HR/f)	0.16 (0.15)*	0.62 (0.29)	0.25 (0.17)*	0.24 (0.25)*	0.28 (0.20)*	0.0001
\overline{RR}	0.91 (0.13)	0.96 (0.14)	0.89 (0.16)	0.84 (0.15)*	0.88 (0.13)*	0.005
$ \overline{CDRR} $	0.031 (0.02)	0.022 (0.014)	0.025 (0.014)	0.028 (0.02)	0.027 (0.017)	0.14
SH_{α}	0.42 (0.29–0.54)*	0.57 (0.46–0.68))	0.73 (0.66–0.82)†*	0.76 (0.68–0.84)†*	0.80 (0.75–0.82)†*§‡	0.0001
$\overline{RI_{-1}}$	0.53 (0.15)	0.60 (0.12)	0.47 (0.10)*	0.44 (0.09)†*	0.45 (0.08)†*	0.0001
$ \overline{CDRI_{-1}} $	0.07 (0.03)	0.17 (0.07)†	0.33 (0.09)†*§	0.21 (0.07)†*	0.35 (0.06)†*§	0.0001

changes are less than one heart period. Small transitions, considerably less than one heart period, occur for pattern I and these are proportional to the changes in RR interval as f follows HR along integer ratio lines.

Heart rate and breath cycle characteristics for each coupling pattern

Table 2 shows mean values for HR/f , RR interval, f and measures of their variability, for each coupling pattern.

HR/f

Pattern II coupling had a greater mean $\overline{HR/f}$ (approximately 6) than other coupling patterns (3–4). HR/f variability (SD (HR/f)) was also greatest for pattern II and, as expected, least for pattern I. Within the pattern II coupling epochs, entrainment ratio variability correlated with f , decreasing as f increased.

Ventilatory frequency

Mean ventilatory frequency differed significantly between coupling patterns (ANOVA $P < 0.0001$) and, as observed in the HR/f plot, was lower for pattern II coupling than for other patterns. Breath duration variability ($|\overline{CDI-I}|$) also differed; it was greatest for pattern II coupling and least for pattern I.

Heart rate

Heart rate was slower in pattern II coupling than for other coupling patterns or uncoupled epochs, but $|\overline{CDRR}|$ (a measure of sinus arrhythmia) was similar for all patterns.

RI_{-1} interval and RI_{-1} interval variability

RI_{-1}

The coupling interval, Ci , represents the interval between the triggering heart beat and the onset of inspiration. Changes in Ci therefore influence variations in breath cycle duration. Throughout this study, we regard RI_{-1} as an

approximation of the true coupling interval. Mean RI_{-1} interval was longest in pattern II coupling and least for patterns III, IV and uncoupled epochs. The observed RI_{-1} intervals were similar to previously reported values by us and others. There was a positive correlation between RI_{-1} interval and ventilatory ($P = 0.0001$, $r = 0.48$) period, in addition to heart period for all coupled epochs.

RI_{-1} variability

RI_{-1} variability differed between coupling patterns. Mean RI_{-1} consecutive difference was greatest for pattern III and uncoupled epochs, and least for pattern I. There was a significant difference in RI_{-1} variability between patterns I and II, patterns independent of heart rate and ventilatory frequency. This suggests that the changes in coupling interval relate to variations in entrainment ratio; greater variations in entrainment ratio are associated with larger variations in RI_{-1} interval.

Components of breath cycle duration for each coupling pattern

Initially, we defined each coupling pattern by the changes occurring in two variables, the entrainment ratio (n) and RI_{-1} ($\approx Ci$). Therefore, it can be seen from equation (1) that the nature of ventilatory variability differs according to coupling pattern, and that this variability can be divided into two components: (a) that caused by coupling interval variation ($\Delta Ci_{3/2} + \Delta Ci_{1/2}$); and (b) that caused by the entrainment ratio/mean RR interval variation ($n_2(\overline{RR}_2) - n_1(\overline{RR}_1)$). Comparing these variables for each coupling pattern we observed that the relative importance of each differs between patterns.

Pattern I

During pattern I coupling, the entrainment ratio (n) is constant and coupling intervals (Ci) vary little from breath

to breath. Ideally, if we regard n and C_i as constant, equation (1) reduces to $\Delta I - I = 0$, implying absence of ventilatory variability. In reality, C_i varies a little from breath to breath and RR interval may change between breaths because of heart rate trends. Figure 4 shows for pattern I the changes in the two variables ($n_2(\overline{RR}_2) - n_1(\overline{RR}_1)$) and ($\Delta C_{i_{3/2}} + \Delta C_{i_{1/2}}$). Breath-to-breath changes are very small for each component and therefore so too is overall variability. The observed value for $\Delta I - I$ was 0.12 s which is only 4% of the mean ventilatory period or 13% of the heart period. Ventilatory variability in pattern I is therefore small. Other than the small variation in coupling interval, as entrainment ratio is constant, the main contribution to variability is related to changes in mean heart period from one breath to the next (equation (1)). These small changes in ventilatory and heart period are directly proportional; ventilatory period follows the changes in heart rate and therefore the HR/ f relationship moves along lines of integer relationship (as in Fig. 4).

Pattern II

Pattern II coupling is characterized by variations in entrainment ratio. Coupling interval also is more variable than pattern I ($|\overline{CDRI}_{L1}|$ 0.17 vs 0.07 s). In Figure 4, although the variation in ($n_2(\overline{RR}_2) - n_1(\overline{RR}_1)$) is large, variation is also occurring in ($\Delta C_{i_{3/2}} + \Delta C_{i_{1/2}}$). The observed $\Delta I - I$ value was 0.76 s, which is 13% of the mean ventilatory period, or 80% of the mean heart period. It can be seen that although the change in ventilatory period is largely determined by the change in entrainment ratio, the effect of C_i may be significant. Thus quantal ventilatory variability, exactly equal to one heart period, is unlikely if C_i is highly variable. As the variability in C_i is inversely proportional to ventilatory frequency, exact heart period quantal variation is least probable at low ventilatory frequencies, and as frequency increases, other coupling patterns (I, III, IV) associated with different patterns of ventilatory variability become more likely. It should also be noted that n and mean RR are not independent. If n increases (or decreases) from one breath to the next, the value of the mean RR interval also changes. The additional heart period caused by the change in entrainment ratio has a duration fractionally longer than the preceding heart periods because of the waning effect of sinus arrhythmia towards the end of the breath. An increase in n therefore also causes an increase in mean RR interval for that breath.

Pattern III

Pattern III coupling is characterized by both alternating entrainment ratio and an RI_{L1} interval which alternates between two values. In all epochs of pattern III coupling, the shortest of two alternating RI_{L1} intervals is preceded by the ventilatory period spanning the greatest number of heart beats. Thus the coupling interval which follows the longest ventilatory period is shorter than the alternate interval. The observed $\Delta I - I$ value was 0.22, which is 7% of the mean ventilatory period or 25% of the mean heart period. Thus although pattern III coupling is associated with varying

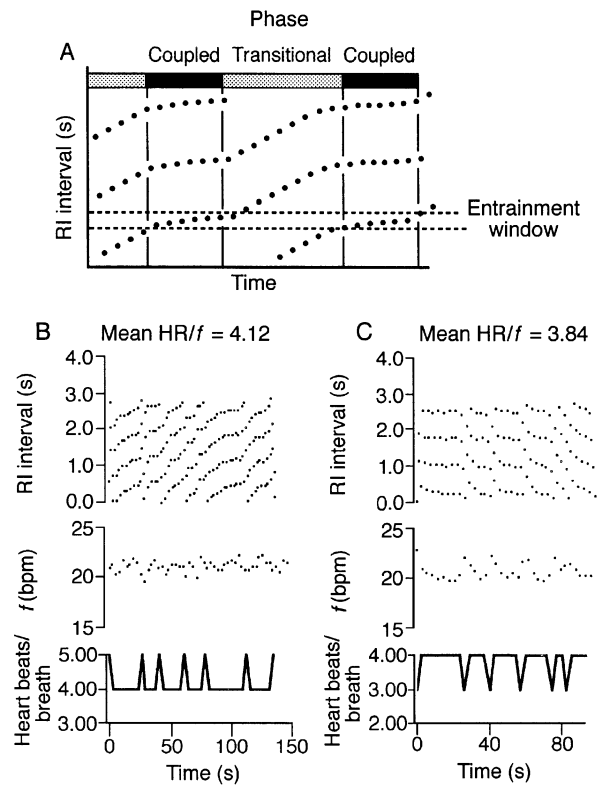


Fig 5 Pattern IV coupling: RI plot (schematic) showing coupled and transitional phases (A), pattern IV coupling with HR/ f a little over integer (B) and a little under integer ratio (C). Note in B, the upward sweeping RI plot, increasing number of heart beats/breath and brief decreases in ventilatory frequency associated with the transitional phases. Note in C, the downward sweeping RI plot, decreasing number of heart beats/breath and brief increases in ventilatory frequency associated with the transitional phases.

entrainment ratio, variation in C_i is large and related to n in such a way that the quantal fluctuations in breath cycle duration are comparatively small and considerably less than one heart period. The changes in ($n_2(\overline{RR}_2) - n_1(\overline{RR}_1)$) and ($\Delta C_{i_{3/2}} + \Delta C_{i_{1/2}}$) shown in Figure 4 for pattern III clearly demonstrate that the coupling interval variation cancels out a good deal of the entrainment changes.

Pattern IV

For pattern IV coupling, the changes in RI_{L1} interval and entrainment ratio are complex. Essentially there are two phases to pattern IV coupling: (i) a coupled phase in which heart and breathing rhythms exhibit pattern I coupling and (ii) a transitional phase in which heart and breathing rhythms slide out of synchrony until the next coupling phase (Figs 4, 5). The relative durations of the coupling and transitional phases were observed to be highly variable; the coupling phase was, on occasion, no more than a transient holding of the RI_{L1} at a constant level for a few breaths and on other occasions could extend into a long period of pattern I. The transitional phase could occur rapidly, over two breaths, or be extended over many breaths. During the transitional phase, the trend in RI_{L1} increases or decreases

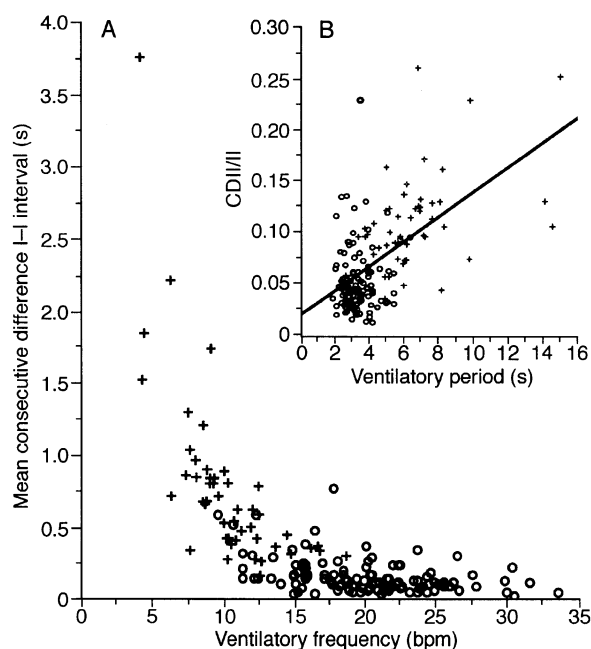


Fig 6 Ventilatory frequency vs ventilatory variability (mean absolute consecutive difference of ventilatory periods ($|CDI-I|$)). +=Pattern II; ○=patterns I, III and IV.

according to the HR/f ratio. If HR/f is a little over integer, the trend in RI_{-1} is increasing and if below integer the trend is decreasing (Fig. 5). Although entrainment ratio is constant during the coupling phase, during the transitional phase (Fig. 5) the number of heart periods in one of the breaths increases by one if $HR/f > \text{integer}$ and decreases by one if $HR < \text{integer}$. Because of the decrease or increase which occurs during the transitional phase, this pattern accommodates an HR/f ratio a little off integer ratio. The frequency of the transitions, and hence the frequency of an increase or decrease, varies according to the overall HR/f ratio. Thus if HR/f is close to integer, transitions are infrequent, if HR/f is further from integer, transitions are more common.

The comparative changes in $(n_2(RR_2) - n_1(RR_1))$ and $(\Delta Ci_{3/2} + \Delta Ci_{1/2})$ (Fig. 4) show a pattern in which, during the coupling phase, as in pattern I, little variation occurs in either variable. During the transitional phase, variation occurs in entrainment ratio and coupling interval but these effects, to a degree, cancel each other out. Comparison of ventilation frequencies with phases showed clear evidence of changes in ventilation during the transitional phase in some subjects. If the entrainment ratio decreased, the ventilatory period was shorter, and if increased, the ventilatory period was longer (Fig. 5). These ventilatory changes were most apparent where the transitional phase was rapid.

Relationship between ventilatory period and ventilatory variability

Taking all epochs, there was a non-linear negative relationship between ventilatory frequency and respiratory cycle variation ($|CDI-I|$). As f decreases, there is a rapid increase in $|CDI-I|$ below approximately 15 bpm (Fig. 6A). As a

proportion of the ventilatory period, $|CDI-I|$ also increased with increasing ventilatory period (Fig. 6B; $|CDI-I|/I-I$ vs $I-I$; $r=0.57$, $P<0.0001$). Thus breathing cycle variation increases disproportionately with increasing cycle duration. Plotting these relationships according to coupling pattern clearly demonstrates that the increase in variability at low ventilatory frequencies is predominantly associated with pattern II coupling and if pattern II epochs are excluded from the plot of $|CDI-I|/I-I$ vs $I-I$, there is no correlation between variability and ventilatory period ($r=0.04$, $P=0.65$). The ventilatory variability associated with pattern II coupling therefore explains the non-linear relationship between ventilatory frequency and variability.

Discussion

During spontaneous breathing under general anaesthesia, gross changes in heart rate and ventilatory frequency occur in response to changes in autonomic tone and ventilatory drive. Although intuitively we might believe that changes in the HR/f relationship occur smoothly, in fact the variation is characterized by sudden transitions, oscillations and constraint to lines of integer relationship. The rapid variations in the HR/f relationship are caused primarily by changes in ventilatory period. Although heart rate shows cyclic variations within a breath, caused by sinus arrhythmia, from breath to breath heart rate does not exhibit sudden transitions other than during abnormalities of rhythm. This difference between heart rate and ventilatory variation results from the different mechanisms of sinus arrhythmia and coupling. The variation in heart rate caused by sinus arrhythmia is a modulation of the sinus rate; RR interval variation caused by sinus arrhythmia is generally smooth and transient, varying only a little from one breath to the next.¹ In contrast, with coupling, cardiac activity triggers inspiratory onset and therefore (at least in pattern I and II coupling) ventilatory period is limited to multiples of the heart period.⁵ Variation in entrainment ratio, as occurs in pattern II coupling, creates quantal variations in breathing period approximating to one or more heart periods. On the HR/f plot, these changes are seen as jumps in breathing frequency between integer ratio lines.

Coupling patterns I–IV are distributed on the HR/f plot over specific regions and, as coupling pattern is associated with characteristic ventilatory patterns, the pattern of breath cycle variation differs according to the region of the plot and hence the values of HR and f . Breath cycle variation is therefore a non-linear phenomenon, that is there is no simple relationship between cycle duration, cycle variation and heart period. The different patterns of variation for each coupling pattern can be summarized as follows.

Pattern I

Pattern I occurs at breathing frequencies greater than approximately 10 bpm when HR and f are in integer ratio. The pattern is associated with little breathing variability

and what exists is related to small variations in coupling interval and mean RR interval. In pattern I, breathing frequency follows the changes in heart rate, moving along lines of integer relationship until another pattern of coupling ensues.

Pattern II

Pattern II coupling occurs at low breathing rates, irrespective of the HR/ f relationship. The number of heart periods elapsing before inspiration is triggered varies irregularly from breath to breath. Quantal jumps in breathing period may therefore be seen as entrainment ratio varies. At low breathing frequencies, the coupling interval varies considerably from breath to breath and therefore the jumps are rarely an exact multiple of the heart period. When coupling interval is more constant (generally at higher f), the jumps approximate more closely to quanta of one heart period.

Pattern III

Pattern III coupling occurs at breathing rates greater than 12 bpm when HR and f are in half integer relationship. It is associated with alternating entrainment ratio (as in 3,4,3,4,3,4,3:1, etc) and RL_{-1} interval (Fig. 4). Because the RL_{-1} interval is shorter if the ventilatory period has been prolonged by one heart period, quantal fluctuations in ventilatory period occur but these are significantly less than one multiple of the heart period.

Pattern IV

Pattern IV coupling occurs at breathing frequencies greater than 12 bpm where HR and f are a little over or below integer relationship. The coupling is associated with alternating coupled–transitional phases. During the coupled phase the pattern is similar to I with little breath cycle variability observed. Over the transitional period however, an increasing or decreasing entrainment ratio is associated with transient lengthening or shortening of the breath cycle period.

Therefore, the behaviour of the breathing frequency time series is determined by: (a) the specific pattern of coupling (patterns I–IV) which influence the variations in coupling interval and entrainment ratio, (b) the heart period and (c) the underlying ventilatory drive which must influence overall ventilatory frequency. As the pattern of coupling is influenced in a non-linear manner by the values of HR and f , and heart period in turn is influenced by autonomic neural, humoral and mechanical factors, it is plain that ventilatory variability is a consequence of the complex interaction of related factors. The non-linear nature of the variability is therefore understandable, explaining much of the difficulty researchers have found in attempting to find underlying order in ventilatory variation using spectral and non-linear methods.^{15–18} Coupling is strong during anaesthesia and sleep and weak in awake aroused subjects.^{19,20} Under waking

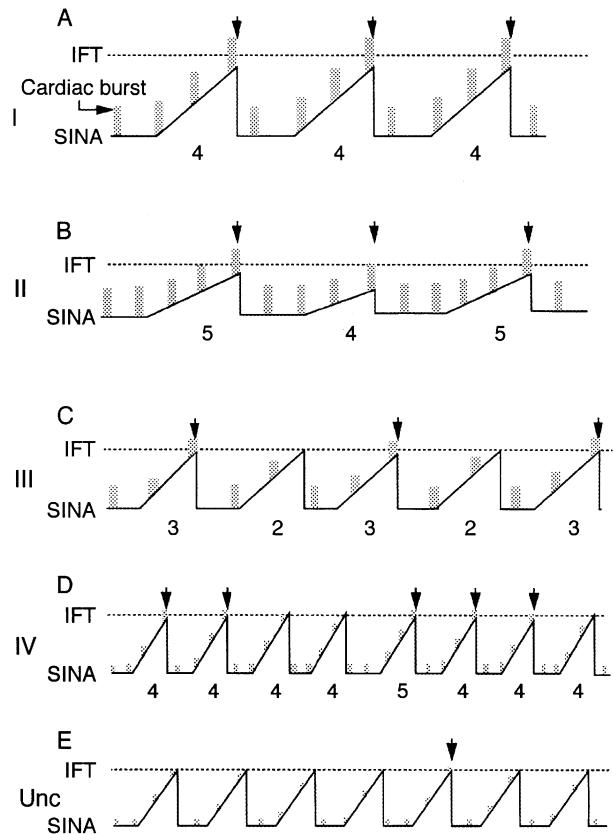


Fig 7 Proposed hypothesis for generation of coupling pattern. Ramping spontaneous inspiratory neuronal activity (SINA) initiates inspiration when the inspiratory firing threshold (IFT) is reached. Superimposed on the SINA are cardiac-related bursts which may also trigger inspiratory onset (arrow). See discussion for a full explanation.

conditions therefore, the addition of cognitive factors could be expected to add further to the complexity of ventilatory variability.

Although the cause of the specific coupling patterns is not known, this would be of considerable relevance to an understanding of ventilatory variability. Without electrophysiological data, we suggest a tentative, explanatory hypothesis. Assume that inspiration starts when increasing spontaneous inspiratory neuronal activity reaches an inspiratory firing threshold. At the firing threshold, inspiration occurs and the inspiratory neurones are reset to a basal level and are refractory for a short period. The slope of the spontaneous neuronal activity is determined by the intrinsic respiratory drive. Ventilatory frequency under these conditions we will call *intrinsic* ventilatory frequency. We suggest that coupling occurs because a signal of cardiovascular origin reaches the brainstem and provides a cardiac-related burst which augments intrinsic spontaneous neuronal activity. The duration of this augmentation is short but it provides a window during which inspiration is initiated if the augmented spontaneous activity exceeds the firing threshold (Fig. 7). The preceding ventilatory period of a cardiac burst-initiated inspiration will always be shorter than one which occurs spontaneously. If ventilatory drive

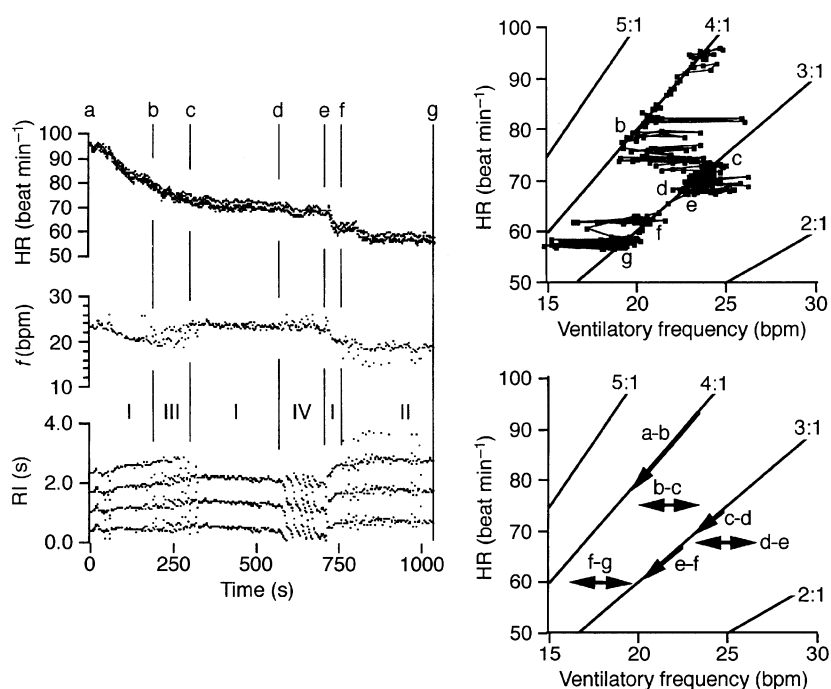


Fig 8 Example of multiple coupling patterns occurring over 18 min, with heart rate, ventilatory frequency and RI interval vs time (left) and an HR/ f plot (right). Heart rate decreases throughout the time series and therefore the HR/ f plot can be followed from top to bottom. From the initial values (a), the decrease in heart rate is accompanied by a corresponding decrease in breathing frequency during a period of 4:1 pattern I coupling; this is seen as a downward movement along the 4:1 integer ratio line. At b, heart rate alone continues to decrease, the coupling pattern changes to pattern III and ventilatory frequency shows oscillations between the smaller frequency and its initial value. On the HR/ f plot, this is seen as an oscillation between the 3:1 and 4:1 integer ratio line. At c, ventilatory frequency stabilizes at its initial value and both heart rate and ventilatory frequency decrease slightly in 3:1 integer ratio during another period of pattern I coupling. At d, there is a small decrease in HR and a change to pattern IV coupling with a downward sweeping RI plot (i.e. HR/ f is now a little less than an integer). At e, fentanyl 50 μ g has been administered and both HR and f decrease; HR/ f moves down the 3:1 integer ratio line during a transient period of pattern I coupling. At f, a pattern II emerges as ventilatory frequency shows intermittent quantal falls. We suggest this time series can be interpreted as follows. Intrinsic ventilatory frequency may be reasonably constant until time e, but between a and b, decreasing heart rate has dragged the actual ventilatory frequency downwards (at 4:1 entrainment) until a change to a lower entrainment ratio allows it to return to its initial frequency. Ventilatory frequency therefore returns, via pattern III and then I coupling to a 3:1 entrainment ratio, returning ventilation frequency to its original value. Later administration of the opioid caused a decrease in ventilatory frequency and a decrease in heart rate. While initially maintaining a 3:1 pattern I entrainment, the greater effect of the opioid on ventilatory frequency causes it to occasionally fluctuate (pattern II) to lower values.

(and hence rate) is low, the slope of the spontaneous activity is small and therefore, unless heart rate is very slow, the cardiac-related bursts will always trigger inspiratory onset (e.g. Fig. 7B). Small changes in inspiratory slope or magnitude of the cardiac-related bursts leads to a variable number of heart beats before each inspiration. This would explain why pattern II is present at low f . At greater breathing frequencies, the slope of the spontaneous inspiratory activity is greater, increasing the likelihood that inspiration is initiated by natural inspiratory activity. If intrinsic ventilatory frequency is close to an integer multiple of cardiac frequency, cardiac bursts initiate every inspiration (pattern I), as in Figure 7A. If intrinsic ventilatory frequency is in half integer relationship with HR, then every second breath is initiated by the cardiac burst, and alternate breaths are initiated by spontaneous firing. Because the preceding ventilatory period of the spontaneously initiated inspiration is longer than the cardiac burst-initiated inspiration, this gives the appearance of pattern III (Fig. 7C). We suggest that in some subjects, the effect of the cardiac burst may

be less, which is consistent with the observation that some individuals couple strongly throughout their time series and others show little or absent coupling. In this situation, patterns I and II, as above, may still occur. However, if HR/ f is not quite an integer ratio then for some periods, breaths are initiated by the reduced cardiac burst, but as the two rhythms go out of synchrony, spontaneously initiated inspiration returns. This pattern would be repeated, giving the alternating coupled–transitional phases of pattern IV (Fig. 7D). If HR/ f is not in integer relationship and burst magnitude is small, few if any breaths would be initiated by the cardiac burst (Fig. 7E), particularly if the spontaneous inspiratory activity slope was great (at higher frequencies). This is consistent with the presence of uncoupled epochs only at breathing frequencies >10 and would explain why the uncoupled epochs were mainly non-integer.

During pattern I coupling there is constant entrainment of ventilation by the cardiac cycle. Ventilatory frequency therefore may be ‘dragged along’ by changes in heart rate as the HR/ f relationship moves along an integer ratio line

(Fig. 8). It follows that small changes in measured ventilatory frequency need not signify any change in intrinsic ventilatory frequency. It is therefore important that in pharmacological and physiological studies of anaesthetized, and perhaps also naturally sleeping subjects, researchers should not misinterpret changes in breathing frequency as a change in the underlying ventilatory drive, which is more accurately measured as minute ventilation (frequency \times tidal volume).

Coupling was observed to be invariably present at low ventilatory frequencies. As coupling is a triggering of ventilatory onset by cardiac action, it follows that inspiration is usually triggered by cardiac action when ventilatory frequencies are low. Above, we put forward a hypothesis to explain this phenomena and it can be seen (for example in Fig. 7B) that if the cardiac burst was absent, a significant decrease in ventilatory frequency would occur. Therefore, it may be important to consider if coupling is a significant trigger to breathing at low ventilatory frequencies. In the context of our study, bradypnoea was almost certainly associated with opioid administration. Although we cannot exclude a specific effect of the opioid, it is possible that the cardiac cycle assumes a role as respiratory pacemaker during ventilatory depression. As coupling occurs during normal sleep, it would be interesting to explore the relationship between coupling and central sleep apnoea and SIDS. It is perhaps also significant that disturbances in cardiac rhythm and in particular bradycardia and even frank sinus arrest may occur in association with central sleep apnoea. How these prolongations in heart period affect ventilation is also perhaps an area worthy of future study.

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