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Cardioventilatory coupling during anaesthesia

D. C. GALLETLY AND P. D. LARSEN

Summary

In 20 spontaneously breathing patients undergoing minor surgical procedures under general anaesthesia, we examined the timing relationship of heart beat and ventilation. Patients received propofol 2–2.5 mg kg^{-1} and fentanyl 1 μg kg^{-1} and breathed a mixture of 1–1.5% isoflurane and 66% nitrous oxide in oxygen. We recorded ECG R wave times and the start of each inspiration. We observed that: (1) all subjects showed evidence of phase coupling in which heart beats occurred at constant phases of the ventilatory cycle; (2) there was a significant preference for whole number ratios of heart rate to ventilatory frequency; (3) phase coupling was associated frequently with quantal changes in heart rate or ventilatory frequency, or both; (4) six coupling patterns were described according to the timing relationship between the ECG R wave and start of inspiration and according to changes in the number of heart beats within each ventilatory period; (5) phase coupling was achieved primarily by transient changes in ventilatory period. Phase coupling, in concert with respiratory sinus arrhythmia, may optimize the performance of the thoracic pump, matching cardiac filling to venous return. Coupling may therefore have anaesthetic relevance in conditions of impaired cardiac performance or hypovolaemia. (*Br. J. Anaesth*. 1997; **79:** 35–40).

Key words

Heart, heart rate. Ventilation, frequency. Monitoring, electrocardiography. Monitoring, ventilation. Cardiorespiratory system, effects.

Heart rate variability is a consequence of periodic fluctuations in sympathetic and parasympathetic outflow to the heart. Baroreflex inputs to autonomic neurones within the brainstem modulate this efferent activity and, in turn, ventilation modulates the degree to which these baroreceptor inputs influence the firing of autonomic neurones. Respiratory sinus arrhythmia is the result of this ventilatory modulation.

In addition to sinus arrhythmia, heart beats may become "phase coupled" to respiration, such that heart beats occur at constant phases of the respiratory cycle. Although this coupling is poorly seen in alert and active human subjects, it is clearly present during sedation,[1] sleep[2] and in conditions of low cognitive and behavioural activity.[3]

Cardioventilatory coupling in mammals was first described by Walter Coleman in 1921 after experiments performed at the London Zoological Gardens in Regents Park. In one of several classic articles[4,5] he describes how: "The movements of the whiskers of a resting leopard were perfectly regular and indicated its heart rate as 54. The metronome was set at that rate with subdued sound, and expansions of the lungs ceased at strokes of metronome as follows: 5, 5, 5, 6, 5, 5, 5, 6, 5, 5, 5, 6, 3. The animal stirred at 3. This and many other tests indicate that usually with animals at rest and always during sleep the breath begins at multiples of the heart-rate".

In humans, cardiorespiratory synchronization was first described by Galli in 1924.[6] In subsequent years the subject was largely forgotten until, from the 1950s, groups of German physiologists (Hildebrandt, Bucher, Engel, Raschke, Kenner and others)[2,3,6–10] attempted to further define the interaction and determine its mechanism. The subject of cardioventilatory phase coupling is largely confined therefore to German language publications and despite its possible relevance, the anaesthesia literature is devoid of discussion on the subject.

In 1972, Engel, Jaeger and Hildebrandt,[7] using statistical methods, demonstrated the presence of phase coupling in anaesthetized adults and children. Since then advances in computer-based digital signal processing and graphical analysis techniques have made it possible for a more detailed examination of the phenomenon. In this study we sought to further define the frequency and nature of cardioventilatory coupling in patients undergoing surgical procedures under general anaesthesia.

Patients and methods

After obtaining Ethics Committee approval, we studied 20 consenting, unpremedicated ASA I and II adult patients undergoing elective orthopaedic or gynaecological surgery. None was taking regular medications or had evidence of cardiorespiratory disease.

Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and maintained by spontaneous inhalation of

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1–1.5% isoflurane and 66% nitrous oxide in oxygen. After induction, a laryngeal mask was inserted and increments of fentanyl 50–100 μg or morphine 5–10 mg were given as required. In two patients, vecuronium was administered for neuromuscular block and in these, mechanical IPPV was applied to give an end-tidal carbon dioxide partial pressue of 4.7–5.3 kPa. In both patients, spontaneous ventilation recordings were obtained before neuromuscular block.

We monitored arterial oxygen saturation (Sp_{O_2}), end-tidal carbon dioxide concentration, end-tidal isoflurane concentration (Datex AS3), heart rate, ECG (lead CM_5, Corometrics Neo-Trak 502) and timing of inspiration.

Ventilatory timing was measured by incorporating a Ruben non-return valve into the T of the circle absorption system. The valve was modified by addition of a photodetector and light beam across the path of the valve shuttle. This generated a 1.5-V square wave signal while the valve was open (i.e. from start inspiration to end inspiration). Using this system a small delay may be expected from the onset of inspiration until opening of the valve shuttle, however, we considered this delay small in comparison with the duration of a heart period.

For a minimum of 5 min, ECG and photodetector output were recorded continuously using a Macintosh IIcx computer with 16 bit ADC board (National Instruments) and a sampling rate of 500 Hz. Recording of cardioventilatory data began after laryngeal mask insertion and continued until the end of surgery.

ANALYSIS

Analysis of phase coupling was based on the method described by Kenner, Pessenhofer and Schwaberger.[8] From the stored ECG data, we measured the time of each R wave peak and, from the ventilatory signal, we determined the time of each inspiratory onset. From these data, we calculated the interval between each R wave and the following, in addition to the preceding, start of inspiration (RI intervals). RI intervals for each heart beat were then plotted against time of R wave occurrence (RI plot). RI intervals for R waves preceding the inspiration were given a negative subscript and RI intervals after an inspiration were given a positive subscript: RI_{-1} for the beat preceding the inspiration and RI_{+1}, RI_{+2}, etc, for beats after the inspiration

A fixed relationship, or coupling, between heart beats and inspiration is revealed in an RI plot as horizontal banding in which values of $RI_{\pm n}$ maintain relatively constant values over time.

In addition to calculating RI intervals, we determined the degree to which heart rate and ventilatory frequency approached a whole number ratio. We calculated for all time series and for each breath the ratio of heart rate to ventilatory frequency where heart rate was calculated from the median of seven consecutive beats. Integer preference (IP) was defined as a heart rate to ventilatory frequency ratio subtracted from its closest integer value (a ratio of 3.67 becomes $3.67-4=-0.33$, a heart rate to ventilatory frequency ratio of 5.01 becomes $5.01-5=0.01$). The mean absolute value ($|IP|$) of this integer preference was calculated for each subject. $|IP|$ values close to 0 indicate an integer ratio.

As a measure of respiratory sinus arrhythmia we took a representative 256-s, artefact-free segment of the RR interval time series. Using previously described methods we performed a fast Fourier analysis on this segment.[11] A measure of ventilatory heart rate modulation was determined by calculating the area under the power spectrum curve between 0.15 and 0.4 Hz.

Statistical analysis was performed only on spontaneously breathing segments in those patients who subsequently underwent artificial ventilation.

All software was purpose written in LabView 2 (National Instruments).

Results

Mean patient age was 39 (range 18–66) yr; 15 were female and mean duration of data recording was 23 (range 6–70) min. Cardioventilatory coupling was observed in all patients. A representative example of data obtained from one subject is shown in figure 1.

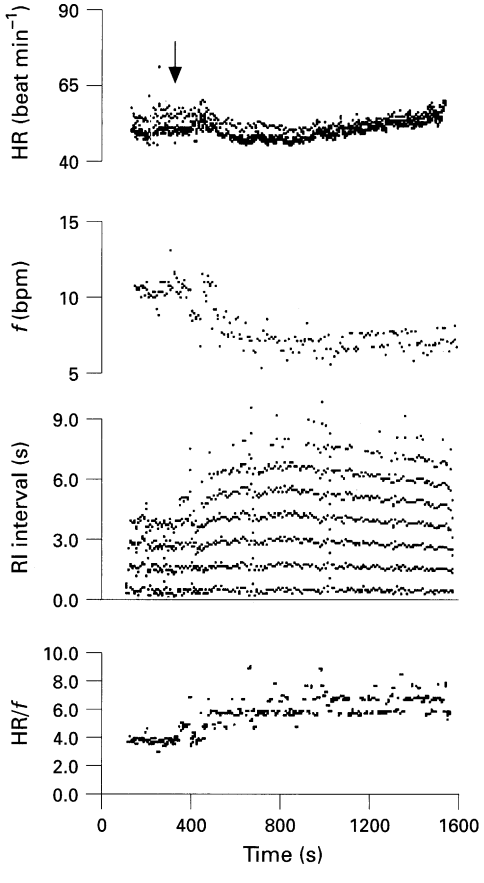

Figure 1 Representative data from one spontaneously breathing patient. Fentanyl 50 μg i.v. was given at 400s (arrow). Beat-to-beat heart rate (HR), breath-to-breath ventilatory frequency (*f*), RI interval and heart rate/ventilatory frequency ratio (HR/*f*) are shown. The RI plot shows horizontal banding indicating cardioventilatory coupling. The increase in number of bands reflects the increasing number of RI intervals per breath as ventilatory frequency decreases after administration of the opioid. Note quantal changes in HR and *f* (shown as banding of their individual time series) and whole number steps in HR/*f* ratio.

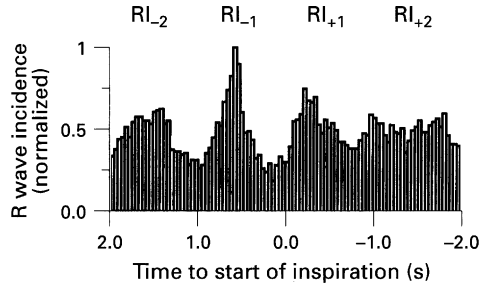

Figure 2 Histogram of R wave occurrence, relative to start of inspiration, normalized and averaged for all subjects.

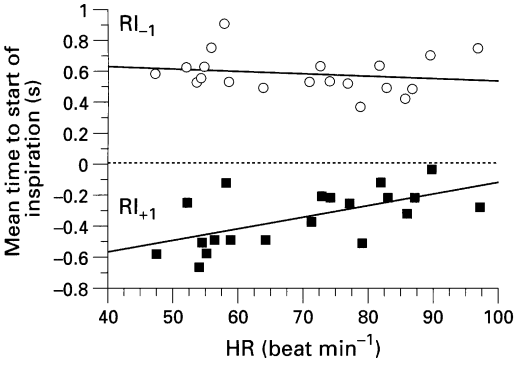

Figure 3 Mean RI_{-1} and RI_{+1} for 20 subjects *vs* mean heart rate (HR). Note the relative constancy of RI_{-1} independent of RR interval (heart rate)

R WAVE ALIGNMENT TO INSPIRATION

Figure 2 is an averaged and normalized histogram of RI intervals for all subjects and shows a peak R wave incidence, corresponding to RI_{-1}, at 0.5 s before the start of inspiration. The peak corresponding to RI_{+1} was less apparent as were other R wave alignments. Thus relative to start inspiration, RI_{-1} was the least variable R wave position. Mean RI_{-1} values for all subjects were 0.51 (SD 0.1) s. Mean RI_{+1} inversely correlated with mean heart rate ($P<0.005$) whereas the correlation between mean RI_{-1} and heart rate was not statistically significant (fig. 3).

QUANTAL HEART RATE AND VENTILATORY FREQUENCY ADJUSTMENTS

Both heart rate and ventilatory frequency were observed to fluctuate at times in a quantal manner. This appeared as banding of the beat-to-beat heart rate (or RR interval) and breath-to-breath ventilation rate time series (fig. 1).

Quantal heart rate changes were observed only during periods of cardioventilatory phase coupling. At these times, because R waves occurred at roughly constant intervals after the start of inspiration, RI_{+1} was influenced differently by vagal withdrawal than RI_{+2}, RI_{+3}, and so on (fig. 4). Thus the RR interval after inspiration was shorter than subsequent intervals giving a banded appearance to the heart rate time series. The width of these bands varied depending on the degree of respiratory sinus arrhythmia.

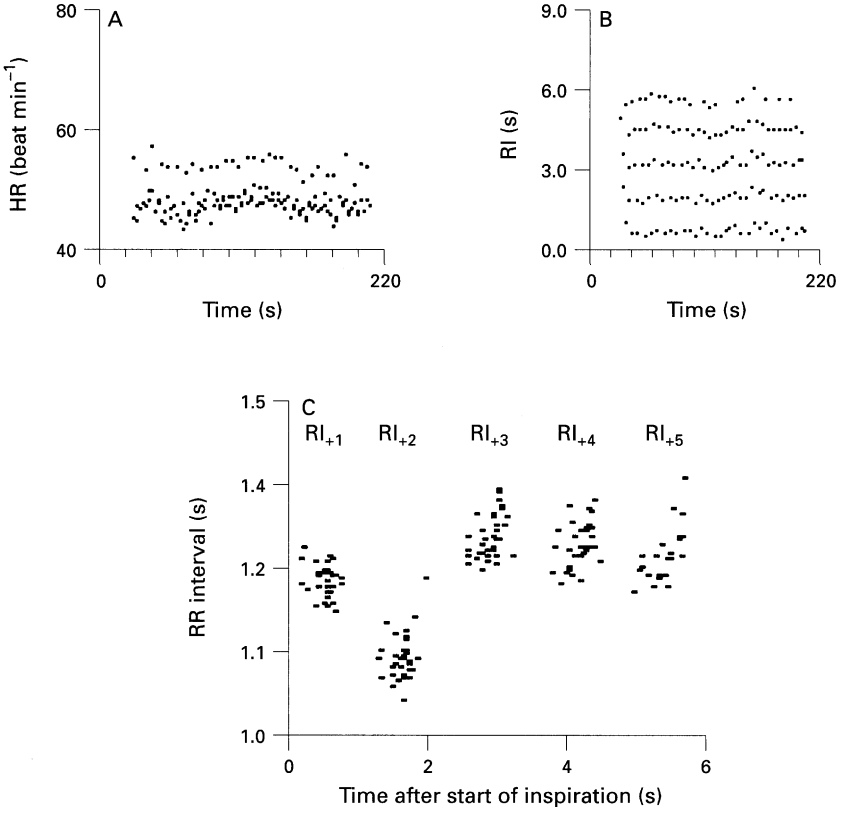

Figure 4 A: Heart rate (HR) time series, B: RI plot and C: RR interval plotted against time after start of inspiration. Note the quantal changes in HR (shown as banding of the HR time series) as a result of the greater degree of vagal withdrawal imposed on RI_{+1} compared with RI_{+2} RI_{+3}, RI_{+4} and RI_{+5}.

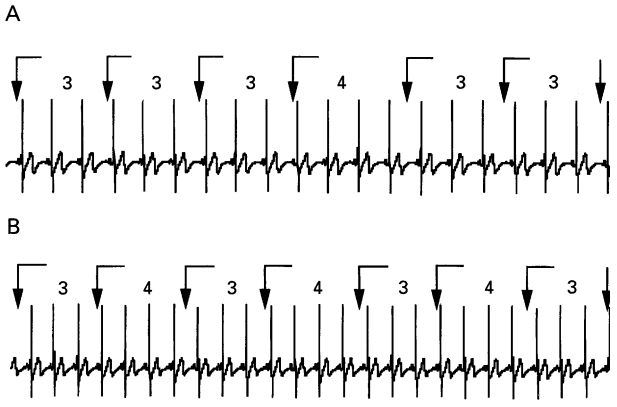

Figure 5 ECG and ventilation in one subject showing; A: a single prolongation in ventilatory period during a synchronized pattern of constant 3:1 ratio coupling; B: alternating 3:1, 4:1 coupling with alternating RI interval, also shown in figure 8D. Arrow indicates start inspiration and horizontal bar the duration of inspiration; numbers refer to heart beats within each ventilatory period.

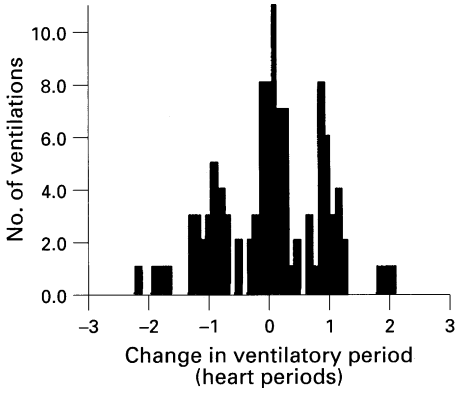

Figure 6 Histogram of breath-to-breath change in ventilatory period as a multiple of the heart period. Data were taken from the subject of figure 1 and show that changes in ventilatory period were frequently in one heart period steps.

Quantal changes were also observed in ventilation. The banded appearance in a ventilation rate time series is seen in figure 1. The quantal change in ventilatory frequency corresponds to transient rate fluctuations as ventilation jumps between different heart rate to ventilatory frequency integer ratios while heart rate is relatively constant. An example is seen in figure 5A where 3:1 coupling is interrupted by a single 4:1 coupling. Because the ventilatory period is extended by approximately one heart period, the observed ventilatory frequency time series banding width (fig. 1) corresponds to approximately one heart period. The histogram in figure 6 shows the distribution of ventilatory periods measured as a multiple of the heart period in one subject and demonstrates the quantal ventilatory adjustments at multiples of the heart period.

INTEGER PREFERENCE

Synchronized coupling, where the heart rate to ventilatory frequency ratio (and number of heart beats within each ventilatory period) remained a constant whole number for periods longer than 60 s,

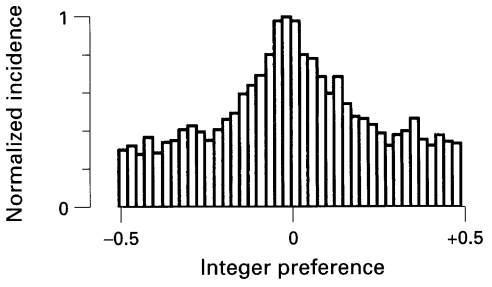

Figure 7 Histogram of integer preference, normalized and averaged for all subjects.

was observed in 50% of subjects. The mean |IP| for all subjects was 0.21 (0.07). This was significantly different ($P<0.05$; Student's t test) from a mean of 0.25 which would be expected if there was no preference for integer or non-integer ratio. Figure 7 shows the histogram of IP values averaged and normalized for all subjects; a clear peak at IP = 0 is seen. Rapid transitions between integer ratios are also seen in the heart rate to ventilatory frequency ratio plot of figure 1 and in figure 5.

Although we observed the expected diminution of respiratory sinus arrhythmia with age (correlation between area under the ventilatory portion of the RR interval spectrum and age, $P<0.05$), the presence of coupling (RI plots) appeared unaffected and there was no correlation between age and integer preference (mean |IP|).

PATTERNS OF COUPLING

A variety of coupling patterns were observed in the RI plots with subjects commonly showing transition from one to another.

(a) Synchronous coupling (fig. 8A) with constant RI alignments and a strict whole number heart rate to ventilatory frequency ratio. This was observed, for periods longer than 60 s, in 10 (50%) subjects.

(b) Uncoupled with unstructured RI plots (fig. 8B). This was seen in only two (10%) subjects both of whom demonstrated high degrees of respiratory sinus arrhythmia.

(c) Uncoupled with slowly changing RI alignments (fig. 8C). This was observed during periods of intermittent positive pressure ventilation (two of two subjects) and for short periods in six (30%) spontaneously breathing subjects.

(d) Non-synchronous coupling with double banding of the RI plot (fig. 8D). RI intervals for one breath were similar to those two breaths in advance, however consecutive breaths had different RI intervals. Ventilatory period and heart rate to ventilatory frequency ratio alternated between two values. The jumps in ventilatory period were not exactly equal to one heart period, thus RI alignment is slightly different for alternate breaths. This pattern was seen in six subjects (30%). An example is shown in figure 5B.

(e) Coupling with a similar appearance to synchronized coupling but with a varying number of heart beats within each ventilatory period (fig. 8E). This common pattern (100% of subjects) occurred where the heart rate to ventilatory frequency ratio

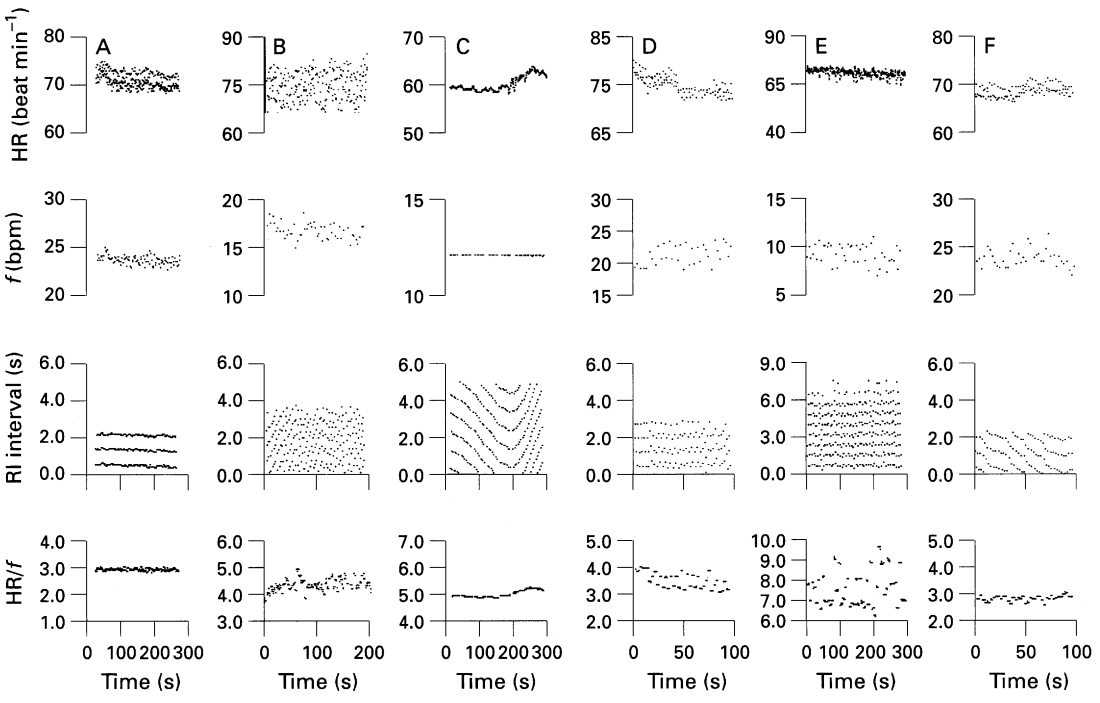

Figure 8 Six observed patterns of cardioventilatory coupling. For each coupling pattern, the figure shows beat-to-beat heart rate (HR), breath-to-breath ventilatory frequency (*f*), RI interval and heart rate/ventilation rate ratio (HR/*f*).

varied but quantal changes in ventilatory period allowed synchronization of R waves to inspiration for each breath.

(f) Non-synchronous coupling with slurring of the RI plot at preferred RI alignments was seen in five (25%) subjects. In figure 8F heart rate and ventilatory frequency are a little out of whole number ratio and RI_{-1} values gradually change away from the preferred 0.5 s. As the RI_{-1} value approaches 0 however, a rapid change in ventilatory periods brings the RI value back to the preferred alignment.

Discussion

In this study we observed cardiorespiratory phase coupling in all of our spontaneously breathing anaesthetized subjects. Although the specific pattern of coupling varied between subjects, and over time, it was rare to observe complete absence.

In order to achieve synchronization of the heart rhythm with ventilation, adjustments to either heart beat timing or ventilation, or both, must occur. We observed that constancy of RI intervals was most pronounced for the R wave immediately preceding inspiration rather than that which follows. RI_{-1} therefore was the most constant RI interval. This suggests that start of inspiration is triggered by an event associated with the preceding heart beat. As fluctuations in RR interval caused by respiratory sinus arrhythmia (fig. 4) occurred only after the start of inspiration, it is likely that these RR fluctuations are of little importance for RI alignment and therefore it is the inspiratory onset itself which is being adjusted to the preceding heart beat. These ventilatory adjustments were seen in our previous study of midazolam sedated patients and in this study (fig. 1) where ventilatory period jumped in a quantal manner to maintain RI alignment despite changing numbers of R waves within each ventilatory period. Kenner, Pessenhofer and Schwaberger[8] noted in rabbits that coupling was achieved by rapid and transient fluctuations in ventilatory frequency and observations of Hinderling,[10] in 1967, that coupling persists in patients with artificial cardiac pacemakers, clearly indicates the importance of modulation of ventilatory period. Quantal ventilatory frequency changes were first noted in anaesthesia by Goodman,[12 13] who ascribed the phenomena to a central multifrequency oscillator.

Afferent cardiovascular input which triggers phase shifts in ventilatory timing are not known with certainty. In experimental animals, coupling is abolished by vagotomy[8] and deafferentation of vagal fibres from the right atrium[14] and persists in the presence of artificial cardiac pacing and artificially induced pulsatile carotid flow.[9] Thus, afferent baroreceptor or atrial stretch receptor information, or both, is probably important in mediating phase coupling.

Control of cardioventilatory timing is thus a balance between respiratory sinus arrhythmia, achieved through heart rate adjustment, and phase coupling achieved through ventilatory adjustment. The relative importance of each however may vary depending on the subject and condition. It is known that with increasing age, respiratory sinus arrhythmia diminishes, whereas we observed no effect of age on coupling or integer preference. In contrast, sinus arrhythmia persists at all levels of cognitive arousal, whereas phase coupling is seen best during relaxation, sleep and anaesthesia.

It is traditionally believed that the increase in heart rate during inspiration (respiratory sinus

arrhythmia) is of practical importance. As the negative intrathoracic pressure of inspiration causes increased venous return, vagolysis during the inspiratory period augments the performance of this "thoracic pump" and, with the Starling mechanism, helps match cardiac output to venous return. It is possible that cardioventilatory phase coupling may optimize the thoracic pump further. The R wave occurs approximately 0.5 s before the onset of inspiratory airflow. At inspiration therefore, ventricular ejection has occurred and the AV valves are opening, allowing rapid ventricular filling. In the presence of phase coupling, ventricular filling occurs at the same time that venous return is increasing as a result of negative intrathoracic pressure. Because of vagal withdrawal caused by respiratory sinus arrhythmia, a shortened RR interval occurs for the next heart beat allowing further filling and ejection of the heart during the inspiratory period. Thus phase coupling, in concert with sinus arrhythmia and the Starling mechanism, may optimize matching of venous return and cardiac filling.

In summary, respiratory sinus arrhythmia and cardioventilatory phase coupling together contribute to the timing of breathing and heart beats during anaesthesia. The phenomenon is readily apparent to the anaesthetist if excursions of the breathing bag and ECG tone are compared in spontaneously breathing patients. Observation of this link between breathing and heart beats clearly indicates the intimate relationship between cardiac and ventilatory dynamics.

References

1. Galletly DC, Larsen PD. Coupling of spontaneous ventilation to heart beat during benzodiazepine sedation. *British Journal of Anaesthesia* 1997; **78**: 100–101.
2. Raschke F. The respiratory system—features of modulation and coordination. In: Haken H, Koepchen HP, eds. *Rhythms in Physiological Systems*. Berlin: Springer-Verlag, 1991; 155–164.
3. Hildebrandt G, Daumann FJ. Die koordination von puls-und aterhythmus bei arbeit, *Internationale Zeitshriff fur angewandte Physiologie einshliesslich Arbeitsphysologie* 1965; **21**: 27–48.
4. Coleman WM. On the correlation of the rate of heart beat, breathing, bodily movement and sensory stimuli *Journal of Physiology (London)* 1921; **54**: 213–217.
5. Coleman WM. The psychological significance of bodily rhythms. *Journal of Comparative Psychology* 1921; **1**: 213–220.
6. Raschke F. The hierarchical order of cardiovascular–respiratory coupling. In: Grossman P, Janssen KHL, Vailt D, eds. *Cardiorespiratory and Cardiosomatic Psychophysiology*. London: Plenum Press, 1986; 207–218.
7. Engel P, Jaeger A, Hildebrandt G. Uber die beeinflussung der frequenz- und phasenkoordination zwischen herzschlag und atmung durch verschiedene narkotika. *Arzneimittel Forschung (Drug Research)* 1972; **22**: 1460–1468.
8. Kenner T, Pessenhofer H, Schwaberger G. Method for the analysis of entrainment between heart rate and ventilation rate. *Pflugers Archiv* 1976; **363**: 263–265.
9. Bucher K, Bucher KE. Cardio-respiratory synchronisms: synchrony with artificial circulation. *Research in Experimental Medicine* 1977; **171**: 101.
10. Hinderling P. Weitere charakterisierung von synchronismen zwischen kreislauf und atmung. *Helvetica Physiologica et Pharmacologica Acta* 1967; **25**: 24–31.
11. Gallety DC, Tobin P, Robinson B, Corfiatis T. Effect of 30% nitrous oxide inhalation on spectral components of heart rate variability in conscious subjects. *Clinical Science* 1993; **85**: 389–392.
12. Goodman NW. Chaos in ventilatory timing in anaesthetized man? *British Journal of Anaesthesia* 1990; **65**: 274–275.
13. Goodman NW. Bimodality of expiratory time in patients anaesthetized with propofol. *British Journal of Anaesthesia* 1995; **74**: 129–133.
14. Meier M, Bucher K. Zum mechanismus dur pulssynchronen atmung. Beutrag zur analyse der besonderen rolle des linken vagus. *Archives Internationales de Pharmacodynamie et Therapie* 1961; **131**: 348.