Relationship between cardioventilatory coupling and respiratory sinus arrhythmia

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Summary
Recent studies have suggested a role for respiratory sinus arrhythmia in improving pulmonary gas transfer. However, the physiological role of cardioventilatory coupling is unknown. We have tested the hypothesis that cardioventilatory coupling aligns heart beats at positions of the ventilatory cycle where they are maximally affected by respiratory sinus arrhythmia (RSA). In 15 anaesthetized, spontaneously breathing subjects, we recorded continuously the timing of inspiration and the ECG. We then plotted the change in RR interval which occurred, as a result of RSA, after onset of inspiration (RSA plot). By comparing these RSA plots with the distribution of heart beats during the ventilatory cycle, we were able to examine the positioning of heart beats relative to acceleration of heart rate as a result of RSA. In all but two subjects we observed that during periods of strong cardioventilatory coupling, heart beats occurred at positions in the ventilatory cycle where they were maximally affected by RSA. In the presence of strong coupling, the shortest possible RR interval occurred during late inspiration, the longest possible RR interval occurred immediately before the start of inspiration. We suggest that cardioventilatory coupling may have a physiological role in optimizing RSA, perhaps to improve cardiopulmonary performance during sleep. (Br. J. Anaesth. 1998; 80: 164–168)

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Respiratory sinus arrhythmia (RSA) is the variation in heart beat interval with respiration. Since its description by Carl Ludwig in 1847 the mechanism of RSA has been the subject of considerable research interest. Currently it is believed that RSA results from modulation of vagal efferent activity to the cardiac sinus node through gating of excitatory input to the vagal motor neurons from lung inflation afferents.1 Inspiration is accompanied by vagal withdrawal and a corresponding increase in heart rate, expiration is accompanied by increased vagal tone and a decrease in heart rate. The magnitude of RSA varies according to the degree of vagal tone and may be reduced by standing, age and administration of drugs which interfere with muscarinic cholinergic receptors.2

A separate interaction between heart beats and respiration is cardioventilatory coupling (CVC), an entrainment phenomena in which ventilation and heart beats become synchronized in whole number ratios and heart beats appear to fall in constant timing relationship with inspiratory onset. Coupling is seen best under conditions of low arousal: sleep, sedation and general anaesthesia. The synchronization of gill movements to heart beats was first described in fish by Schoenlein in 1895,3 the coupling of ventilation to heart beats in mammalian species by Coleman in 19214 and in humans by Galli in 1924.5

The mechanism of CVC is thought to be triggering of inspiratory timing by arterial or intracranial pressor receptor afferents.6 Unlike RSA which is the modulation of cardiac timing by pulmonary afferent information, CVC is a modulation of inspiratory timing by haemodynamic afferent information.

Despite their important effects on governing the interaction between breathing and heart rate, the link between CVC and RSA is not known. However, as coupling aligns inspiratory onset to heart beats, then it must also position heart beats where they are subjected to varying degrees of vagal modulation from RSA. Although the physiological role of CVC is not known, there is a general belief that RSA may help stabilize cardiovascular variables in the face of fluctuating intrathoracic pressure6 and recent work suggests that it may improve pulmonary oxygenation.7 If RSA has a role in improving cardiopulmonary performance, then the positioning of heart beats where they are maximally affected by RSA could have some physiological benefit. In this study, we have examined the hypothesis that CVC aligns heart beats relative to inspiratory onset such that the inter-beat interval is maximally affected by RSA.

Patients and methods
After obtaining Ethics Committee approval, we obtained data from 20 consenting, adult patients undergoing elective surgical procedures under general anaesthesia. None was receiving 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 1–1.5% isoflurane and 66% nitrous oxide in oxygen. After induction, a laryngeal mask airway was

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Cardioventilatory coupling and respiratory sinus arrhythmia

ANALYSIS

Cardioventilatory coupling

Cardioventilatory coupling was assessed by measuring the time of each R wave peak from the ECG and the time of each inspiratory onset. We then determined the time interval between each R wave and the immediately following, and preceding, inspiratory onset (RI intervals). RI intervals and R waves for heart beats preceding the inspiration were given a negative subscript and those after inspiration were given a positive subscript: R_{-1} for the beat preceding the inspiration and R_{15}, R_{12} etc for consecutive beats after inspiration. RR intervals were given a subscript according to the their bounding R waves: R_{13/14} for the interval between R_{13} and R_{14}. This nomenclature is explained in figure 1. RI_{n} intervals were plotted against time of R wave occurrence (RI plot). Coupling of heart beats and ventilation is revealed in these plots as horizontal banding, in which values of RI_{n} remain constant over time.

Because the degree and pattern of cardioventilatory coupling varies in any individual over time, RI plots commonly show periods of poor coupling where heart beats occur in no fixed relationship to inspiratory onset and periods of stronger synchronous coupling where heart beats occur, to varying degrees, in constant timing relationship to inspiratory onset. In part, this patterning varies according to the degree to which heart rate and ventilatory rate are in whole number ratio.

RSA plots

Shortening of RR interval, which occurs after the onset of inspiration as a result of RSA, was displayed graphically by plotting, for each R wave, the normalized preceding RR interval (duration of the preceding RR interval divided by the mean RR interval; the mean being calculated empirically from a window 10 beats on each side of the interval under examination) against the time at which that heart beat decreased after the onset of inspiration. Mean values of normalized RR were then obtained for each 0.1-s interval after inspiratory onset and the curve of respiratory sinus arrhythmia (RSA plot) constructed by interpolating these points. These RSA plots were established from those portions of the RI time series in which coupling was least apparent (weak or absent coupling), during which time heart beats occurred at all phases of the ventilatory cycle and the full extent of the RSA curve could be seen. From these plots we then measured the time from inspiratory onset to: (a) the time at which RR interval acceleration began; and (b) the nadir of the RSA curve (fig. 2).

From segments of the RI plot which showed strongest coupling (heart beats and ventilations were in reasonable synchrony for periods of longer than 50 breaths) we constructed histograms of R wave distribution after inspiratory onset. We then superimposed these plots and the previously constructed RSA plots to determine where, within the RSA curve, groupings of heart beats occurred during cardioventilatory coupling (fig. 3). The mean time to these R wave groupings from inspiratory onset (RI_{11}, RI_{12},...) was calculated and compared with the onset of acceleration and nadir points of the RSA curve.

All data acquisition and raw data analysis were performed using software developed in LabView 2 (National Instruments) and purpose written by the authors. Statistical analysis was performed using Statview 4 on a Macintosh LCIII personal computer.

Results

Of the 20 subjects, 15 had RI plots suitable for analysis (six males, nine females, mean age 30.7 (range
18–62) yr; nine received an opioid, five morphine, four fentanyl). In the remaining five subjects, the degree of coupling remained constant throughout the recording period and no clear separation between periods of strong and weak or absent coupling were obtained.

From the 15 suitable recordings, during periods of weak or absent coupling, the scattered distribution of heart beats throughout the ventilatory cycle allowed RSA plots to be obtained, all subjects showing the expected heart rate acceleration after inspiratory onset. The nadir of the RSA curve (i.e. the time of an...
R wave which has been preceded by the shortest possible RR interval) varied between subjects, with a mean time from inspiratory onset of 1.35 (SD 0.32) s. The onset of acceleration (i.e. the time of an R wave which has been preceded by the longest possible RR interval) occurred at a mean time of 0.43 (0.23) s after inspiratory onset.

Data epochs used for establishing the RSA curve and strongly coupled R wave groupings were not significantly different with regard to mean RR interval (0.896 vs 0.893 s; \( P = 0.95 \), paired \( t \) test) or ventilatory frequency (20.2 vs 19.7 bpm; \( P = 0.76 \), paired \( t \) test).

RSA plots from strongly coupled segments all showed clustering of heart beats at discrete time intervals after inspiratory onset. Superimposition of these strongly coupled R wave groupings and the previously constructed RSA curves (fig. 2) showed that during strong coupling, the heart beats corresponding to the R1 and R2 groupings generally occurred on, or close to, the acceleration onset and nadir of the RSA curve, respectively. The distribution of heart beats and corresponding RSA plots for all subjects are shown in figure 3. The mean RI1 for strongly coupled beats was not significantly different from the time to RSA nadir (RI1 1.29 (0.22) s (95% confidence intervals (CI) 1.18–1.40) vs nadir 1.35 (0.32) s (95% CI 1.19–1.50); \( P = 0.22 \), paired \( t \) test). Power analysis indicated that there was an 80% probability of a difference of 10% or greater being statistically significant. Similarly, RI1 was not significantly different from the acceleratory onset of the RSA plot (RI1 0.418 (0.16) s (95% CI 0.340–0.497) vs acceleration onset 0.429 (0.23) s (95% CI 0.314–0.544); \( P = 0.94 \), paired \( t \) test).

The observations in this study link the timing of CVC to that of RSA suggesting that, during coupling, heart beats are positioned in such a way that vagal modulation of RSA is maximized. In the absence of CVC, heart beats occur at random positions within the RSA curve and are subjected to varying degrees of vagal modulation. Less inspiratory acceleration of RR interval might be expected if heart beats occur at the sides of the RSA curve. In the presence of CVC however, heart beats were generally subjected to the maximal effects of RSA. RR \( _{1/2} \) was the shortest possible interval for that RSA curve implying the greatest degree of vagal withdrawal. RR \( _{1/2} \) was the longest possible interval implying that, during strong coupling, vagal withdrawal at the cardiac sinus pacemaker begins to occur only after the R1 heart beat.

Any putative optimization of RSA by CVC implies a physiological benefit from these processes. Whether the relationship between RSA and phase coupling is simply fortuitous however, or the result of evolutionary design remains open to question. Demonstration of this relationship strengthens the case for their having some physiological significance. A commonly held view with regard to RSA is that it compensates for the haemodynamic effects of varying intrathoracic pressure with ventilation, perhaps matching cardiac output to the variation in venous return or reducing the fluctuations in mean arterial pressure. Evidence for this haemodynamic benefit is poor and an alternative hypothesis has been put forward recently with the demonstration, in dogs, that in contrast with the condition where RSA is absent, artificially induced RSA had no effect on cardiac output, but significantly improved pulmonary oxygenation: reducing the ratio of physiological dead-space to tidal volume, decreasing shunt fraction and increasing oxygen uptake. The mechanism of this effect may be a simple reduction of the time over which blood is replaced within pulmonary capillaries when alveoli are filled with fresh gas, and a lengthening of blood replacement time towards the end of expiration when \( V/Q \) mismatch is more likely and the alveoli are filled with gas of reduced \( P_{A_O_2} \) and increased \( P_{A_CO_2} \).

Alone, RSA would be unable to achieve synchronization of heart beat timing to ventilation as heart beat timing is determined by the independent sinus pacemaker which is only slowed or accelerated by vagal activity. By triggering inspiration from baroreceptor afferents however, heart beats can be made to occur in exact relationship with the inspiratory period. Thus in the presence of coupling, the shortest possible RR interval and hence pulmonary capillary transit time occurs as the alveoli are filling with fresh gas. The longest RR interval and capillary transit time occur at the end of the ventilatory cycle when the alveoli are filled with “stale” alveolar gas. Although this effect may have little significance for well ventilated areas of the lung, it may become important in those areas where ventilation is low relative to perfusion or in those subjects where FRC approaches closing volume.

If pulmonary gas exchange is improved by RSA and this in turn is optimized by CVC, then this would be consistent with the conditions under which RSA and coupling are known to occur. It is well recognized that sleep, sedation and general anaesthesia, and the accompanying supine posture, may be associated with impaired ventilation, gas exchange and reduced functional residual capacity. Under normal physiological conditions, coupling is best seen during sleep. Sinus arrhythmia is also of greatest amplitude during sleep and in the supine posture because of increased vagal tone. It is therefore possible that these mechanisms act to reduce the effects of sleep or supine posture, or both, on disordered gas exchange. It is also perhaps of note that both RSA and phase coupling occur less frequently in REM sleep than in non-REM and this may explain in part why REM sleep is associated with poorer gas exchange than non-REM sleep.

In this study, in order to maximize the accuracy of data collection, we have used data from patients undergoing general anaesthesia. Anaesthesia is plainly a non-physiological state, and the degree of RSA may be altered by the effects of anaesthetic agents and adjuvants. Heart rates of our patients (mean 66 beat min\(^{-1}\)) were similar to those occurring...
during natural sleep\textsuperscript{11} and the timing of inspiratory onset, relative to $R_\text{p}$, was the same as that found for awake resting and sleeping subjects who exhibit cardioventilatory coupling.\textsuperscript{3} Ventilatory frequencies in our patients (mean 20 bpm) were generally a little higher than those found during sleep (15 bpm\textsuperscript{11}) and therefore study of the interaction between RSA and coupling in natural sleep would be warranted.

We have demonstrated a close relationship between RSA vagal modulation and heart beat timing during strong cardioventilatory synchronization, where heart beats and inspiration are in perfect synchrony. However, this pattern of coupling occurs to a variable extent; in some anaesthetized patients it makes up the entire data record whereas in others it is absent. We have described previously at least six patterns of coupling.\textsuperscript{8} Again the relevance of this interaction between RSA and CVC may depend on the pattern of coupling seen in sleeping subjects and the degree of RSA “optimization” seen with each pattern.

Respiratory sinus arrhythmia diminishes with advancing age whereas phase coupling persists.\textsuperscript{2,3} Although this may simply reflect the robustness of the phase coupling mechanism in contrast with the effect of ageing on vagal tone, the persistence of coupling with age may help to maintain the maximum inspiratory acceleration of heart rate in the face of diminishing RSA magnitude. Alternatively, it is possible that coupling may have physiological benefits independent of any effect on optimizing RSA.

In summary, during anaesthesia, cardioventilatory coupling places heart beats at positions relative to inspiratory onset where they are maximally affected by the vagal modulation of respiratory sinus arrhythmia. This interaction between respiratory and cardiac timing strengthens the argument for their having significant and perhaps common physiological roles. Despite its potential importance, cardioventilatory coupling is not incorporated in current models of respiratory sinus arrhythmia and the present trend towards spectral or frequency domain measurement of RSA only serves to mask the timing relationship between heart beats and ventilation at the expense of obtaining frequency information alone. Disordered cardioventilatory timing relationships may have significant implications for critically ill patients, the provision of IPPV and abnormalities of cardiac rate control.

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**References**