Cardioventilatory coupling: effects of IPPV

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Cardioventilatory coupling (CVC) is the temporal coherence of respiratory and cardiac rhythms. We have suggested that this coherence is the result of triggering of inspiratory onset by a preceding cardiovascular afferent. One implication of this triggering hypothesis is that coupling should only exist under conditions of spontaneous ventilation and not under conditions where the ventilatory period is fixed, as during intermittent positive pressure ventilation (IPPV). This study compared the degree of CVC in 20 ASA I female subjects, aged 21–50 yr, 10 of whom were breathing spontaneously and 10 were undergoing mechanical ventilation. Over 5–10 min, we recorded the timing of consecutive ECG R waves and inspiratory onsets. Coupling was demonstrated by examining these epochs for constant timing relationship between R waves and inspiration (RI intervals). Constancy of RI intervals was examined graphically (RI plot) and quantitatively using the Shannon entropy of RI interval distribution. We observed CVC in all spontaneously breathing subjects but in none of those receiving IPPV. In spontaneously breathing subjects, temporal alignment with inspiratory onset was greatest for the heart beat preceding inspiration. We conclude that although coupling has been shown to persist in the presence of electrical cardiac pacing, IPPV disrupts the coupling process, consistent with the view that in anaesthetized subjects, coupling is the triggering of inspiratory onset by a preceding heart beat and not the converse.

Keywords: cardiorespiratory system, effects; ventilation, intermittent positive pressure; heart, heart rate

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In anaesthetized, spontaneously breathing subjects, there is often a constant time interval between inspiratory onset and a preceding heart beat. This phenomena is termed cardioventilatory coupling and is distinct from respiratory sinus arrhythmia (RSA), the vagally mediated modulation of heart rate according to respiratory phase.

We have proposed that the mechanism of coupling involves a signal related to cardiac action, perhaps pressoreceptor in origin, triggering the onset of inspiration via brain stem afferents. However, alternative models of cardioventilatory coupling have also been proposed. Weiss and Salzano examined a phenomena whereby under certain circumstances the ratio of heart rate to breathing frequency becomes integer (whole number ratio (WNR)). WNR is seen clearly during cardioventilatory coupling when heart and breathing rhythms are locked in exactly repeating patterns of coherence. Examining WNR in anaesthetized dogs, Weiss and Salzano observed its presence during artificial ventilation. These authors proposed that respiration modulates heart rate to form WNR, and that this involves a reflex arc with afferent vagal activity from pulmonary stretch receptors and efferent vagal activity to the sinus node. This hypothesis is plainly at variance with a model whereby heart beats trigger ventilation.

If cardioventilatory coupling is the trigger for inspiration by a cardiovascular afferent, then during intermittent positive pressure ventilation (IPPV) no coupling should be seen. Therefore, in this study we examined the coupling relationship between heart beat and ventilation in anaesthetized subjects who were either ventilated artificially or spontaneously breathing.

Patients and methods

After obtaining approval from the Ethics Committee, we studied 20 consenting, unpremedicated female subjects undergoing minor elective orthopaedic or gynaecological procedures. All were ASA I and none had evidence of cardiorespiratory disease. Anaesthesia was induced with propofol 2–2.5 mg kg\(^{-1}\) and fentanyl 75 µg, and a laryngeal mask airway was inserted. Anaesthesia was maintained by inhalation of 1–1.5% isoflurane and 66% nitrous oxide in oxygen. Subjects were divided into two groups of 10 subjects according to surgical requirements. In group 1, subjects breathed spontaneously, while group 2 received rocuronium 40 mg and underwent mechanical ventilation (Ohmeda 7800 Ventilator) at a rate of 10–12 bpm with tidal volume adjusted to maintain $P_{\text{ET}}CO_2$ at 5.3 kPa.
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Fig 1 Generation of RI interval plots. A: Six consecutive inspiratory onsets (determined from the pneumotachograph signal) and the ECG signal for within each breath. The timing of each R wave is determined from the ECG. B: Time interval from each ECG R wave to the following onset of inspiration is calculated. These intervals are termed RI intervals, and are denoted relative to the onset of inspiration. RI intervals for R waves preceding inspiration are designated by negative subscripts, and thus RI1 is the interval from the R wave immediately before the onset of inspiration. C: RI intervals plotted against the time at which each R wave occurred (RI interval plot). Horizontal banding is seen on the RI interval plot in the presence of coupling, as values for RI−1, RI−2, etc, are constant from breath to breath.

We monitored plethysmographic oxygen saturation (SpO2), end-tidal carbon dioxide partial pressure (PetCO2), percentage end-tidal isoflurane (%ETiso), non-invasive arterial pressure (Datex AS3), ECG (lead CM5, Corometrics Neo-Trak 502) and respiratory airflow (pneumotach, Hans Rudolph).

For 5–10 min (at least 50 breaths), before the onset of surgery, ECG and pneumotach output were recorded continuously using a Macintosh IICx computer with 16 bit ADC board (National Instruments) and a sampling rate of 500 Hz.

Analysis

For each subject, we extracted an epoch of cardiac arrhythmia-free data, including at least 50 breaths. From this epoch, we measured the time of each R wave peak and the time of each inspiratory onset. From these data, we calculated the time 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 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 following an inspiration were given a positive subscript: RI−1 for the beat preceding inspiration and RI1, RI2, etc, for the beats following inspiration. A fixed relationship, or coupling, between heart beat and inspiration is revealed in an RI plot as horizontal banding in which values of RI−n maintain relatively constant values over time (Fig. 1).

In spontaneously breathing subjects, we have noted previously that the interval between inspiration and the preceding R wave (RI1) appeared more constant than the interval between inspiration and the following R wave (RI1), thus suggesting that inspiration is triggered by the preceding heart beat. If we assume that mechanical ventilation cannot influence the timing of a preceding heart beat, then for IPPV to be capable of entraining the heart rhythm it would be expected that the interval between inspiration and the following R wave (RI1) would be the most constant. Therefore, we extracted individual RI−1 and RI1 values as time series for comparison.

In order to quantitate the degree of cardioventilatory coupling under the two conditions, we used a measure derived from information theory: Shannon Entropy (SH). Claude Shannon, in 1949, demonstrated the method for calculating the amount of uncertainty, or entropy, of a given probability distribution. This measure has been used widely in a range of biological applications where quantitative description of data regularity is required. As an index of diversity the statistic is known as the Shannon–Weaver index and a full, worked example is given in Zar. In the context of our study, we are concerned with the distributions of RI−1 and RI1 intervals. Strong coupling is associated with a constant RI1 interval and absent coupling with an RI1 interval which changes from breath to breath. In this manner, a series of RI1 intervals that were identical in value (associated with strong cardioventilatory coupling) would contain no uncertainty and SH would approach 0. Conversely, a series of RI1 intervals that were all different (i.e. where cardioventilatory coupling is absent) would contain a high degree of uncertainty and SH would approach 0.

Degree of coupling
would therefore range between SH\(_{\alpha}=1\) (absent coupling) to SH\(_{\alpha}=0\) (fully coupled).

To calculate SH\(_{\alpha}\), we examined 50 successive RI\(_1\) and 50 successive RI\(_{-1}\) intervals and placed each of these series into 10 bin histograms, the outer limits of which ranged between 0 and the mean RR\(_{1/-1}\) interval (the interval which spans inspiratory onset) for that data segment. SH\(_{\alpha}\) is calculated from the distribution of points within this histogram:

\[
SH = - \sum_{b=1}^{N} Pb \cdot \log(Pb)
\]

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

\[
SH_{\alpha} = SH/SH_{\max}
\]

where \(P=\) observed histogram bin probability, \(h=\) bin number and \(N=\) number of histogram bins.

In order to compare the calculated Shannon entropy values with an entirely random (i.e. an uncoupled) system, we calculated the SH\(_{\alpha}\) generated from 10 000 series of 50 random numbers between 0 and 1. From the distribution of these values we determined the expected 0.05, 0.01 and 0.001 probability limits for SH\(_{\alpha}\).

WNR was calculated using the method of Weiss and Salzano. Over 25 breaths the number of heart beats were counted (\(N\)) and the ratio \(N/25\) was calculated. A WNR was confirmed if \(N/25\) equalled an integer value \(\pm 0.05\). The \(N/25\) ratio was calculated for breaths 1–25 and 26–50 for each subject.

For each individual, we calculated mean RR interval (RR) and respiratory frequency (\(f\)). We quantitated the degree of RSA as \(\Delta RR_{\max - \min}\) (the maximum RR interval minus the minimum RR interval within each breath) and \(\Delta RR_{\max - \min}/RR\) (\(\Delta RR_{\max - \min}\) divided by mean RR interval) for each subject. We extracted \(P_{\text{CO}_2}\), %ET\(\text{ISO}\), and \(S\text{pO}_2\) at 1-min intervals throughout the recording period and non-invasive arterial pressure measurements before and after the 5-min data epoch. We compared mean \(P_{\text{CO}_2}\), %ET\(\text{ISO}\), \(S\text{pO}_2\), SAP, DAP, RR, \(\Delta RR_{\max - \min}\), \(\Delta RR_{\max - \min}/RR\) and \(f\) between the two groups using an unpaired \(t\) test. We compared SH\(_{\alpha}\) for RI\(_1\) and RI\(_{-1}\) in the IPPV and spontaneously breathing groups with the probability distribution of SH\(_{\alpha}\) for randomly generated data. Direct comparison of SH\(_{\alpha}\) for RI\(_1\) and RI\(_{-1}\) within groups was made using the Wilcoxon signed rank test and between groups using the Mann–Whitney \(U\) test.

Data manipulation was performed using purpose written software in LabView 2 (National Instruments). Statistical tests were performed using Statview 4.5 (Abacus Concepts).

### Results

There was no significant difference between the mechanically ventilated and spontaneously breathing groups in age, mean \(P_{\text{CO}_2}\), %ET\(\text{ISO}\), RR, \(f\), \(S\text{pO}_2\), SAP or DAP (Table 1).

The degree of RSA was reduced significantly in the IPPV group (Table 1). In three subjects in the IPPV group, the RSA heart rate relationship was the converse of that observed in spontaneously breathing subjects (i.e. RR interval increased during inspiration and decreased during expiration).

Cardioventilatory coupling was evident as horizontal banding in the RI plots of all 10 spontaneously breathing subjects, but in none of the 10 subjects undergoing mechanical ventilation (Fig. 2). Histograms of RI interval

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>IPPV</th>
<th>Spontaneously breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (11)</td>
<td>31 (10)</td>
<td>ns</td>
</tr>
<tr>
<td>99 (1)</td>
<td>99 (1)</td>
<td>ns</td>
</tr>
<tr>
<td>0.95 (0.19)</td>
<td>0.82 (0.17)</td>
<td>ns</td>
</tr>
<tr>
<td>0.068 (0.035)</td>
<td>0.031 (0.019)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>0.072 (0.034)</td>
<td>0.037 (0.017)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>12.1 (4.9)</td>
<td>11.5 (1.7)</td>
<td>ns</td>
</tr>
<tr>
<td>115 (13)</td>
<td>109 (12)</td>
<td>ns</td>
</tr>
<tr>
<td>61 (8)</td>
<td>59 (10)</td>
<td>ns</td>
</tr>
<tr>
<td>0.706 (0.433–0.890)</td>
<td>0.957 (0.914–0.980)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.735 (0.465–0.899)</td>
<td>0.967 (0.910–0.985)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Table 1 | Age, plethysmographic oxygen saturation (SpO\(_2\)), end-tidal carbon dioxide partial pressure (P\(e\)\(\text{CO}_2\)), RR interval, maximum RR interval minus the minimum RR interval within each breath (\(\Delta RR_{\max - \min}\)), ventilatory frequency (\(f\)), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), proportional Shannon Entropy of the RI\(_1\) interval distribution (SH\(_{\alpha}\) of RI\(_1\)), proportional Shannon Entropy of the RI\(_{-1}\) interval distribution (SH\(_{\alpha}\) of RI\(_{-1}\)), and the number of subjects demonstrating a whole number heart rate/ventilatory frequency ratio (WNR) are given for the spontaneously breathing and IPPV groups. Values are mean (SD) except for SH\(_{\alpha}\) of RI\(_1\) and SH\(_{\alpha}\) of RI\(_{-1}\) which were compared using the Mann–Whitney \(U\) test. Within-group comparisons of SH\(_{\alpha}\) of RI\(_1\) and SH\(_{\alpha}\) of RI\(_{-1}\) were made using the Wilcoxon signed rank test (*\(P<0.05\)).

Fig 2 Representative RI interval plots and RI interval histograms are shown for (a) a spontaneously breathing subject and (b) an IPPV subject. Histograms show frequency of heart beat occurrence for 4 s before and 4 s after inspiratory onset (at time=0).
plots (Fig. 3) similarly showed clear peaks corresponding to inspiratory alignments in the spontaneously breathing subjects, but not in those undergoing mechanical ventilation. SH$_\alpha$ of both RI$_{-1}$ and RI$_{+1}$ intervals was significantly less in the spontaneously breathing group than in the IPPV group. RI$_{-1}$ and RI$_{+1}$ SH$_\alpha$ values for all subjects in the IPPV group were close to the median value for the random data sets. RI$_{-1}$ and RI$_{+1}$ SH$_\alpha$ values for the spontaneously breathing subjects were outside the P=0.001 level generated from the random data. In the IPPV group, there was no difference between SH$_\alpha$ for RI$_{-1}$ vs RI$_{+1}$, whereas SH$_\alpha$ was significantly lower for RI$_{-1}$ compared with RI$_{+1}$ in the spontaneously breathing group (Table 1).

The IPPV group showed WNR in four of 20 samples, compared with six of 20 in the spontaneously breathing group (ns).

Discussion

We believe that cardioventilatory coupling is best represented as a constant temporal alignment between a heart beat and a following inspiratory onset. We have suggested previously that this alignment is achieved by a cardiovascular afferent, perhaps pressoreceptor, triggering the onset of inspiration. Contrary views have also been expressed. Weiss and Salzano, in 1971, suggested that respiratory activity adjusted heart rate in order to form WNR of heart rate to ventilatory rate. Raschke and Hilderbrant, in 1979, suggested that temporal alignment is achieved by adjustment of RR interval length by a corresponding inspiration, and recently Schäfer and colleagues suggested that synchronization between cardiovascular and respiratory rhythms was caused by a mutual interaction of brain stem oscillators.

We have demonstrated in anaesthetized subjects that, in the absence of spontaneous ventilation, cardioventilatory coupling is entirely disrupted, with the temporal alignment between heart beats and inspiration not being distinguished from a random relationship. There was no evidence in our study to support any increased WNR during IPPV, as noted in dogs by Weiss and Salzano. Although Weiss and Salzano believed that WNR was the same as cardioventilatory coupling, as described by some early German authors, it should be noted that WNR and cardioventilatory coupling are not synonymous. Cardioventilatory coupling may occur, for example, in the presence of a changing number of heart beats within each breath, as seen in the record of Figure 2A. Under these conditions, cardioventilatory coupling is present in the absence of WNR. Further, Hildebrandt and Daumann, studying the effects of exercise on cardioventilatory coupling, noted that with increasing exercise coupling is disrupted, but WNR becomes increasingly evident, and therefore suggested that WNR and cardioventilatory coupling were separate phenomena. It is possible that WNR simply reflects the fortuitous convergence of HR and $f$ towards an approximate integer ratio (4.0) at their maximum levels of activity, without any constant timing relationship.

Hinderling, investigating cardioventilatory coupling in subjects whose hearts were paced electrically but were breathing spontaneously, found that temporal alignment was as strong during cardiac pacing as it was in normal subjects. This, together with our observation that coupling does not occur during mechanical ventilation, suggests that it is a cardiac signal which produces the inspiratory alignment and not vice versa. Further support was seen in our spontaneously breathing subjects where the heart beat which preceded inspiration was more consistently aligned to inspiratory onset (lower SH$_\alpha$) than the heart beat which followed inspiration.

Although the mechanism (or mechanisms) by which cardiac action initiates inspiratory onset has not been identified, several potential neural pathways exist. In addition to the well known efferent vagal outflow from the brain stem to the heart, there are well described afferent inputs from cardiac and non-cardiac pressoreceptor structures in addition to pulmonary stretch receptors and chemoreceptors. The brain stem receives pressoreceptor input from the atria, ventricles, pulmonary vasculature, aortic arch and carotid sinus. After synchronising within the nucleus tractus solitarius, these inputs are distributed widely to areas of the brain stem associated with cardiac and respiratory activity. Ventilatory rhythm is believed to originate within an area of the medulla known as the pre-Botzinger complex of the rostral ventral respiratory group and several neuronal pathways connect the pre-Botzinger complex with afferent pressoreceptor input. Consistent with these neuroanatomical observations are those experiments in animals which have demonstrated immediate alterations in respiratory frequency and tidal volume after acute changes in arterial pressure, cardiac chamber distension and pulmonary vascular congestion.
In this study, we used Shannon entropy to quantify the relationship between inspiratory timing and heart beat. Although our previous studies on cardioventilatory coupling have relied on qualitative description of the graphical RI plot, Shannon entropy offers a simple measure of RI distribution which allows direct comparison of RI time series. Shannon entropy has been used previously in a wide range of biological applications and warrants further study in relation to factors affecting cardioventilatory coupling.

The observations of this study apply to anaesthetized human subjects, ventilated to near normal physiological values. It is possible however that in non-anaesthetized subjects, or under different physiological conditions, IPPV could entrain the cardiac rhythm. In addition, we cannot exclude alternative forms of coupling, coexisting or alternating with triggering of inspiration by heart beat. However, to our knowledge no direct observation of entrainment by IPPV has been made and no clear evidence of alternative coupling mechanisms has been presented.

We observed significantly less RSA during IPPV than during spontaneous breathing, both in terms of ΔRR and the ΔRR adjusted for heart rate. This difference is well described and most likely represents a combined pressure reversal effect of IPPV, vagal withdrawal secondary to reduced venous return and an alteration in brain stem ventilatory rhythmogenesis; also, a small vagolytic contribution from rocuronium cannot be excluded. The reverse RSA (inspiratory heart rate deceleration) seen in three subjects undergoing mechanical ventilation has been noted previously by Yli-Hankala and colleagues.

In summary, cardioventilatory coupling could not be demonstrated during intermittent positive pressure ventilation in anaesthetized subjects. Although it is possible that other forms of cardioventilatory coupling may exist under other circumstances, our observations are consistent with the hypothesis that coupling derives primarily from triggering of inspiratory onset by preceding cardiac activity.

Acknowledgement

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References

4 Weiss HR, Salzano J. Control mechanisms of whole number ratios of heart rate and breathing frequency. J Appl Physiol 1971; 31: 466–71
9 Raschke F, Hildebrandt G. The mutual interaction between the RR interval time and the onset of inspiration. Pflogers Arch 1979; 382: R43
20 Wierda JM, Schuringa M, van den Broek L. Cardiovascular effects of an intubating dose of rocuronium 0.6 mg kg⁻¹ in anaesthetised patients, paralysed with vecuronium. Br J Anaesth 1997; 78: 586–7