Cardioventilatory coupling in atrial fibrillation

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Cardioventilatory coupling is an entrainment phenomena, distinct from respiratory sinus arrhythmia, whereby heart and breathing rhythms show temporal coherence. Coupling is commonly observed during rest, sleep and anaesthesia. Five graphical methods, each with different underlying mechanistic assumptions, have been suggested for studying this entrainment relationship: (a) time relationship between inspiration and a preceding heart beat, (b) time relationship between inspiration and a following heart beat, (c) phase of the cardiac cycle at which inspiration occurs, (d) phases of the ventilatory cycle at which heart beats occur and (e) ‘relative phases’ over multiple ventilatory cycles at which heart beats occur. In eight elderly human subjects with atrial fibrillation, breathing spontaneously during general anaesthesia, we recorded heart period and ventilatory time series and compared each of the graphical methods used for demonstration of coupling. We observed cardioventilatory coupling in seven of eight subjects. In each of these seven subjects, coupling was best described, both qualitatively and quantitatively, in terms of the relationship between inspiration and a preceding heart beat. The variation of the interval between inspiration and a preceding heart beat was less than for any other phase or time relationship. These data support a model of cardioventilatory coupling in which a heart beat triggers the onset of inspiration, rather than modulation of cardiac timing by ventilation or a phase relationship between the two systems.

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Cardioventilatory coupling (CVC) is an interaction between heart beat and breathing in which the two rhythms demonstrate temporal coherence. In human subjects, CVC is evident at rest, and during natural sleep, benzodiazepine sedation and general anaesthesia. Coupling is less apparent in active subjects.

In anaesthetized subjects, coupling is seen as a period during which inspiration starts at a fixed interval (approximately 0.5 s) after an ECG R wave. We have suggested that inspiration is triggered by a pressoreceptor afferent to the brainstem, and that this afferent input is initiated by a heart beat which precedes inspiration. Consistent with this explanation, our method for demonstration of CVC uses a plot of consecutive heart beat timings (R waves) in relation to the following inspiratory onset (RI intervals), examining these plots for constant temporal alignment between inspiration and a preceding heart beat (RI plot).

Although we believe that coupling involves the alignment of inspiration to a preceding heart beat and hence use a plot of RI intervals, four alternative viewpoints and associated graphical methods were found in the literature. The five approaches can be divided into those that view coupling as a time relationship and those that consider the interaction to be a phase relationship.

Time relationships

(a) Inspiration is triggered by a preceding heart beat. Coupling is therefore demonstrated by showing a constant interval between inspiration and a preceding heart beat.

(b) A heart beat is triggered by a preceding inspiration. Coupling is demonstrated by showing a constant interval between inspiration and a following heart beat.

Phase relationships

(c) Inspiration is synchronized to a specific phase of the cardiac cycle. Coupling is demonstrated by showing inspiration at specific phases of the cardiac cycle.

(d) Heart beats are synchronized to specific phases of a single ventilatory cycle. Coupling is demonstrated by showing heart beats at specific phases of the ventilatory cycle.

(e) Heart beats are synchronized to phases of m ventilatory cycles where m is a number greater than 1. This mechanism
allows for non-integer coupling entrainment ratios of, for example, 7/2 (repeating pattern of seven heart beats distributed over two consecutive ventilatory cycles). Coupling is demonstrated by showing heart beats relative to phases of a cycle equal to m ventilatory cycles (the ‘relative phase’).

No comparison has been made of these five putative mechanisms and their associated plotting methods. In a coupled system where heart rate and ventilation are locked in perfect whole number ratio, heart beat–inspiratory alignments (a–e above) are apparent, irrespective of the methodology. In subjects with atrial fibrillation, however, the RR interval time series is highly irregular and any differences between the five methodologies should become accentuated. Lack of appreciable vagal modulation in atrial fibrillation, particularly in elderly subjects where RSA, even in sinus rhythm, is small, should preclude efferent modulation of cardiac timing if this was important in the coupling process (as in b–e above).

In this study, we have examined the time and phase relationships between heart beats and ventilation in anaesthetized, spontaneously breathing elderly subjects with atrial fibrillation. We were interested specifically in determining if cardioventilatory coupling is present in the absence of a regular sinus rhythm and which of the five methods gave the best representation of cardioventilatory coupling.

**Patients and methods**

After obtaining approval from the Ethics Committee and written informed consent, we studied eight subjects presenting for elective surgery who were in stable atrial fibrillation. Patients were anaesthetized, spontaneously breathing elderly subjects with atrial fibrillation, mean ages 72–92 (mean age 81) yr, in atrial fibrillation. Mean heart rate, ventilatory cycles for m = 2, 3 and 4. \( m \psi \) for m = 1–4 were plotted as a time series.

In addition to plotting these time series, we plotted the distribution of points within these time series as 100 bin histograms.

For each interval and phase position, we calculated mean (SD) values. Because of their different measurement units, coefficients of variation (CV) were calculated to compare the dispersion of RR and \( \psi (R_{\text{R}}) \). A Wilcoxon signed rank test was used to compare CV RR and CV \( \psi (R_{\text{R}}) \).

Repeated measures ANOVA was used to compare the relative dispersion (SD) of RR, RR, IR, IR, IR, IR and IR, IR, IR, IR intervals and the relative dispersion of \( \psi (R_{\text{R}}) \) and \( \psi (R_{\text{R}}) \). Pearson correlation coefficient was calculated for RR vs RR and for \( \psi (R_{\text{R}}) \) vs RR for each subject. Data acquisition and analysis were performed using custom-written software in Labview 2.2 (National Instruments). Statistical tests were performed using Statview.

**Results**

We studied six females and two males, aged 72–92 (mean age 81) yr, in atrial fibrillation. Mean heart rate, ventilatory
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Fig 1 Nomenclature: from the R wave and inspiratory timing signals, the time interval from the onset of the Ith inspiration to the preceding R waves (RI–1, RI–2, RI–3, ...) and following R waves (IR1, IR2, IR3, ...) are calculated. R waves preceding the Ith inspiration are given a negative subscript, and R waves following Ith are given a positive subscript. RR intervals and II intervals are denoted by the subscripts of the two bounding R waves and inspiratory onsets, respectively. The diastolic phase (Cφ) for Ith is calculated as Cφ(Ith) = RI–1 /RR–1. The ventilatory phase (Vφ) is calculated for R–x heart beat as Vφ(R–x) = IR1 /II n/n–1. The relative ventilatory phase (ψ) is calculated as ψ(R–x) = RI–x /I–I n/( n–m).

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<td>Age (yr)</td>
<td>81</td>
<td>72</td>
<td>92</td>
<td>88</td>
<td>82</td>
<td>73</td>
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<tr>
<td>Heart rate</td>
<td>85.3 (13.5)</td>
<td>97.1 (21.1)</td>
<td>80.9 (22.7)</td>
<td>76.3 (12.5)</td>
<td>88.9 (13.9)</td>
<td>74.5 (19.3)</td>
<td>65.0 (14.2)</td>
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<td>116/69</td>
<td>139/87</td>
<td>110/60</td>
<td>105/55</td>
<td>137/89</td>
<td>117/76</td>
<td>133/84</td>
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<tr>
<td>Ventilatory frequency</td>
<td>18.2 (1.4)</td>
<td>21.6 (2.5)</td>
<td>17.8 (2.7)</td>
<td>23.7 (1.8)</td>
<td>22.5 (2.7)</td>
<td>15.3 (2.4)</td>
<td>14.9 (1.7)</td>
<td>13.5 (2.5)</td>
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<td>sd RI–1</td>
<td>0.215</td>
<td>0.299</td>
<td>0.198</td>
<td>0.257</td>
<td>0.209</td>
<td>0.153</td>
<td>0.144</td>
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<tr>
<td>sd IR1</td>
<td>0.224</td>
<td>0.305</td>
<td>0.219</td>
<td>0.329</td>
<td>0.222</td>
<td>0.221</td>
<td>0.285</td>
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<td>cv RI–1</td>
<td>0.687</td>
<td>0.899</td>
<td>0.719</td>
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<tr>
<td>cv Vφ(R–1)</td>
<td>0.707</td>
<td>0.920</td>
<td>0.738</td>
<td>0.695</td>
<td>0.717</td>
<td>0.295</td>
<td>0.328</td>
<td>0.734</td>
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<td>Digoxin, frusemide</td>
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<td>Digoxin, enalapril, sotalol</td>
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Table 1 Age (yr), heart rate (mean (sd) beat min–1), systolic/diastolic arterial pressure (mm Hg), ventilatory frequency (mean (sd) bpm), sd of RI–1 and IR1, coefficient of variation (cv) of RI–1 and Vφ(R–1), and medications for each subject. J. P. C. was the only subject who failed to demonstrate cardioventilatory coupling in the RI interval plot.

Cardioventilatory frequency, arterial pressure and medications are given in Table 1. Cardioventilatory coupling was evident in the RI interval plots of seven of the eight subjects. Representative examples of RI interval, IR interval, Cφ and Vφ time series plots and histograms for four subjects are shown in Figure 2.

RI plot

In each of the seven subjects displaying coupling, banding of the RI interval plot was most clearly defined for heart beats immediately preceding inspiration. There was a significant difference in variation (sd) of the RI–1, RI–2 and RI–3 intervals (P = 0.0005, repeated measures ANOVA) (Fig. 3A) and in each subject the sd of RI–1 was significantly lower than that of the other RI intervals, indicating that the most consistent time relationship was between inspiration and the immediately preceding heart beat. The RI–1 band occurred, in six subjects with coupling, in the range 0.45–0.85 s before inspiration. In one subject with coupling however, although the most dominant band occurred 0.85 s before inspiration, a second band immediately preceded inspiratory onset by approximately 0.1 s. This was considered to represent triggering by R–2 in conjunction with a short following RR interval.

The individual who did not demonstrate cardioventilatory
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Fig 2 Representative time series and histograms: for RI intervals, IR intervals, diastolic phase ($C\phi$) and ventilatory phase ($V\phi$). Subjects (i - P. S. J.), (ii - N. S. B.) and (iii - K. C. J.) showed banding of the RI interval and ventilatory phase plots consistent with cardioventilatory coupling. Subject (iv - J. P. C.) showed no constant relationship between heart beats and inspiration using any of the four methods.

Fig 3 Mean (SD) (A) RI and IR intervals and (B) ventilatory phase. Repeated measures ANOVA found significant differences between RI and IR intervals ($P < 0.001$) and between the ventilatory phases of $R_1$, $R_2$ and $R_3$ waves ($P = 0.001$). For each measure and in all subjects, the $R_1$ heart beat was associated with the least variation.

coupling in the RI interval plot had the highest heart rate in the study (Table 1). Although this may be a significant observation, the number of subjects within the study was too small to examine the correlation between heart rate and coupling.

**IR plot**

There was evident banding in the IR plot of two subjects and the best defined band in each was that which immediately followed inspiration. The mean SD of $IR_{+1}$ was significantly less than of $IR_{+2}$ or $IR_{+3}$ ($P < 0.0005$, repeated measures ANOVA). In all seven subjects who showed coupling in the RI plot, SD of $IR_{+1}$ was greater than that of $RI_{+1}$. Thus although alignment between inspiration and the following R wave was seen in a small number of cases, this is likely to be explained by the natural consequence of $RI_{+1}$ alignment.

**Diastolic phase**

Between subjects, inspiratory onset did not occur at a constant position in the cardiac cycle. A diffuse distribution corresponding to the first half of the cardiac cycle was observed in four subjects and the latter half in one. In each of these subjects clear evidence of cardioventilatory coupling was observed in the RI interval plots. In all seven subjects demonstrating cardioventilatory coupling in the RI
plot, there was no correlation (Pearson r) between RL\textsubscript{1} interval and the RR interval which spanned inspiratory onset (RR\textsubscript{i-1/i+1}), but there was a significant inverse relationship in each subject between diastolic phase (\(\phi\)) and RR\textsubscript{i-1/i+1} interval. Since \(\phi = \text{RL}_1 / \text{RR}_1\), this findings suggests that RL\textsubscript{1} is a constant and that diastolic phase simply represents the changing heart rate in the face of constant RI\textsubscript{1} alignment. In keeping with this observation was the finding that in all subjects, RI\textsubscript{1} was always less variable than IR\textsubscript{1}.

Ventilatory phase (\(V\phi\))

In all seven subjects showing coupling in the RI interval plots, we observed banding of the ventilatory phase (\(V\phi\)) plots. In each subject these bands were less well defined by visual inspection than the bands which preceded inspiration in the RI plots. In all subjects the cv of \(V\phi(\text{RI}_1)\) was greater than that of RL\textsubscript{1} (cv \(V\phi(\text{RI}_1)\) vs cv RI\textsubscript{1}, \(P=0.05\), Wilcoxon signed rank test) indicating that the time relationship was always less variable than the phase relationship.

The variability of \(V\phi\) increased from \(V\phi(\text{RI}_2)\) to \(V\phi(\text{RI}_3)\) (\(P=0.001\), repeated measures ANOVA) (Fig. 3n). This was also observed visually; in all subjects showing banded \(V\phi\) plots (seven), the best defined bands occurred towards the end of the ventilatory cycle, that is before inspiration. Thus heart beats were not evenly distributed according to phase but, as in the RI interval plot, the major alignment was between onset of inspiration and IR\textsubscript{1}.

Relative ventilatory phase (\(mV\psi\))

There was no apparent banding in any of the eight subjects in the \(mV\psi\) plots at \(m=2\), 3 or 4, other than that which corresponded to the banding seen in the \(V\psi\) plots. In no subject was the cv of \(mV\psi(\text{RI}_1)\) at \(m=2\), 3 or 4 less than the cv of RI\textsubscript{1}. Therefore, we found no evidence for phase locked coupling up to \(m=4\).

Discussion

We have found cardioventilatory coupling in elderly anaesthetized subjects with atrial fibrillation and compared five methods for demonstration of coupling. Our observations are consistent with triggering of inspiration by a single preceding heart beat rather than IR interval, diastolic or ventilatory phase relationships.

Bucher, Hinderling, and Engel and Hildebrandt viewed coupling as an entrainment in which inspiration falls at fixed positions of the cardiac cycle (diastolic phase). The mechanism for diastolic phase entrainment was suggested by Raschke and Hildebrandt\textsuperscript{9} to involve modulation of the heart period which spans inspiratory onset (i.e. the position of R\textsubscript{1}). In subjects with a normal cardiac rhythm and steady heart rate, a reasonably constant diastolic phase relationship must follow from a constant RI\textsubscript{1} alignment. With the near random nature of ventricular depolarization in atrial fibrillation and in elderly subjects (in whom vagal tone and RSA are low) it is unlikely that vagal modulation could alter the positioning of R\textsubscript{1} sufficient to result in diastolic phase alignment. In this study, \(V\phi\) was highly variable. Furthermore, RL\textsubscript{1} was constant in the face of changing RR interval whereas \(V\phi\) was inversely related to RR interval. This indicates that the observed \(V\phi\) alignment was a consequence of RI\textsubscript{1} alignment alone.

In 1975, Kenner, Pessenhofer and Schwabeger described a graphical method for demonstration of cardioventilatory coupling from which our own RI interval plot has been derived.\textsuperscript{5} Rather than plotting intervals between R waves and the following inspiration (RI plot) however, Kenner, Pessenhofer and Schwabeger plotted intervals from inspiration to the onset of an arterial pulse pressure wave (IA plot) and suggested that the ECG R wave could be used as an alternative (IR plot). This form of plot would be suitable if inspiration triggered the onset of a beat heart. Although Kenner, Pessenhofer and Schwabeger believed that ventilation was modulated by heart beats, it is probable that methodological considerations made it easier to time the interval between an electronic signal triggered by inspiration and the following cardiac signals. As with diastolic phase, IR alignment follows from RI\textsubscript{1} alignment, given a relatively constant heart rate. Again, with the irregular rhythm of atrial fibrillation, the SD of IR intervals was significantly greater than that of RI\textsubscript{1}, and the IR relationship was considerably less apparent than the RI relationship by visual inspection of time series plots.

Most authors who have used diastolic phase and IR interval plots believed, certainly in their later articles, that cardioventilatory coupling was achieved by alterations in respiratory timing.\textsuperscript{13,14} The clearest demonstrations of this were made by Hinderling, who showed that subjects with paced cardiac rhythms demonstrated cardioventilatory coupling ‘just as intensely as healthy subjects’\textsuperscript{7} and Bucher and Bucher who demonstrated the presence of coupling in rabbits with a pulsatile artificial circulation.\textsuperscript{14} That these observations were in conflict with the assumptions implicit in diastolic phase and IR methodologies was not noted.

Ventilatory phase (\(V\phi\)) was first used by Niizeki, Kawahara and Miyamoto in 1993.\textsuperscript{10} The underlying assumption present in a ventilatory phase plot is that cardioventilatory coupling is the consequence of synchronization between cardiovascular and respiratory oscillators but there is no fixed time relationship between a cardiac and respiratory event. Therefore, it would be expected that no \(V\phi(\text{RI}_1)\) band should show better alignment than others. In our study, however, the most consistent phase relationship evident in all seven individuals who showed structured \(V\phi\) plots corresponded to the heart beat immediately preceding inspiration. Furthermore, \(V\phi(\text{RI}_1)\) showed a greater cv than the RI\textsubscript{1} interval in all subjects with coupling thus indicating that the coupling mechanism is better described in terms of RI interval alignment than ventilatory phase.

As a modification of the approach of Niizeki, Kawahara
and Miyamoto, Schafer and colleagues\textsuperscript{11} recently proposed that heart beats may be synchronized to whole number multiples of the ventilatory cycle (‘relative’ phase). We found no evidence of coupling when analysed up to four ventilatory periods, other than that which showed coupling over a single ventilatory period. The proposed mechanism of relative phase coupling involves mutual interaction between two oscillators. However, clearly a mutual interaction is not necessary for coupling. Hinderling and Butcher’s observations (above) indicate that coupling can be achieved by the respiratory system reacting to a cardiovascular signal alone, and we have demonstrated that coupling persists in the presence of a highly irregular cardiac rhythm free of significant vagal modulation.

If cardioventilatory coupling results from triggering of inspiration by a preceding heart beat, the RI–1 interval should be the key time relationship in cardioventilatory coupling. In previous studies of anaesthetized subjects in sinus rhythm, the RI\textsubscript{1} interval ranged from 0.4 to 0.9 s (mean 0.51 s).\textsuperscript{3} This is similar to the dominant RI interval histogram peaks observed during atrial fibrillation. In one of our subjects however (Fig. 2 (iii)), a well defined band (RI–2) occurred 0.85 s before inspiration whereas a following group of heart beats (RI–1) immediately preceded inspiration (at approximately 0.1 s). We suggest that in this subject, R–2 was the trigger, but because the heart rate was fast and the heart period was less than the comparatively long RI–2 interval (0.85 s), a non-triggering R–1 band occurred before inspiration. Although R–1 is generally the triggering heart beat, under some circumstances therefore the trigger may be R–2.

In summary, we have shown that cardioventilatory coupling occurs in elderly subjects in atrial fibrillation. Comparing five methods of graphical interpretation, our findings are consistent with the hypothesis that coupling is a triggering of inspiratory onset, by a signal arising from a heart beat preceding inspiratory onset. Although our results do not preclude alternative (time- or phase-related) interactions, these were not apparent under the conditions of this study.

Acknowledgements
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References
2. Galletly DC, Larsen PD. Coupling of spontaneous ventilation to heart beat during benzodiazepine sedation. Br J Anaesth 1997; 78: 100–1
9. Raschke F, Hildebrandt G. The mutual interaction between the RR interval time and the onset of inspiration. Pflugers Arch 1979; 382: R43
12. Rawles JM, Rowland E. Is the pulse in atrial fibrillation irregularly irregular? Br Heart J 1986; 56: 4–11