Quantal ventilatory variability during spontaneous breathing anaesthesia

P. D. Larsen*, Y. C. Tzeng and D. C. Galletly

Department of Surgery and Anaesthesia, Wellington School of Medicine, PO Box 7343, Wellington, New Zealand

*Corresponding author. E-mail: peter.larsen@wnmeds.ac.nz

Background. Cardioventilatory coupling is the triggering of inspiratory onset by preceding cardiac activity. We have observed two forms of coupling with a bimodal ('quantal') variation of respiratory period.

Methods. We investigated the variables of inspiratory duration (T_I), expiratory duration (T_E), and tidal volume (V_T) where respiratory period variation was bimodal. In 25 anaesthetized spontaneously breathing subjects we took 11 samples of recording where the variation of respiratory period was quantal.

Results. In eight of these epochs the variation in respiratory period was associated with fluctuations in the number of heart beats per breath (entrainment ratio) with a constant time interval between inspiration and the immediately preceding heart beat (coupling interval), which we define as pattern II coupling. During pattern II coupling, the quantal variations in respiratory period were entirely caused by variation in T_E, with no associated changes in either T_I or V_T. The other three epochs with quantal variations in respiratory period were observed in pattern III coupling, where an alternating fluctuation in both entrainment ratio and coupling interval occurs. During pattern III coupling, quantal fluctuations were observed in T_E, T_I, and V_T.

Implications. Cross correlation analysis suggested that when pattern III was present, T_I was dependent upon the preceding T_E, which differs markedly from traditional views on the interaction between inspiratory and expiratory duration. V_T was linearly related to T_I, and so could also be determined by the preceding T_E during this type of coupling.

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A current concept of respiratory control is that the output from central respiratory neurones may be described in terms of two components, respiratory drive and respiratory timing.1–4 Respiratory drive is usually expressed as the mean rate of airflow during inspiration, or tidal volume (V_T) divided by inspiratory duration (T_I). Based upon the assumption that the increase in lung volume is essentially linear with respect to time, respiratory drive is considered independent of respiratory timing.1 Respiratory timing is a function of T_I and expiratory duration (T_E), although the precise mechanisms governing T_I and T_E are not fully understood.5–7 It is generally considered that T_E is primarily dependent upon the preceding T_I, and thus factors controlling T_I have received greater attention than those controlling T_E in studies of the control of respiratory timing.24

During spontaneous breathing under general anaesthesia, each of the primary respiratory variables (T_I, T_E, and V_T) most commonly fluctuates about a mean value with a normal, unimodal distribution.48 However, in 1995 Goodman describes a bimodal breath-to-breath respiratory frequency in patients breathing spontaneously under general anaesthesia.9 The bimodality was caused by breath-to-breath changes in T_E, and was not associated with significant changes in either T_I or V_T, both of which had normal, unimodal distributions.

We have described a phenomenon that we have called cardioventilatory coupling, where the onset of inspiration occurs a fixed time interval after an ECG R wave.10–14 We have argued that this coupling is caused by the immediately preceding heart beat triggering the onset of inspiration.

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mathematical model based upon this hypothesis can generate the patterns that are seen clinically.\textsuperscript{15} We have suggested that coupling is responsible for much of the breath-to-breath seen during spontaneous breathing under general anaesthesia, including the bimodality described by Goodman.\textsuperscript{10,11,16}

Breath-to-breath variation associated with cardioventilatory coupling can be described in terms of two factors, the consistency of the coupling interval (the interval between inspiration and the immediately preceding heart beat, termed the RL\textsubscript{1} interval), and the consistency of the number of heart beats within each breath (entrainment ratio).\textsuperscript{10,11} Where both coupling interval and entrainment ratio are constant (pattern I coupling) we have shown that breath-to-breath ventilatory variability is small.\textsuperscript{11} There are two circumstances in which bimodal (‘quantal’) breath-to-breath respiratory frequency variability is seen. One of these, which we have termed pattern II coupling, is where the coupling interval is constant, but the entrainment ratio varies between breaths. Changes in the entrainment ratio with a constant coupling interval results in a change in ventilatory period corresponding to one or more heart periods. The second circumstance in which quantal breath-to-breath variation is observed we have termed pattern III coupling. During pattern III coupling we observe an alternating fluctuation in both entrainment ratio and coupling interval.\textsuperscript{10,11} In the case of pattern III coupling, the breath-to-breath fluctuation in ventilatory period is a little less than one heart period, as coupling interval is reduced when the entrainment ratio increases.

We have not investigated previously the relationship between cardioventilatory coupling and any respiratory variable other than inspiratory timing. This study examined the breath-to-breath changes in Ti, Te, and VT that occur during cardioventilatory coupling. We chose to look at these changes during the quantal respiratory variation seen in pattern II and pattern III coupling, on the basis that when respiratory period changes significantly and repeatedly, changes in Ti, Te, and VT would be easiest to detect. Understanding the influence of cardiac activity on both inspiratory and expiratory duration and tidal volume could improve understanding cardioventilatory coupling in respiratory control, and into the regulation of respiratory timing and respiratory drive.

Methods

After gaining ethical approval and written informed consent, we studied 25 unpremedicated subjects aged 18–45 yr, ASA 1 or 2, undergoing elective surgery.

All subjects lay supine and were anaesthetized with propofol (3 mg kg\textsuperscript{-1} i.v.) over 30 s. Patients then breathed isoflurane 1% in nitrous oxide 66% and oxygen 33% via a facemask and circle absorption system. A laryngeal mask airway (LMA\textsuperscript{®}) was inserted after approximately 2 min.

We measured arterial oxygen saturation (\(\Delta S_{PO2}\)), end tidal carbon dioxide (Datex Oscar, Datex-Ohmeda, Helsinki, Finland), non-invasive arterial pressure (Dinamap), and ECG (lead CM5, Corometrics Neo-trak 502, Corometrics, CT, USA) in all the patients.

Ventilatory airflow was measured by incorporating a pneumotachograph (Hans Rudolph 4813) connected to a differential pressure transducer (Vacumed 4500, Vacumetrics, CA, USA) between the tracheal tube and the circle absorption system. The ECG and flow signals were digitized at 500 Hz using an A-D conversion board (DAQCard 516, National Instruments, Austin, TX, USA) and recorded a Macintosh G3 laptop computer. Data recording began after a stabilization period of 5 min after laryngeal mask insertion and was for a minimum of 10 min duration before surgery.

Data analysis

The method for determination of cardioventilatory coupling has been described previously.\textsuperscript{11} From the stored ECG and ventilatory signals we determined the time of each R wave and of the start of each inspiration. From these times we determined the interval between each R wave and the following start of inspiration (RI interval time series). R waves preceding inspiratory onset are given a negative suffix. Thus, the RI\textsubscript{1} interval is the interval between inspiration and the R wave that immediately precedes it. The RI interval time series was plotted against the time of R wave occurrence (RI interval plot). In these RI interval plots, horizontal banding indicates cardioventilatory coupling as R waves have a constant time relation to inspiratory onset.

RI interval plots were examined by eye for epochs of at least 30 ventilatory periods that showed patterns I, II, or III defined as:

1. Pattern I. An epoch with at least 95% of breaths containing the same number of heart beats (i.e. identical entrainment ratio) and constant RL\textsubscript{1} interval.
2. Pattern II. An epoch length in which entrainment ratio is fluctuating and RL\textsubscript{1} interval is constant.
3. Pattern III. An epoch length in which the RL\textsubscript{1} interval and the entrainment ratio alternated between two values from breath to breath, the RL\textsubscript{1} interval for one breath was similar to that two breaths later.

For each breath, in addition to determining the time of inspiratory onset, we also determined the ventilatory period (inspiratory onset to next inspiratory onset), Ti, Te, VT (by digital integration of inspiratory airflow), and VT/Ti.

All data acquisition and calculation of variables was done using custom written software in Labview 5.1 (National Instruments). Data are presented as mean (SD).

Results

We collected data from 25 subjects (mean age 29 (SD 6) [range 18-45] yr, nine males) and from these we obtained

\textsuperscript{1}LMA\textsuperscript{®} is the property of Intavent Limited.
eight epochs of pattern II, and three epochs of pattern III coupling.

**Pattern II coupling**

As described previously,\textsuperscript{11} pattern II epochs occurred at low respiratory frequencies (10.6 (3.3) bpm). During pattern II coupling, quantal variation in respiratory period was observed (Fig. 1), associated with variations in the entrainment ratio (number of heart beats per breath). The fluctuations in respiratory period were primarily from changes in Te, with little corresponding change in Ti (Fig. 2). There was no statistical correlation between Te and either the preceding or following Ti in any of the pattern II coupling epochs.

While there was considerable breath-to-breath variability in both Vt and Vt/Ti during pattern II coupling, this variation was not associated with quantal fluctuations in the ventilatory period. There was no statistical correlation between Vt and either Te or Ti in the example shown in

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**Fig 1** Representative plots of heart rate (HR, beats min\textsuperscript{-1}), ventilatory period (s), inspiratory duration (Ti, s), expiratory duration (Te, s), tidal volume (Vt, ml), mean inspiratory flow rate (Vt/Ti, ml s\textsuperscript{-1}), and RI interval (s), during (A) pattern II and (B) pattern III coupling.
Figure 1, although in four of the eight recorded pattern II epochs there was a statistically significant relationship between Ti and VT. In none of the eight pattern II epochs was VT correlated with TE.

Pattern III coupling epochs were observed at greater respiratory frequencies than pattern II epochs (23.4 bpm, range 22.2–25.6). During epochs of pattern III coupling, quantal variation in respiratory period was associated with both alternating entrainment ratios and coupling intervals (Fig. 1). Unlike pattern II coupling, during pattern III coupling quantal variation was observed in both TE and Ti, although these two variables changed in a reciprocal manner. Thus, for the example shown in Figure 1, the mean consecutive difference of the ventilatory period (0.46 s) was equal to the mean consecutive difference of TE (0.55 s) minus the mean consecutive difference of Ti (0.09 s).

Ti and TE were significantly related in all pattern III epochs. Cross correlation analysis showed that in all three cases the strongest statistical relationship was a positive correlation between TE and the following Ti. That is, a short TE was followed by a short Ti, whereas a long TE was followed by a long Ti.

During pattern III coupling, VT was also bimodal. The relationship between VT and Ti was linear (Fig. 3); shorter inspirations were associated with reduced tidal volumes, although the time series of VT/TI in Figure 1 does show a slight bimodal distribution. In the other two recorded pattern III epochs, the relationship between VT and Ti was also linear, but the time series of VT/TI did not show the bimodal distribution seen in Figure 1.

Discussion

In this study there was little evidence of any change in respiratory drive associated with cardioventilatory coupling. VT/TI did not change in a quantal fashion during pattern II coupling, and although there was a suggestion of a bimodal distribution during one epoch of pattern III coupling, this was less pronounced for the other respiratory variables, and
the relationship between $T_I$ and $V_T$ appeared to be linear (Fig. 3). In contrast, ventilatory timing was clearly influenced by coupling, as had been expected. Based upon Goodman’s description of bimodal respiratory variation, we had thought that the breath-to-breath changes in ventilatory period occurring during pattern II and III coupling would be caused by changes in $T_E$. While this was the case during pattern II coupling, the pattern III coupling epochs showed a different pattern of ventilatory variability with $T_I$ and $V_T$ changing in a bimodal fashion from breath-to-breath.

The reciprocal changes in $T_I$ and $T_E$ observed during pattern III coupling suggest that successive breaths are differentially influenced by cardiac input. We have proposed that during pattern III coupling there is an alternating pattern of cardiac triggered and non-cardiac triggered breaths. According to such a model, the triggered breath would be preceded by a shortened $T_E$, and following the early initiation of inspiration, $T_I$ would be shortened, while the non-triggered breath would follow a longer $T_E$ and be associated with a longer $T_I$. The fluctuations observed in $V_T$ may be largely explained on the basis of changes in $T_I$.

If the early initiation of a breath caused by coupling were associated with a reduced $T_I$ (and therefore also a reduced $V_T$), then it is possible that in pattern I coupling, where every breath is initiated by a heart beat, every inspiratory period is reduced in length. Examining the pattern I epochs collected in the current study we found four instances where a single breath in the middle of a pattern I epoch appeared to be uncoupled. A representative example of this is shown in Figure 4. In this case the non-coupled breath (defined as the breath preceded by the shorter $R_{I-1}$ interval) was associated with a longer $T_I$, slightly increased $V_T$, and was preceded by a lengthened $T_E$. Thus, the early triggering of breaths that occurs during pattern I cardioventilatory coupling appeared to be associated with a decrease in the preceding expiratory duration, and the subsequent inspiratory duration was as seen during alternate breaths in pattern III coupling epochs. The reduction in $T_I$ in turn tends to reduce $V_T$ of the triggered breath.

We did not observe fluctuations in $T_I$ during pattern II coupling, where the quantal changes in ventilatory period were a result of changes in $T_E$ only. The quantal changes in pattern II coupling correspond to changes in entrainment ratio (number of heart beats per breath) without any change in coupling interval ($R_{I-1}$). According to our model, each breath is still being initiated by a cardiac signal, and thus the initiation of inspiration is the same from breath-to-breath, with no difference in the effect on $T_I$ and $V_T$.

Fig 4 An example of pattern I coupling, with plots of heart rate (HR, beats min$^{-1}$), ventilatory period (s), inspiratory duration ($T_I$, s), expiratory duration ($T_E$, s), tidal volume ($V_T$, ml), and $R_I$ interval (s). A single breath, with the time of inspiratory onset marked by the vertical line, appears uncoupled (reduced $R_{I-1}$ interval), and is associated with a longer $T_I$ and a greater $V_T$. Note that the preceding ventilatory period is longer, as is the preceding $T_E$. 

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Because cardioventilatory coupling is the early initiation of inspiration, one consequence of coupling is to increase the respiratory frequency. We have suggested previously that this increase in respiratory frequency may lead to an increase in minute ventilation if tidal volume was unchanged. However, any effect of the increase in respiratory frequency observed during coupling on minute ventilation is at least partially offset by the observed decrease in Ti and the associated decrease in VT.

Several studies have shown that electrical stimulation of non-respiratory afferents or of specific brain stem regions during expiration can result in the early initiation of inspiration\textsuperscript{5} 17 18 and, in one of these studies, the authors noted that the following inspiratory period was also reduced in length.\textsuperscript{18} It is therefore possible that there is a considerable range of afferents, both cardiac and non-cardiac, that are capable of the early initiation of inspiration, and that a general consequence of early inspiratory onset may be to shorten the subsequent inspiratory duration. Thus, under circumstances in which inspiration is triggered to occur early, by cardiac, locomotor, auditory, or other inputs, inspiratory duration and tidal volume will depend upon the preceding expiratory duration as in pattern III coupling. This differs markedly from the more commonly described relationship between respiratory variables in which Ti determines the following Tr.\textsuperscript{2 4}

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