Coupling of spontaneous ventilation to heart beat during benzodiazepine sedation

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Summary
We have examined in eight male volunteers the effect of midazolam sedation on the relationship between timing of spontaneous ventilations and heart beat. On 2 study days, subjects received either midazolam 0.1 mg kg\(^{-1}\) or saline placebo while recordings were made of ECG and ventilatory impedance pneumography. We observed in all midazolam-treated subjects clear evidence of synchronous or non-synchronous coupling between ventilation and heart beat. Non-synchronous coupling was seen in two placebo-treated subjects, one of whom had slept during the recording period. We conclude that cardioventilatory coupling is a major determinant of ventilatory timing in sedated subjects. (Br. J. Anaesth. 1997; 78: 100–101)

Key words

During midazolam sedation in volunteers, we have previously observed phasic coupling of ventilatory amplitude with slow oscillations (approximately 0.02 Hz) in arterial pressure, heart rate and digital plethysmography.\(^{1}\) We postulated that linking of cardiorespiratory periodicities might be a result of coupling between regulatory centres within the brain stem. In this study we examined further the effect of midazolam on the relationship between ventilation and heart rate. Specifically, we examined the effect of the benzodiazepine on synchronization between heart beat and ventilation.

Methods and results
After obtaining Ethics Committee approval and informed consent, we studied eight healthy fasting male volunteers, mean age 22 (range 20–27) yr and mean weight 71 (67–79) kg. On 2 study days, supine subjects breathed oxygen 5 litre min\(^{-1}\) from a Hudson mask. ECG (CM5) and ventilation (impedance pneumograph, Corometrics Neo-Trak 502) were recorded using a Macintosh IIcx computer (16 bit ADC, sampling rate of 500 Hz). Recording began after a 15-min stabilization period. Twenty minutes later subjects received midazolam 0.1 mg kg\(^{-1}\) i.v. or an equivalent volume of normal saline. Twenty minutes later, flumazenil 0.5 mg or saline was administered i.v. The order of administration of drug and placebo was randomized to ensure an equal number of subjects received placebo or active drug on the first occasion.

Observation of cardioventilatory synchronization was based on a method described by Kenner, Pessenhofer and Schwaberger.\(^{2}\) From the stored ECG data, we determined the timing of each R wave. The ventilatory signal was filtered to remove cardiovascular artefacts and the time of the peak of each inspiration was determined. We calculated for each R wave the time interval until the next ventilatory peak (RV interval). The RV interval for consecutive R waves was plotted against the time of R wave occurrence. Synchronization of heart rate and ventilation is shown as tight horizontal banding of the RV interval, indicating a constant time relationship between heart beat and the following ventilation. The number of bands indicates the entrainment ratio or number of heart beats within each ventilatory period.

Cardioventilatory synchronization was observed in two of eight subjects after administration of midazolam; one subject synchronized with a heart rate/ventilatory frequency ratio of 4:1 (fig. 1) and another at a ratio of 3:1. In both, synchronization persisted throughout the sedation period. Synchronization was not observed after placebo.

In the six other midazolam-treated subjects and in two placebo controls (one of whom had slept during the recording period), less distinct bands were observed in the RV plots. This is seen also in the subject in figure 1 in the 10 min before administration of midazolam. Closer examination of these bands showed them to be composed of variable numbers of heart beats during each ventilatory period (generally 3, 4 or 5). Despite this variability, RV intervals were within discrete bands. As we consider that these indicate a form of coupling between ventilation and heart beats, we refer to this phenomena as non-synchronous coupling (NSC).

In all midazolam-treated subjects, flumazenil ended the period of synchronization or reduced the clarity of the NSC bands. During the period of synchronization shown in...
are shown under the horizontal line. Occasional periods of 5:1 coupling (HR) in a subject showing non-synchronous coupling (12–20 min) and 4:1 cardioventilatory synchronization after administration of midazolam. Occasional periods of 5:1 coupling are shown under the horizontal line.

figure 1, the ratio of heart beat to ventilation alternated between two whole number ratios (shown as a fifth sparse band between 35 and 40 min). During this episode, ventilation was constantly synchronized to every fourth heart beat but occasionally the following ventilation would be delayed while it “waited” for a fifth.

Comment

Entrainment phenomena occur frequently in physical, mathematical and biological systems where two oscillators are coupled. Many such entrainment phenomena have been described in physiology; breathing rate and heart rate may become entrained with step rate during running, cycling or rowing. In sleeping adults, the onset of inspiration most frequently occurs during the diastolic phase of the cardiac cycle and the equivalent of our non-synchronous coupling has been described in sleeping infants.

Some cardioventilatory interaction is necessary as conditions which increase heart rate tend also to demand increased ventilatory frequency. The benefits of NSC and synchronization are less clear. Several authors have argued that synchronization of locomotor and respiratory rhythms may cause a beneficial improvement in energy utilization, and in relation to our own observations, optimal pulmonary blood flow, gas exchange or cardiac work might best occur with a heart beat occurring during a particular phase of respiration. We believe that cardioventilatory coupling may be important for optimal performance of the thoracic pump which may require heart beat to fall within the range of the inspiratory period. If coupling is of benefit to the thoracic pump then plainly this effect is minimal in the awake and alert state. NSC and synchronization were observed only in subjects who were sedated or who had lain quietly for several minutes. This may suggest the role of coupling is evolutionally vestigial, or its role is important only during sleep.

The nature of the interaction between cardiac and respiratory rhythm generators is not understood with certainty. It is known that cardioventilatory entrainment ceases in animals when bilateral vagotomy is performed. Thus efferent or afferent input from pulmonary stretch receptors or baroreceptors may play a part in the feedback interaction. In our study, NSC and synchronization were observed despite the mild vagolytic effect of midazolam (an increase in heart rate occurred in all midazolam-treated subjects and in none of the controls) (fig 1). Kenner, Pessenhofer and Schwaberger found in rabbits “rapid and transient variations in the ventilatory rate appear to be mainly responsible for rapid entrainment”. Similarly in humans we observed that entrainment of ventilation by heart rate clearly occurred where the respiratory period alternated between whole number ratios equal to the the heart period while heart rate remained relatively constant.

Goodman noted that some anaesthetized patients exhibit a “bimodality of ventilatory frequency”, that is ventilatory frequency settled at two possible values between which it variably alternated. Although the author suggested that this indicated the existence of a multi-frequency oscillator within the respiratory centre, the effect can be explained easily by cardioventilatory coupling, with ventilatory frequency varying between two entrainment ratios.

Current concepts of respiratory control focus on an independent respiratory oscillator modulated by chemo- and mechanoreceptor inputs. It is clear, however, that during sleep and sedation, the timing of ventilation is coupled or even synchronized for long periods to cardiovascular events. The clinical relevance of this coupling is unknown, although its recognition may have implications for the interpretation of studies involving analysis of heart rate variability, breathing periodicities and models of their genesis.

References