Bimodality of expiratory time in patients anaesthetized with propofol

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Summary

In the records of breathing from five of 32 patients in two previous studies, the distribution of expiratory times appeared bimodal. Records of breathing from another 40 patients anaesthetized for up to 1 h with propofol infusions were examined; there was clear evidence of bimodality in the distribution of expiratory time in 14 records. The bimodality was independent of tidal volume or inspiratory time, and seemed to be caused largely by differing durations of expiratory pause. In six records there was a change of state between unimodality and bimodality. There was no obvious common factor to explain the bimodality or why a change of state should occur. (Br. J. Anaesth. 1995; 74: 129-133)

Key words

Anaesthetics i.v., propofol. Ventilation, effects.

Each of the primary ventilatory variables (tidal volume, inspiratory time and expiratory time) usually follows a unimodal and normal (Gaussian) distribution about its mean during periods of quiet awake breathing. Expiratory time has the greatest variability. Inspiratory time and tidal volume are correlated; inspiratory time and expiratory time are correlated also, but more weakly. This was described originally by Newsom Davis and Stagg [1]. Later investigators studying awake subjects [Robbins PA, personal communication; 2-6] or anaesthetized patients [7-15] have described similar findings. When breathing is more irregular, the distribution of the variables can be bimodal or multimodal, but this is usually because breaths with tidal volumes that are much different from the mean tidal volume also have inspiratory and expiratory times different from their means. Shea and colleagues [16] commented that derived variables (such as mean inspiratory flow and inspiratory duty cycle) are distributed normally 90% of the time.

Five of 32 patients included in two of our studies [17, 18] showed a bimodal distribution of expiratory time. The bimodality was independent of inspiratory time or tidal volume. Vibert and co-workers analysed long periods of breathing from cats [19] and humans [20] and decomposed the overall distributions of breathing rate statistically into a number of component normal distributions. In cats the distribution was trimodal, corresponding to sleep–wake state. In humans, although there were changes from one breathing rate to another, the polymodal or Gaussian histograms were not as clear as those from cats. Vibert and co-workers suggested that breathing rate was driven by a multi-oscillator, one or other state dominating for a time. This was not our observation, which looked more as if the rate was bistable, flipping to and fro between the two co-existing modes. I suggested that this might be a non-linear, chaotic process [21].

There are methods for distinguishing between chaotic processes and randomness in time series, but it is not easy with data from breathing, which are not absolutely "clean". One method is that of Sugihara and May [22]. Using data from a later study [23], we attempted to identify a chaotic process. The results of the analyses were equivocal.

What is not equivocal is that the bimodality of expiratory time is a real phenomenon and remains unreported, except in passing in our earlier studies. This study investigates some features of this bimodality.

Patients and methods

Forty patients gave written informed consent to take part in various studies of breathing while anaesthetized. All were approved by the local Ethics Committee. Some of the findings of these studies, and the general methods, have been reported previously [23-25].

All patients were ASA I, of slim build, and judged clinically to have easily managed airways under general anaesthesia. The 31 patients (25 women) from whom some findings have been reported already were aged 23-52 yr and weighed 49-83 kg; nine received a benzodiazepine for premedication. The nine other patients (seven women) were within the same ranges for age and weight and were unpremedicated. All patients were monitored by pulse oximetry. A cuff for non-invasive arterial pressure monitoring was placed, but it was not used unless indicated clinically because of disturbance to breathing.

All patients were anaesthetized with a sufficient induction dose and then an infusion of propofol...
Figure 1 Frequency histograms of the residuals (rsd) generated by regression of expiratory time (TE) against elapsed time. Each histogram is from a single patient (record number shown) anaesthetized with an infusion of propofol. Expiratory time from these eight patients was bimodal for all or most of the record. Occasional outliers because of sighs have been omitted, but all 14 sighs that occurred during NS27 are included.

13 mg kg\(^{-1}\) h\(^{-1}\). The infusion was stepped down at 10-min intervals to 11 and then 9 mg kg\(^{-1}\) h\(^{-1}\); the interval was prolonged if a patient was judged clinically to be anaesthetized lightly. Ten of the patients [23] had been receiving a sedating infusion of propofol for 20 min before induction of anaesthesia and they breathed air or oxygen via a face mask. All other patients breathed air, oxygen-enriched air, or oxygen and nitrous oxide via a laryngeal mask airway with continuous capnography.

No other drugs were given until the end of the study when the patients were given drugs to allow tracheal intubation. Recording of breathing continued until the anaesthetist commenced manual ventilation.

Breathing was recorded by respiratory inductance plethysmography (Respitrace model 10.9000 or AMI Model 150, Studley Data Systems), calibrated by multiple linear regression and analysed and stored on computer (Acorn BBC B+) using a simple algorithm: each beginning of inspiration was taken as the time when the volume signal exceeded a threshold above the preceding minimum; each end of inspiration was when the volume signal exceeded a threshold below the preceding maximum. Tidal volume was calculated as the difference between the minimum and maximum volume signals. Tidal volume, inspiratory time, ventilatory cycle time and clock time were collected for each recorded breath and expiratory times were calculated as cycle time minus inspiratory time.

The program ignored breaths of tidal volume less than 50 ml or ventilatory frequency more than 45 b.p.m. (default values); thus there was a gap in the record to flag the occurrence of invalid breaths. There was no other automatic rejection of artefacts. The plethysmographic signal was watched throughout recordings, and the breath numbers were noted during periods of disturbance. These breaths were flagged later and not included in the analysis.

Tidal volumes, and inspiratory and expiratory times were plotted against elapsed time and as frequency histograms and the plots checked for conspicuous bimodality. If a variable changes with time, the frequency histogram is broadened. To correct for this, least squares regression of the variable against elapsed time (usually linear but sometimes polynomial) was performed and the frequency histograms of the residuals checked.

Figure 2 Frequency histograms of the residuals (rsd) generated by regression of expiratory time (TE) against elapsed time. Each pair of histograms is from a single patient (record number shown) anaesthetized with an infusion of propofol. Expiratory time from these six patients altered between being unimodal and bimodal during the record (the number at the top right of each histogram is the range of elapsed time in minutes). Occasional outliers due to sighs have been omitted.
Correlations between the primary variables (or between their residuals against time if they altered with time) were observed. Autocorrelations of expiratory times were plotted as current expiratory time against next expiratory time. These plots show if short expiratory times tend to occur together (a cluster of points bottom left quadrant) or if long expiratory times occur together (cluster top right), or if short and long alternate (clusters top left and bottom right).

StatView (SE+Graphics, Abacus Concepts) on a Macintosh Ilsi computer was used for all analyses. No formal statistical analysis for bimodality was performed.

Results

Between 15 and 60 min of breathing, up to about 1000 usable breaths, were available from each patient. No suitable, sufficiently long records were available of patients' breathing while awake or sedated. Of the 40 records studied, 14 time series of expiratory time showed clear visual evidence of bimodality: in eight the bimodality persisted throughout the record or became established after a few minutes of anaesthesia (fig. 1); in six there was a sudden change of state between unimodality and bimodality (fig. 2). No record showed a single mode slowly broadening and then resolving into two modes. Modes differed by about 0.5 s. Modes contained roughly equal numbers of expiratory times (fig. 1: JR06, GG10, TC23, NS27 and MW28; fig. 2: AB01, NK05, ST13 and LP22) or one mode was more or less dominant (fig. 1: JF07, JC16 and RB25; fig. 2: JC06 and IH21).

The program did not partition expiratory time. There were different durations of expiratory pause visible in the plethysmographic signals; the inspiratory and expiratory patterns of short or long breaths were otherwise similar (fig. 3). Many of the features of the bimodality are shown by record GG10 (fig. 4). Two minutes after induction of anaesthesia, expiratory time became obviously bimodal, and remained bimodal, even during disturbance to breathing caused by application of a face mask for oxygen and after injection of a neuromuscular blocker. The contrasting unimodal distribution of tidal volumes and inspiratory times is clear from the frequency histograms (fig. 4).

Discussion

In records from five of 32 patients from earlier studies and from 14 of 40 patients analysed for this report, the distribution of expiratory time was clearly bimodal. The bimodality, which can be seen in the plethysmographic signal, cannot be an artefact of the program. For each breath, clock time, inspiratory time and total cycle time are stored; expiratory time is calculated. A flag is set if the sum of clock time, inspiratory time and expiratory time does not equal
clock time at the start of the next breath. Any incorrect measurement of expiratory time as too long would be balanced by the inspiratory time being too short.

Periodic breathing is well known [26, 27], but in periodic breathing tidal volume and frequency alter together in an exaggeration of the normal tendency for larger breaths to be longer breaths. Neurological, cardiovascular or respiratory disease can disrupt ventilatory patterns, but both rhythm and volume tend to be affected [28, 29]. Breathing that alternates between shorter, smaller breaths and longer, larger breaths can be explained by oscillations in chemical stimuli, although it usually requires low ventilatory frequencies and quite large chemical oscillations. The patients reported here in whom bimodality of expiratory time was seen, and those reported in our earlier studies, were healthy and were not breathing slowly; there is no reason to suppose large chemical oscillations and there was no cardiovascular instability during anaesthesia.

Newsom Davis and Stagg [1] commented that expiratory time had the greatest variability; it was not unimodal in four of their 15 subjects. They did not say if these distributions were bimodal, but commented that the variability was caused partly by swallowing, which did not occur in our subjects. Expiratory pauses were uncommon in their subjects, but were more frequent in subjects with larger variability of expiratory time. Gautier's group [30] showed that active retardation of expiration is important in controlling the duration of expiration in awake cats. Retardation occurs in anaesthetized humans but, although without more detailed analysis of the taped records, I cannot exclude retardation as part of the reason for longer expiratory times, the obvious difference between short and long breaths in the plethysmographic signals was the duration of the expiratory pause.

I do not know what causes bimodality, or why some patients showed it and others did not. There was no common factor. There were no suitable records of awake breathing from any of the patients, but no investigator has described this pattern in any study of normal breathing. It may be that every patient would show the pattern at some time if the recording were long enough. In patients during stable anaesthesia, lying undisturbed, there is unlikely to be any stimulus that could correspond with the synchronous stimulation of afferent nerves that can have within-breath effects in animal experiments [31, 32].

Propofol is the only factor common to all observations in this and previous studies, although there is no evidence that this is the cause. Bimodality is unlikely to have a simple link with "depth" of propofol anaesthesia. In one of the earlier studies, bimodality appeared shortly after an increment of propofol and then persisted (see fig. 4 [18]).

At various stages in the course of these studies patients breathed volatile agents, hyperoxic mixtures and nitrous oxide; their breathing was stimulated by carbon dioxide; increments of alfentanil were given and these caused marked slowing of breathing and increments of propofol caused short-term decreases in tidal volume. Bimodality was seen at various times under all of these circumstances. In one or two patients changes between unimodal and bimodal timing seemed to occur shortly after an alteration in inspired gas mixture, but other modal changes occurred after no apparent alteration.

I suggested [21] that bimodality could be a result of Vibert's competing rhythms from a multi-oscillator in the respiratory centre [20] (even though their descriptions are not the same as those described here) or that the central respiratory timer, more specifically the "on-switch" to start the next breath, has non-linear (chaotic) properties. There is no clear neuroanatomical correlate of any switch [33] but the idea is useful. The respiratory neurones in the medulla have well described patterns of firing, and many of their connections are known [34]. This has led to theoretical models of respiratory rhythm [35, 36]. Models must be able to predict all of the behaviour of the modelled system. They are not yet that perfect, but complex networks can generate behaviour of their own, independent of imposed stimuli. Parkes and co-workers [37] described shortening of expiratory time in rat medullary neurones that occurred independently of any change in conditions. They were particularly careful not to alter pulmonary stretch. Some cells failed to depolarize fully. This mechanism could underlie the bimodality in human expiratory times, and needs incorporating in the models.

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References

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