The characteristics and frequency of augmented breaths during CO_2-induced hyperpnoea of newborn infants

Gary Cohen and David J. Henderson-Smart*

Department of Perinatal Medicine, King George V Hospital, Missenden Road, Camperdown, NSW 2050, Australia

1. Hypercapnic ventilatory responses of thirty-five full term infants aged 1–7 days were evaluated, and the characteristics and incidence of augmented breaths were determined.

2. According to the inspiratory airflow profile and tidal volume (V_T), augmented breaths were categorized as 'type A' (biphasic, $V_T \geqslant 2 \times$ control V_T), or 'type M' (multiphasic, $V_T < 2 \times$ control V_T).

3. Steady-state inhalation of 2–4% CO_2 resulted in a 3-fold increase in the frequency of augmented breaths after 8 min; 80 s rebreathing a mixture containing 5–6% CO_2 resulted in a 20-fold increase in the frequency of these breaths.

4. During eupnoea, 85% of spontaneously occurring augmented breaths were type A. With increasing respiratory drive, there was a disproportionate increase in type M compared with type A breaths: after 80 s rebreathing, 86% of augmented breaths were type M and only 14% were type A.

5. These findings indicate that the hypercapnic hyperpnoea facilitates an inspiration-augmenting reflex in newborn infants. The significance of type M breaths is unclear; they appear to be characteristic of the newborn, and may represent the response of an immature respiratory system to load.

The breathing pattern of adults and infants is normally interrupted by occasional, spontaneous deep inspiratory efforts, called augmented inspiratory efforts or sighs (Bendixen, Smith & Mead, 1964; Thach & Taeusch, 1976; Fleming, Goncalves, Levine & Woollard, 1982; Perez-Padilla, West & Kryger, 1983). Such breaths typically consist of a sudden, additional inspiratory effort occurring at the crest of a normal inspiration, producing a large increase in tidal volume (V_T). They are thought to be important in aiding ventilation through airway re-opening, re-expanding areas of atelectasis and increasing lung compliance (Reynolds, 1962; Thach & Taeusch, 1976; Nicholas, Power & Barr, 1982). Reflexes modifying the spontaneous rate of augmented inspiratory efforts have been described for animals (Cherniack, von Euler, Glogowska & Honma, 1981). However, very little is known about the reflex regulation of these breaths in either infant or adult humans. During measurements of the ventilatory response of newborn babies to CO_2 at different fractional inspired O_2 concentrations (F_{I,O_2}), we noticed that the frequency of augmented breaths increased. We also noticed that during these tests, breaths occurred which could not strictly be classified as 'augmented', but which nevertheless showed evidence of increased inspiratory airflow. Following a retrospective examination of our recordings, we report here the characteristic appearance and frequency of these breaths.

METHODS

Subjects

Thirty-five healthy, full term infants (gestation, 39 ± 0·2 weeks; range, 37–41 weeks) (means ± S.E.M.) were studied within the first week after birth (postnatal age, 87 ± 7·0 h; range, 31–186 h). Studies were performed following a scheduled feed, with the infants swaddled in blankets lying supine in open cots. Since detailed descriptions of the physiological measurements made, as well as the steady-state and rebreathing methodology employed, have been given elsewhere (Cohen, Xu & Henderson-Smart, 1991; Cohen & Henderson-Smart, 1994), only a brief description is given here. Airflow ($\dot{V}$; measured using a nasal mask-pneumotachograph), continuous arterial oxygen saturation (S_{a,O_2}; N-100 pulse oximeter; Nellcor, Hayward, CA, USA), transcutaneous P_{O_2} (Roche 820 transcutaneous electrode; Hoffman La Roche Ltd, Basle, Switzerland), end-tidal P_{CO_2} (P_{ET,CO_2}; O_2–CO_2 analyser Engström-Eliza Duo; Gambro Engström AB, Bromma, Sweden), electroencephalogram, and eye movements were recorded continuously on paper (Grass Instruments

* To whom correspondence should be addressed.

polygraph) and magnetic tape. P_{ET,CO_2}, S_{a,O_2} and $\dot{V}$ signals were also sampled by a personal computer; tidal volume (V_T) was calculated by digital integration of the flow signal. Quiet sleep (QS) and rapid eye movement (REM) sleep are defined as previously (Prechtl, 1974). All studies were approved by the Institution's Ethics Review Committee (King George V Hospital, Camperdown, NSW, Australia) and attending physician, and the written informed consent of each infant's parents was obtained.

Hypercapnic hyperpnoea was produced by either the steady-state or rebreathing method. Rebreathing tests (32 infants, measured on 36 occasions) were performed by subjects rebreathing 5–6% CO_2 at one of three F_{I,O_2} levels: 0·15 (hypoxia), 0·21 (normoxia) or 0·4–0·7 (hyperoxia). S_{a,O_2} measurements confirmed that appropriate changes in arterial oxygenation occurred during these tests (hyperoxic hypercapnia: S_{a,O_2}, 100%; normoxic hypercapnia: S_{a,O_2}, >95%; hypoxic hypercapnia: ramp fall in S_{a,O_2} to < 95%). Three groups of infants were studied on different occasions. For five subjects, normoxic–hypercapnic responses were measured during QS and REM sleep; for ten subjects, hyperoxic (40% O_2), as well as normoxic, responses were measured (QS only); and for eighteen infants, hypoxic, normoxic and hyperoxic (40 or 70% O_2) responses were measured (QS only). Rebreathing tests were typically 1·5–2·0 min in duration. Replicate tests were performed at each F_{I,O_2}. During hypoxic– hypercapnic tests, S_{a,O_2} was not permitted to fall below 85%. To measure steady-state CO_2 responses, subjects inhaled (during QS) 2% CO_2 for 4 min, followed by 4% CO_2 for a further 4 min.

Data analysis

Breaths were designated as augmented (type A) breaths if the V_T was at least twice the V_T of the preceding breaths (Bendixen *et al.* 1964; Thach & Taeusch, 1976; see Fig. 1). A second breath type – multiphasic, or type M breaths – was also characterized. The characteristic feature of these breaths was the occurrence of 'notches' (multiple interruptions to airflow) in the inspiratory waveform. The V_T profile of these breaths was distinctive (Fig. 1). The number and frequency of type A and type M breaths during the initial 80 s of each rebreathing test was compared with that measured during the 80 s control period immediately preceding each test (all tests had a minimum of 80 s data).

Changes in the frequency of type A and type M breaths during steady-state CO_2 inhalation were also studied during QS. The duration of steady-state tests (8 min) in relation to the length of a QS epoch limited the collection of control data to the 4 min preceding each test. Arousal or a change of state interrupted the last minute of nine of the fourteen tests analysed (i.e. the period during which 4% CO_2 was inhaled), necessitating the exclusion of these data. Consequently, fourteen control and 2% CO_2 periods, but only nine 4% CO_2 periods (each of 4 min) were analysed.

Statistical analysis

Data are presented as means ± S.E.M. The significance of changes in the frequency of type A and type M breaths during steady-state and rebreathing tests was evaluated using a two-way ANOVA with the independant variables as time and breath type, F_{I,O_2}, sleep state, and inspired CO_2 concentration, respectively. The effects of the two variables considered separately, as well as simultaneously (the interaction effect), are given where appropriate. $P < 0·05$ was considered to be significant.

RESULTS

Rebreathing

The results of 281 QS tests were analysed. There was a significant increase in the incidence of type A as well as type M breaths during rebreathing, with distinctive temporal distributions evident for both. A peak in type A breaths occurred 20–30 s after rebreathing was initiated,

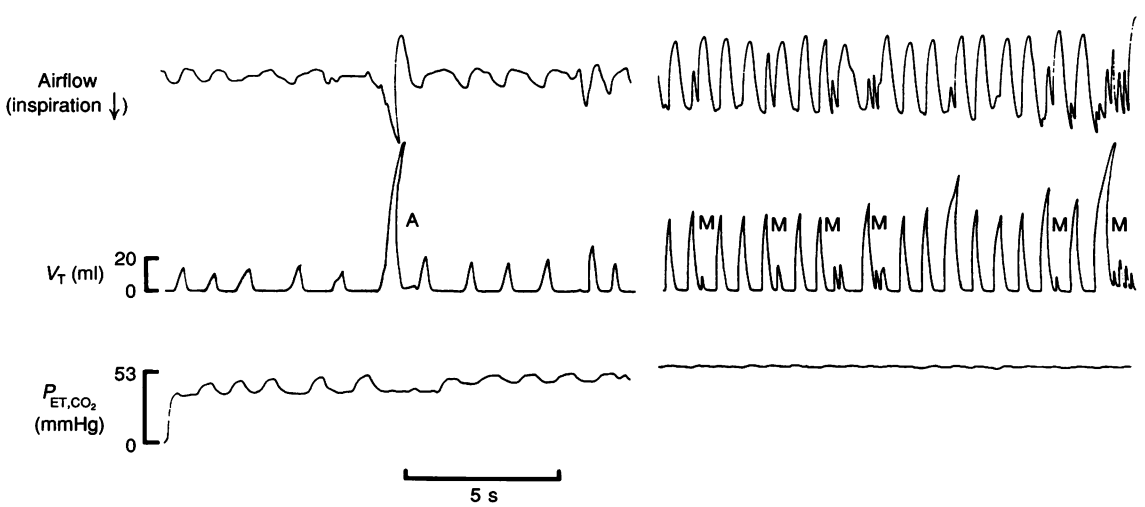

Figure 1

Augmented breaths recorded during the initial (left panel) and final (right panel) 15 s of a typical rebreathing test (total duration of test, 80 s). The characteristic features of type A (biphasic airflow, significant increase in V_T) and type M breaths (inspiratory augmentation attenuated by multiple interruptions of airflow) are illustrated.

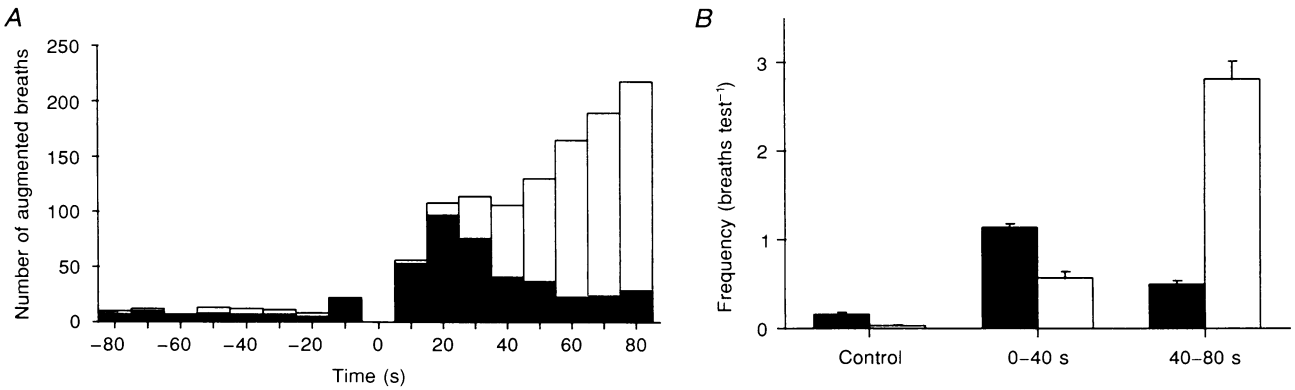

Figure 2

A, number of augmented breaths recorded each 10 s during control and rebreathing periods of 281 QS tests. An early increase and subsequent decline in type A breaths (■), and a simultaneous progressive increase in type M breaths (□) is evident during rebreathing. Note the slight increase in type A breaths during the 10 s preceding the onset of rebreathing. Note that although most (85%) control augmented breaths were type A, during the final 10 s of rebreathing, most (86%) augmented breaths were type M. *B*, data from Fig. 2*A*, showing frequency (breaths test^{-1}) of type A and type M breaths during eupnoea (Control), and the initial (0–40 s) and final (40–80 s) stages of rebreathing. The two distributions are significantly different (two-way ANOVA by time and breath type; interaction $P < 0{\cdot}001$). Control data in this and subsequent figures have been adjusted to reflect the rate over 40 s.

whereas the incidence of type M breaths increased progressively (Fig. 2*A*). The frequency with which these augmented breaths were elicited during rebreathing tests varied considerably between infants (type A: frequency, $1{\cdot}7 \pm 0{\cdot}1$ breaths test^{-1}; range, 0·4–3·4 breaths test^{-1}; and for type M: frequency, $3{\cdot}4 \pm 0{\cdot}5$ breaths test^{-1}; range, 0·2–20 breaths test^{-1}). Time *vs.* frequency profiles of the two breath types were significantly different (Fig. 2*B*; interaction $P < 0{\cdot}001$).

The F_{I,O_2} during the 281 QS tests varied: 68 were hypoxic, 115 normoxic and 98 were hyperoxic rebreathes, as confirmed by S_{a,O_2} measurements. There was no difference between frequencies of type A breaths recorded during these tests (Fig. 3*A*; $P = 0{\cdot}08$ for F_{I,O_2}; interaction $P > 0{\cdot}5$). There was overall a significant reduction in the frequency of type M breaths with increasing F_{I,O_2} ($P < 0{\cdot}03$ for the effect of F_{I,O_2}), however the frequency *vs.* time profiles were not significantly different (interaction $P > 0{\cdot}1$; Fig. 3*B*).

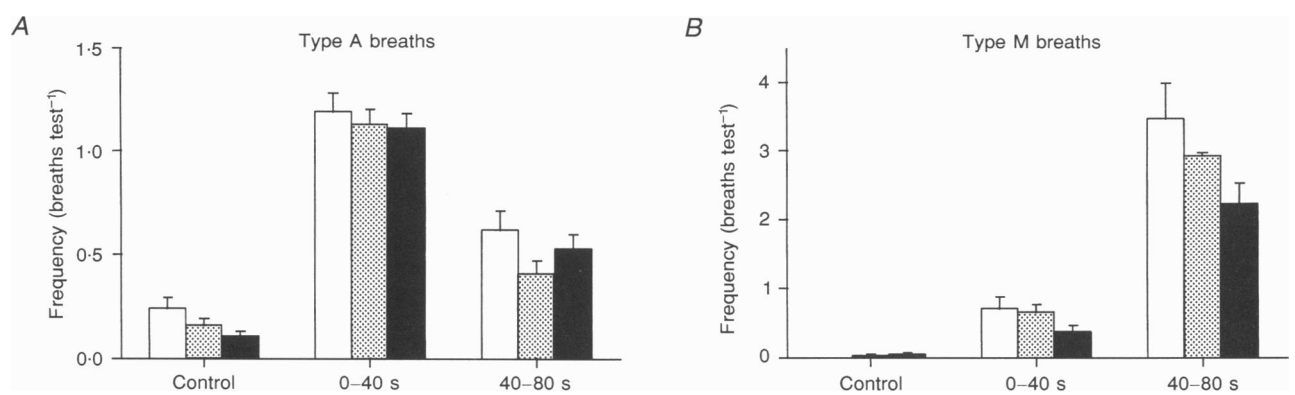

Figure 3

A, frequency of type A breaths preceding (Control) and during (0–40 s and 40–80 s) hypoxic (□, $n = 68$), normoxic (▨, $n = 115$) and hyperoxic (■, $n = 98$) QS rebreathing. Although the increase from control levels was significant (ANOVA, $P < 0{\cdot}001$ for time), the effect of F_{I,O_2} was not significant ($P = 0{\cdot}08$ for F_{I,O_2}; interaction $P > 0{\cdot}5$). *B*, frequency of type M breaths during the same tests. Separately, the effects of time ($P < 0{\cdot}001$) and F_{I,O_2} ($P < 0{\cdot}03$) were statistically significant; the interaction effect, however, was not ($P < 0{\cdot}1$). Note the difference between the ordinate scales of the two panels.

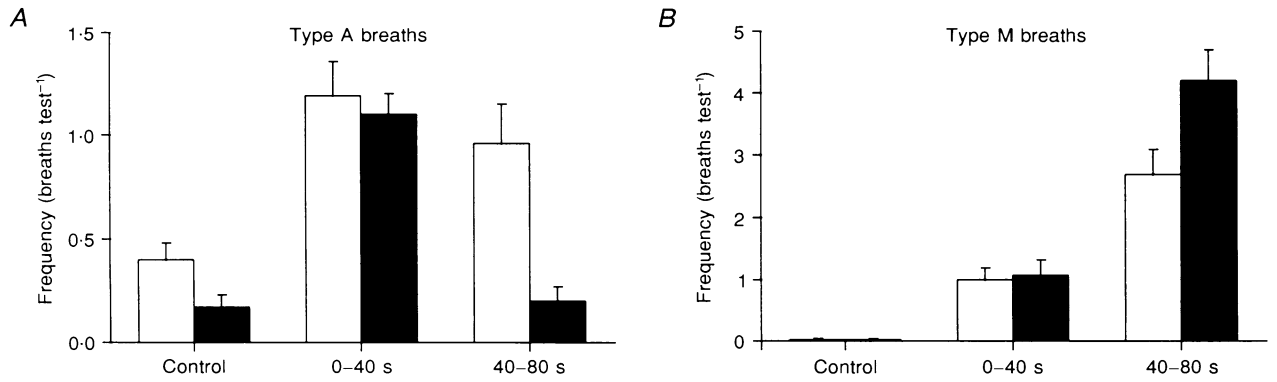

Figure 4

A, frequency of type A breaths during twenty-six REM sleep (□) and thirty QS rebreathing (■) tests (five infants). Note the increased frequency of type A breaths during the control period and final 40 s of rebreathing during REM sleep. The distributions were significantly different (ANOVA; interaction $P < 0{\cdot}02$). *B*, frequency of type M breaths during the same tests, illustrating the relative increase in the frequency of type M breaths during the final stage of QS tests. The two distributions were significantly different (interaction $P < 0{\cdot}02$).

Rebreathing responses of five infants were measured during QS ($n = 30$) and REM sleep ($n = 26$). During eupnoea (i.e. pre-rebreathing control periods), augmented breaths were almost exclusively type A; the frequency with which these breaths occurred was significantly greater during REM sleep compared with QS (36 ± 7 *vs.* 15 ± 5 breaths h^{-1}; $P < 0{\cdot}01$ by Student's unpaired *t* test). Type A breaths were significantly more frequent during REM rebreathing (Fig. 4*A*; interaction $P < 0{\cdot}02$), whereas type M breaths were significantly more frequent during QS tests (Fig. 4*B*; interaction $P < 0{\cdot}02$).

Steady-state tests

The frequency of type A breaths which occurred spontaneously during control (air) breathing (15 ± 5 h^{-1}) was equal to that measured during control periods preceding QS rebreathing tests (no type M breaths recorded). Changes in the frequencies of these breaths during inhalation of 2 and 4% CO_2 were significant for breath type ($P < 0{\cdot}001$) and CO_2 concentration ($P < 0{\cdot}02$), although frequency *vs.* time profiles of type A and type M breaths were not significantly different (interaction $P > 0{\cdot}8$; Fig. 5). Comparison of rebreathing and steady-state CO_2 responses elicited from one infant on two separate occasions (there was a 2 day gap between these tests) indicated that significantly greater changes in P_{ET,CO_2} and V_T occurred during rebreathing (Fig. 6).

DISCUSSION

Virtually no attention has been paid in the past to the occasional deep breaths which occur during CO_2 response tests in humans. In fact, breaths of this sort are usually excluded from the analysis of data to facilitate the calculation of the ventilatory response (for example see: Avery, Chernick, Dutton & Permutt, 1963; Read, 1967; Praud, Egreteau, Benlabed, Curzi-Dascalova, Nedelcoux & Gaultier, 1991; Cohen & Henderson-Smart, 1994). Our data

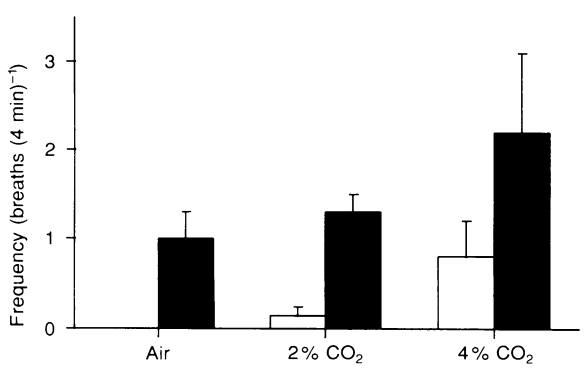

Figure 5

Frequencies of augmented breaths during steady-state tests (□, type M breaths; ■, type A breaths; units are breaths $(4\ min)^{-1}$). The increase in frequency during these tests was significant for breath type ($P < 0{\cdot}001$) and CO_2 concentration ($P < 0{\cdot}02$), although the frequency *vs.* time profiles of type A and type M breaths were not significantly different (ANOVA; interaction $P > 0{\cdot}8$).

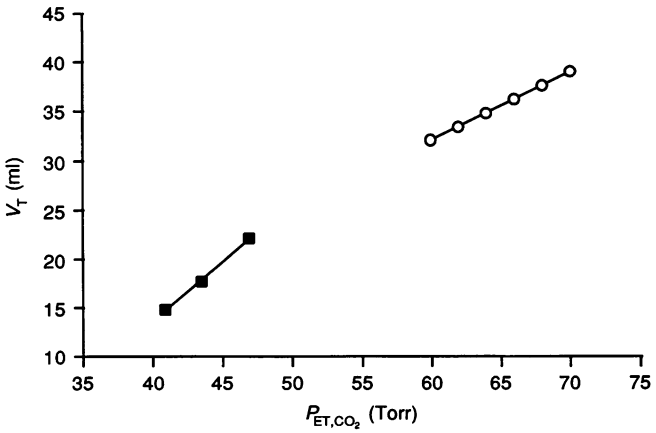

Figure 6

Difference between the P_{ET,CO_2} and V_T levels achieved during hypercapnic hyperpnoea achieved by the steady-state (■) and rebreathing (○) methods. The same infant was tested by both methods; there was a 2-day interval between tests.

indicate that the frequency, as well as the characteristics, of these breaths change during CO_2-stimulated breathing. The analysis of these changes may give some insight into the regulation of breaths which have an important role in maintaining alveolar stability, particularly in the newborn (Thach & Taeusch, 1976; Nicholas, Power & Barr, 1982).

Experimentally, augmented breaths can be elicited by lung hyperinflation (Cross, Klauss, Tooley & Weisser, 1960; Reynolds, 1962; Thibeault, Wong & Auld, 1967; Greenough, Morley & Davis, 1983), hypercapnia, and hypoxia (Reynolds, 1962; Bartlett, 1971; Cherniack *et al.* 1981). Lung inflation is particularly effective in eliciting an augmented inspiration from newborn infants, a phenomenon which has been attributed to the vigor of Head's paradoxical reflex period at this age (Cross, 1961). We found that CO_2-induced hyperpnoea significantly increased the frequency of augmented breaths in newborn infants. Since V_T and P_{a,CO_2} increase during CO_2 inhalation, the increase in frequency probably resulted from the simultaneous recruitment of mechanoreflexes responding to increasing V_T, and chemoreflexes responding to increasing P_{a,CO_2} levels. Changes in these parameters were significantly greater with rebreathing (Fig. 6), and perhaps not surprisingly, the increase in the frequency of these breaths was correspondingly greater (about 20-fold after 70 s rebreathing, compared with the 3-fold increase recorded during an 8 min steady-state test). We found wide differences between infants in the frequency with which type A and type M breaths were elicited by CO_2. Such differences may reflect normal interindividual variation: the frequency of spontaneous sighs occurring during sleep, for example, also varies between individuals (Thach & Taeusch, 1976; Curzi-Dascalova & Plassart, 1978; Fleming *et al.* 1982). We did not find any correlation between the frequency of type A (or M) breaths, and postnatal age at study, although it has also been reported that the frequency with which augmented breaths occur diminishes with increasing postnatal age (Curzi-Dascalova & Plassart, 1978; Fleming *et al.* 1982).

Breaths which we have called type A conform with the usual description of 'classical' augmented breaths: inspiration was biphasic, giving the overall appearance of a breath occurring on top of another breath (Thach & Taeusch, 1976; Cherniack *et al.* 1981; Van Lunteran *et al.* 1983; Mathew, Pronske & Clark, 1988; Watchko, Brozanski, O'Day, Klesh & Guthrie, 1989). Breaths of this sort typically have such a large V_T – easily twice that of preceding breaths – that they are normally defined (as they were in this study) by an increase in V_T of this magnitude (Bendixen *et al.* 1964; Thach & Taeusch, 1976; Perez-Padilla *et al.* 1983; Fleming *et al.* 1984; Mathew *et al.* 1988). We found that during eupnoea, the majority (85%) of breaths which had an additional phase of inspiratory airflow were of this type. The remaining 15% of these breaths were problematic, they were biphasic or multiphasic in appearance but inspiratory augmentation was brief and fragmented. Breaths of this sort have been described before (Thach & Taeusch, 1976; Roberts, Reed, Mathew & Thach, 1986), although no particular significance was attached to the different inspiratory waveforms, all were regarded as variants of the augmented breath. Significantly, V_T profiles were not reported in these studies. We found that the V_T of breaths of this type did not meet the criteria for augmented breaths, and warranted categorizing separately, as type M breaths.

A consequence of making the distinction between type A and type M breaths was that our analysis revealed a change in the relative frequency of the different breath types during hyperpnoea. The frequency of type A as well as type M breaths increased, however, the increase in type M breaths was disproportionately greater, and seemed to be more closely linked with the level of chemical drive. During eupnoea or low-level increases in respiratory drive (steady-state tests), for example, type A breaths predominated. With moderate increases in drive (the first 40 s of rebreathing) the frequency of type A and type M breaths was similar, whilst at high levels of drive (40–80 s of rebreathing), the balance shifted markedly in favour of

type M breaths. The reasons for, and significance of the increase in type M breaths is uncertain. One explanation, suggested by the observed reciprocal, simultaneous increase in type M and decrease in type A breaths (Fig. 2), may be that there was an increased tendency for type A breaths to fragment during vigorous hyperpnoea. This could result from intermittent upper airway obstruction at high inspiratory flow rates, as occurs during snoring (Liistro, Stanescu & Veriter, 1991). The likelihood of this occurring may be accentuated if phase differences develop between the activation of diaphragm and upper airway muscles at high levels of chemical 'drive' (Carlo, Martin & Difiore, 1988).

Alternatively, airflow 'spikes' have been reported to occur in the electromyogram of upper airway muscles during breaths with type M airflow patterns (Roberts *et al.* 1986), suggesting that the inspiratory 'fragmentation' we have described may be neurally patterned. We observed a relatively rapid (within 5–10 s) increase in type A breaths at the start of rebreathing, whereas the increase in type M breaths was somewhat delayed (occurring 10–20 s after the tests commenced). These different time courses are consistent with the differential activation of peripheral and central chemoreceptors (Edelman, Epstein, Lahiri & Cherniack, 1973), suggesting that the direct effects of increasing tissue P_{CO_2} upon brainstem neurones may favour central patterning of type M breaths, whilst classical augmented (type A) breaths may be more readily elicited in response to activation of the peripheral chemoreceptors (Bartlett, 1971). The increase in type A breaths which occurred immediately before rebreathing tests – about the time pneumotachograph was manually switched to the rebreathing circuit (Fig. 2) – suggests that type A breaths may also be elicited in response to mechanical or tactile stimuli. Of course, fragmentation of the inspiratory waveform need not originate centrally. It could also develop indirectly, in response to changes in phasic feedback from stretch receptors, intercostal afferents or upper airway receptors (Knill & Bryan, 1976; Hagan, Bryan, Bryan & Gulston, 1977; McBride & Whitelaw, 1981) during hyperpnoea.

Type M breaths do not appear to have been described for adults (multiple peaks of a different sort have been described; Bendixen *et al.* 1964; Perez-Padilla *et al.* 1983). If this pattern of inspiratory fragmentation is indeed peculiar to, or more frequent during the newborn period, it may reflect the stage of neurological or neuromuscular development attained (Schulte, 1974), or perhaps the intrinsic properties of an immature diaphragm (Muller *et al.* 1979).

The combination of a slight fall in S_{a,O_2} and an increase in P_{a,CO_2} had mixed effects on the incidence of the different types of breaths. No change occurred in the incidence of type A breaths, probably because S_{a,O_2} did not usually begin to fall significantly until 30–40 s after rebreathing commenced (by this time, the peak in type A breaths had already occurred). There was overall, however, a significant increase in the incidence of type M breaths induced by this combined stimulus. This is perhaps consistent with the known effect of hypoxia reducing the threshold of the inspiratory augmenting reflex (Reynolds, 1962; Bartlett, 1971; Cherniack *et al.* 1981).

Significant sleep state-related differences between type A and type M breaths were noted during this study. Type A breaths were more frequent during REM control periods, as well as during REM sleep rebreathing tests. An increased frequency of sighing during REM sleep is a consistent finding in the newborn (Curzi-Dascalova & Plassart, 1978; Alvarez, Bodani, Fajardo, Kwiatkowski, Cates & Rigatto, 1993). As with other characteristic irregularities in breathing pattern during this state, this may simply reflect an excitatory drive to breathe which is not present during QS (Sullivan, 1980). Interestingly, type M breaths were less frequent during REM sleep tests, when the the activity of inspiratory inhibitory reflexes arising from chest wall distortion is likely to be accentuated (Hagan *et al.* 1977). This could argue in favour of a mechanical (obstructive) rather than neural origin of such breaths. It is possible, however, that inhibitory activity from lung and chest wall mechanoreceptors is actually less during REM sleep due to reduced vagal activity (Finer, Abroms & Taeusch, 1976) and a reduced tidal volume and mean inspiratory flow response to CO_2 (Cohen *et al.* 1991). There may be a physiological advantage derived from the higher frequency of type A breaths during REM sleep: in view of the importance which has been attached to augmented breaths in maintaining lung volume, they may help preserve lung volume at a time when it is thought to decrease (Henderson-Smart & Read, 1979).

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