Eur Respir J
1990, 3, 293–298

Expiratory timing in obstructive sleep apnoeas

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ABSTRACT: Diaphragmatic electromyogram was recorded during NREM sleep in 4 patients affected by obstructive sleep apnoea (OSA) syndrome in order to evaluate the behaviour of expiratory time (T_E) in the course of the obstructive apnoea-ventilation cycle. The two components of T_E, *i.e.* time of post-inspiratory inspiratory activity (T_{PIIA}) and time of expiratory phase 2 (T_{E_2}) were separately analysed. T_{PIIA} showed a short duration, with only minor variations, within the apnoea, while its duration was more variable and longer in the interapnoeic periods: the longest T_{PIIA} values were associated with the highest inspiratory volumes in the same breaths. This behaviour seemed regulated according to the need of a more or less effective expiratory flow braking, probably as a result of pulmonary stretch receptors discharge. Conversely T_{E_2} showed a continuous gradual modulation, progressively increasing in the pre-apnoeic period, decreasing during the apnoea and increasing in the post-apnoeic period: these T_{E_2} variations seemed related to oscillations in chemical drive. These data show that T_E in the obstructive apnoea-ventilation cycle results from a different modulation in its two components and suggest that both mechanical and chemical influences play a role in its overall duration.

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Keywords: Expiratory timing; obstructive apnoea; post-inspiratory inspiratory activity.

Received: April 1987; accepted after revision October 26, 1989.

Respiratory timing during sleep in obstructive sleep apnoea syndrome (OSAS) undergoes periodic oscillations, due to the cyclically changing nature and intensity of stimuli influencing respiratory drive throughout the various phases of the apnoea-ventilation cycle [1, 2]. Inspiratory time has been extensively analysed in previous studies, while expiratory time (T_E) has received lesser attention [1, 2]: its variations have been mainly attributed to the effect of changes in chemical drive to breathing. Conversely, no attempt has been made to analyse separately its two components, namely the time of post-inspiratory inspiratory activity (T_{PIIA}) and the time of expiratory phase 2 (T_{E_2}) [3]. Since T_{PIIA} and T_{E_2} are placed under the control of different neuronal groups, their duration is separately regulated [4]. As a consequence, any accurate analysis aimed at understanding how expiration is timed during sleep in OSAS must include the separate evaluation of these two components.

Therefore, the purpose of our study was to analyse the behaviour of expiratory timing components during obstructive apnoea-ventilation cycles in order to evaluate how the different modulation in T_{PIIA} and T_{E_2}, resulting from stimuli of different natures, may affect the overall variations in T_E.

Methods

Four patients (2 males, 2 females) aged 35–57, with normal daytime respiratory function and with severe OSAS (mean apnoea index 66±18 SD) were studied during nocturnal sleep, after informed consent had been obtained.

The following signals were recorded on an eight-channel strip-chart recorder (Hewlett-Packard 7758B): electroencephalogram (C3A2 or C4A1 lead), electro-oculogram and submental electromyogram by surface electrodes, for conventional sleep staging [5]; oxyhaemoglobin saturation (Sao_2) with a pulse ear oximeter (Biox III, Ohmeda, Boulder, Co); diaphragmatic electromyogram with a bipolar oesophageal electrode made of two silver rings 2 mm wide, spaced 18 mm apart, and mounted at the distal end of a modified Swan-Ganz catheter introduced into the oesophagus: a latex balloon was attached to the tip of the catheter and, when inflated, anchored the electrode to the oesophagocardial junction; airflow, with a Fleisch no. 1 pneumotachograph attached to a tight fitting face mask; inspiratory and expiratory volume obtained with the integration of the flow signal.

The diaphragmatic electromyogram, amplified and band

pass filtered between 25 and 500 Hz, was recorded on an FM magnetic tape recorder (Hewlett-Packard 3968A) and was subsequently played back for time domain analysis: the output signal was full-wave rectified and averaged with a 50 msec time constant to obtain the moving average from which the following signals were measured:

- T_E from the peak to the beginning of the following inspiratory activity;
- T_{PIIA} from the peak to the end of any detectable inspiratory electromyographic activity;
- TE_2, expressed as the difference between T_E and T_{PIIA}.

A total of 48 apnoeas, all recorded during non-REM sleep, was selected. For each event a breath-by-breath analysis was performed on a sequence including the three unoccluded breaths immediately preceding the apnoea, all the occluded efforts and the three post-apnoeic breaths following the apnoea. In order to avoid problems deriving from the analysis of apnoeas not homogeneous as concerned the number of occluded breaths, we selected events which all included nine occluded efforts, well represented in the studied sample; in addition, we chose apnoeas that were separated from the surrounding ones by more than 3 unoccluded breaths.

T_E, T_{PIIA} and TE_2 were calculated and averaged for each pre-apnoeic, apnoeic and post-apnoeic breath, and expressed as absolute values ± standard error of the mean. The significance of the variations of T_I, T_E, T_{PIIA} and TE_2 in the pre-apnoeic, apnoeic and post-apnoeic phases was evaluated by the analysis of variance, testing each pair of results, taken separately, by the Fisher's protected least significant difference at a probability level of $p<0.05$ [6]. The relationship between T_E and T_{PIIA}, as well as that between T_E and TE_2 were analysed separately for the three different phases by fitting a simple linear regression function.

The relationship between expiratory timing parameters and lung volumes was then evaluated. In order to compensate for the fluctuations in end-expiratory volume which occur throughout the apnoea-ventilation cycle [7], it was necessary to normalize within each cycle all the measured lung volumes with respect to a stable reference level: for this purpose we arbitrarily chose the second post-apnoeic breath, when the progressive reduction in end-expiratory levels, occurring during the apnoea, is overcome. Therefore as inspiratory volume (V_I) we measured the increase in inspiratory volume with respect to the cited reference level. The relationship of T_{PIIA} and TE_2 to V_I in each analysed interapnoeic breath was evaluated by fitting a single linear regression function.

Results

The selected apnoeas had a mean duration of 23.7±0.9 s and were associated with Sao_2 falls up to 87.3±0.4%.

The behaviour of inspiratory and expiratory timing parameters, as well as of V_I, is shown in fig. 1.

T_I (fig. 1A) tended to decrease in the pre-apnoeic period, where in the third-to-last breath it was significantly longer with respect to the second-to-last and the last one. Then,

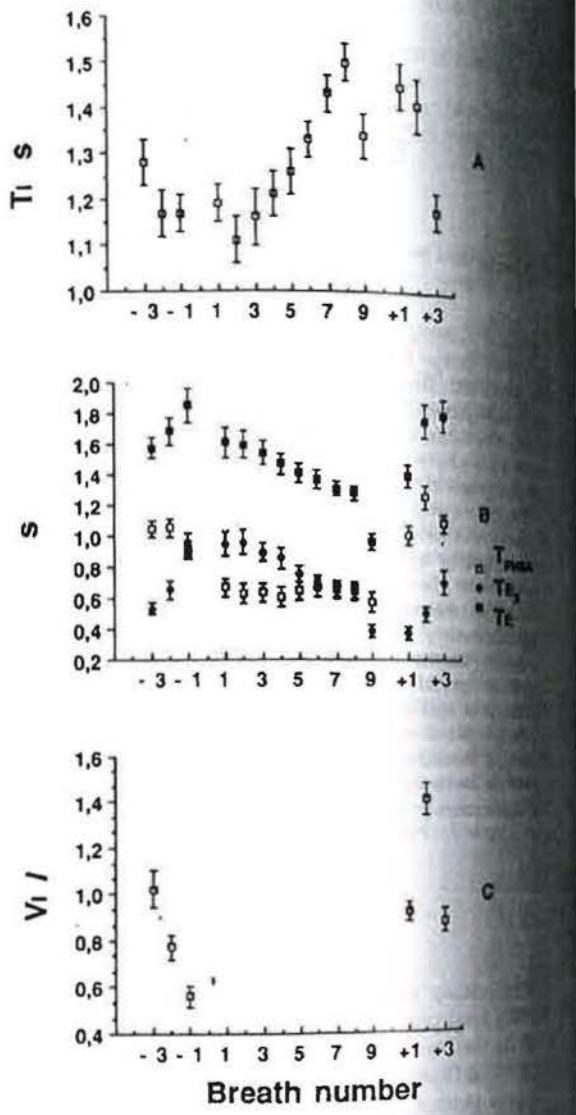

Fig. 1. – Trend of values (mean±SEM) of T_I (panel A), T_E, T_{PIIA}, TE_2 (panel B) and V_I (panel C), in all the subjects. -3 to -1: preapnoeic breaths; 1 to 9: occluded breaths; +1 to +3: postapnoeic breaths.

it showed a marked progressive increase during the occlusion, with a sudden and significant shortening at the last occluded breath; or, after an early prolongation, it tended again to decrease in the post-apnoeic period, but at the third breath it was significantly shorter than the first and second one.

With regard to expiratory parameters (fig. 1B), T_E progressively increased in the pre-apnoeic phase, with a significant difference between the third-to-last and the last breath, and decreased, although not significantly, at the apnoea onset; during the apnoea it slowly decreased, showing a significant difference between the first occluded effort and the breaths from the sixth one to the end of the apnoea. At the resumption of ventilation it suddenly and significantly increased, and kept on increasing in the following post-apnoeic breaths.

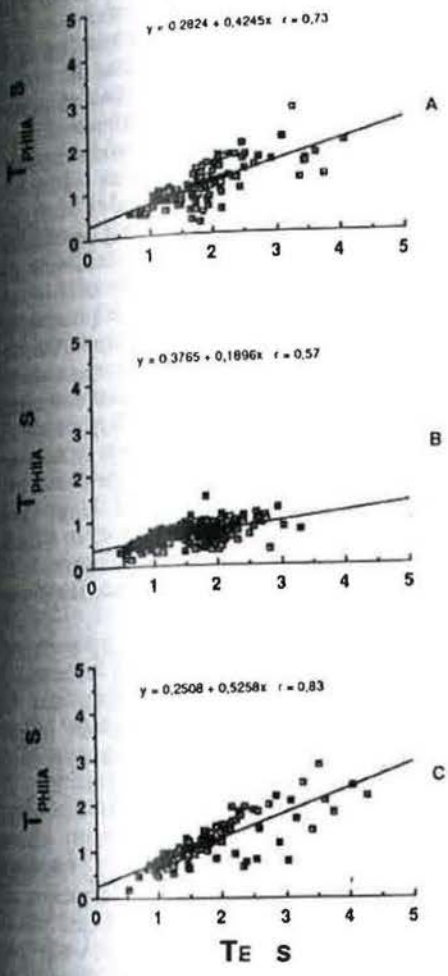

Fig. 2. – Relationship between TE and T_{PIIA} in the pre-apnoeic (panel A), apnoeic (panel B) and post-apnoeic (panel C) phases.

T_{PIIA} showed a slight (but not statistically significant) progressive decrease in the pre-apnoeic period, followed by a sudden and significant drop from the pre-apnoeic period to the onset of the occlusion; during the apnoea it remained stable on small values, all variations being not statistically significant. At the resumption of ventilation it suddenly and significantly increased, reaching the longest duration at the second post-apnoeic breath, where it was significantly higher than both the first and the third post-apnoeic values. T_{PIIA} was significantly correlated to TE in all the phases of the apnoea-ventilation cycle: both the coefficient of correlation and the slope of the regression line were lower for the apnoeic period than for the pre- and post-apnoeic phases (fig. 2.).

TE_2 underwent a progressive increase in the post-apnoeic period, a gradual decrease during the apnoea (with a brisk shortening at the last occluded effort) and a progressive increase in the post-apnoeic period. Negligible and non-significant variations were observed at the apnoea onset or at the resumption of ventilation. In the pre-apnoeic period, the third-to-last and the second-to-last breath were significantly different from the last

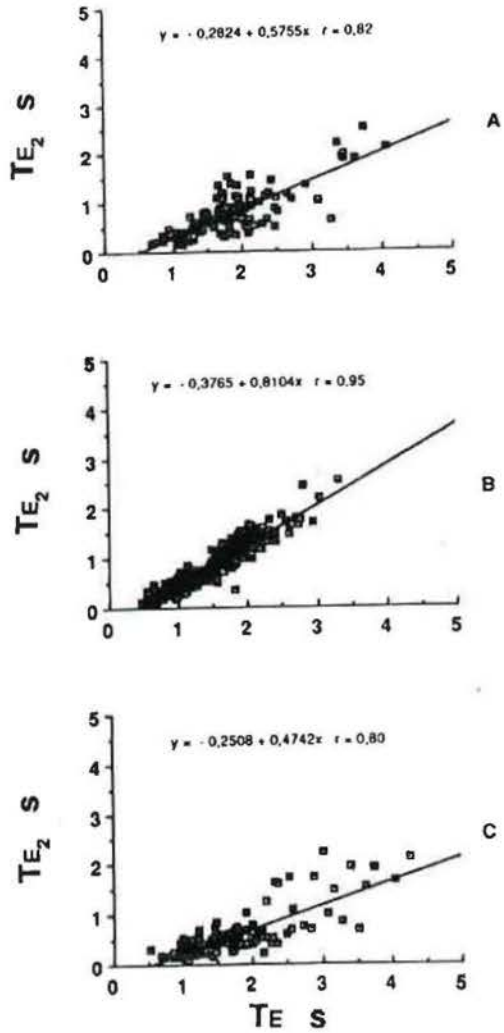

Fig. 3. – Relationship between TE and TE_2 in the pre-apnoeic (panel A), apnoeic (panel B) and post-apnoeic (panel C) phases.

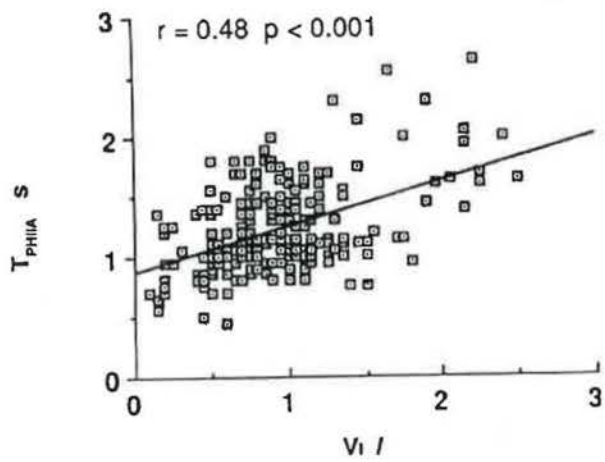

Fig. 4. – Relationship between VI and T_{PIIA} in all the analysed inter-apnoeic breaths.

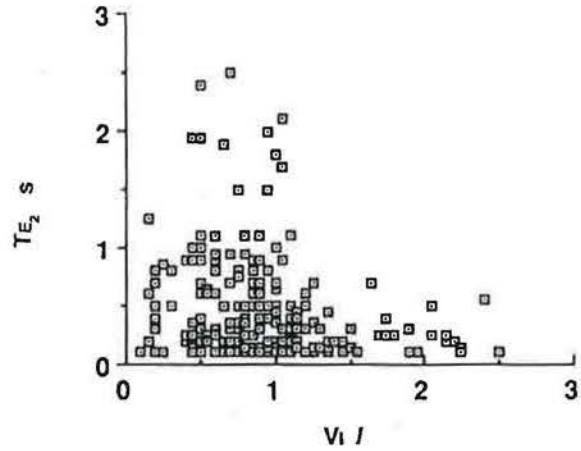

Fig. 5. – Relationship between VI and T_{E_2} in all the analysed inter-apnoeic breaths.

one, while in the apnoeic period the differences were significant between the first occluded effort and the breaths from the fourth one to the end of apnoea; in the post-apnoeic phase, a significant difference was found between the first breath and the third one. T_{E_2} and TE showed a highly significant correlation in all the three examined phases (fig. 3).

For VI, the highest values were reached at the second post-apnoeic breath (fig. 1C). When T_{PIIA} was plotted *versus* this parameter for each analysed breath, a significant correlation was pointed out (fig. 4). Conversely when T_{E_2} was plotted *versus* Vt no such relationship was found (fig. 5).

Discussion

The results of the present study confirm what was previously found for values of TI [2]: the only difference was with regard to the last occluded breath, which in our experience did not augment with respect to the preceding breath, but decreased slightly. As previously suggested [1], the onset of the arousal at the very end of the apnoea, causing a sudden increase in respiratory drive, could explain this sudden shortening.

Conversely, as far as expiratory timing is concerned, the overall TE duration in obstructive apnoeas results from the different and independent modulation of its two components. In fact T_{PIIA} is subjected to a breath-by-breath modulation in the interapnoeic periods, whereas it shows a short and stable duration during the occlusion. Conversely T_{E_2} undergoes continuous, gradual variations throughout the whole apnoea-interapnoeic ventilation cycle. These data suggest that different stimuli, in addition to the chemical ones, may influence expiratory timing.

For T_{PIIA}, the activation of inspiratory muscles during expiration is commonly interpreted as being aimed at reducing the rate of deflation of the lungs. This view is supported by the results of a study carried out on unanaesthetized cats [8]: in these experiments the post-inspiratory activity of the diaphragm was shown to be prolonged when laryngeal structures were by-passed by opening a tracheostomy, suggesting that this activity is regulated according to the need of braking expiratory flow. However, other investigations do not support this point of view: in fact, in anaesthetized cats [9] and in conscious humans [10, 11] no increase in the decay rate of inspiratory muscle pressure during expiration has been found after the application of an expiratory load, whereas an increase, with a shortening in T_{PIIA} would have been expected. These conflicting results could be partly explained on the basis of methods used to study T_{PIIA}. In fact unlike the study of REMMERS [8] and in our study, post-inspiratory inspiratory activity evaluation was not based on the analysis of diaphragmatic electromyogram; in addition, in one study [11] the results, admittedly, could have been influenced by consciousness. Our data support the hypothesis that the need of an expiratory airflow braking influences T_{PIIA}. In fact, we found that as soon as complete obstruction of the upper airway occurs (so that the lungs cannot be inflated), T_{PIIA} is markedly abbreviated; in addition we observed that the largest pulmonary inflations, that occur in the post-apnoeic period, are associated with the longest T_{PIIA}.

Mechanisms responsible for T_{PIIA} prolongation could depend on pulmonary stretch receptors (PSR) discharge. In fact, PSRs are active also during expiration so that the more the lungs are inflated the longer is TE [12]. A great portion of this TE prolongation seems to depend on an effect of PSRs on T_{PIIA}, since it has been demonstrated in lambs [13] that vagotomy abolishes post-inspiratory inspiratory activity. Conversely an effect of chemical stimulation on T_{PIIA}, consequent to the variations in chemical drive in the apnoea-ventilation cycle seems less likely. In fact no significant variation in T_{PIIA} was observed in the apnoeic period, while chemical drive was increasing; in addition the variations in T_{PIIA} in the interapnoeic periods did not show any clearcut trend possibly related to the likely changes in chemical drive occurring during those periods. These findings are not in contrast with the results of previous studies pointing out some effect of hypercapnic [14] and hypoxic [15, 16] stimuli. In fact those studies addressing separately the question of the effect of either stimulus have shown that while hypoxia seems to increase T_{PIIA} [14], the effect of hypercapnia is inconstantly seen and, if present, it is represented by a shortening in T_{PIIA} [15, 16]. Since in our experimental condition both O_2 and CO_2 tensions varied continuously throughout the apnoea-ventilation cycle, it is likely that the opposite effects of the two stimuli prevented the occurrence of any change related to chemical drive.

With regard to T_{E_2}, our data suggest that the observed changes were determined by oscillations in chemical drive: in fact a progressive prolongation was recorded when the latter was decreasing, *i.e.* in the pre-post-apnoeic periods as an effect of ventilation, while a progressive shortening was observed when chemical stimuli were increasing, *i.e.* during apnoea, as an effect of asphyxia. Interestingly, in the pre-apnoeic period the duration of

T_{E_1} is markedly prolonged: this phenomenon appears to be the most peculiar marker of the phase immediately preceding any apnoea. Although to our knowledge no study has been specifically performed on the duration of T_{E_1} as an effect of changing chemical drive so far, we can argue from other investigations that chemical drive and T_{E_2} duration are inversely related: in fact, it is well known that T_E as a whole is reduced when chemical drive increases [15–17]; this variation cannot be entirely accounted for by the cited possible change in T_{PIIA} related to hypercapnic drive [16] since in all cases, when noticed, the abbreviation in T_{PIIA} is less than the observed abbreviation in T_E: therefore in this case the shortening in T_E must be mostly due to T_{E_2}. While the variations in T_{E_1} were very gradual for the most part of the apnoea-interapnoeic ventilation cycle, the change from the second-to-last to the last occluded effort is abrupt and suggests that in this case, besides chemical drive, some additional factor may play a role: as previously indicated for T_I, arousal may account for this phenomenon because of its effect upon neural drive [1].

Conversely, mechanical stimuli related to lung inflation do not seem to play a major role in modulating T_{E_2}: actually in interapnoeic periods the marked changes in lung volume were not accompanied by proportional variations in this parameter. The superimposition of the effect of chemical drive may have been responsible for this finding: in fact, it has been demonstrated [18] that at high chemical drive levels the effects of volume-related vagal afferences on T_E are markedly blunted, and that this effect is proportional to the increase in chemical drive. This phenomenon may be reasonably attributed to T_{E_2} since, as previously discussed, chemical drive seems to have only minor effects on T_{PIIA}. This interpretation holds good in our study since the largest lung inflations were observed in the early post-apnoeic period, when chemical drive was likely to be very high, so as to conceal the effect of PSR discharge on T_{E_2}.

Within each phase of the apnoea-ventilation cycle variations of T_E reflected more closely the variations in T_{E_2} than those in T_{PIIA}. This consideration, already suggested by the inspection of fig. 1B, is confirmed by the evaluation of correlations: in fact a good and comparable degree of correlation between T_{E_2} and T_E is shown in all the phases (fig. 3). Conversely the correlation between T_E and T_{PIIA}, though significant, was of a lesser value (fig. 2). The role of T_{PIIA} in modulating T_E is even less important in the apnoeic phase, as suggested by the very low value of the slope of the correlation, indicating that negligible variations in T_{PIIA} correspond to much larger variations in T_E. Conversely only T_{PIIA} variations at the apnoea onset and after its cessation (due, respectively, to the interruption and resumption of airflow) may account for the parallel sudden variations in T_E occurring on the same occasions, while T_{E_2} is kept nearly unmodified.

In conclusion, expiratory timing during sleep in OSAS is the result of the independent modulation of T_{PIIA} and T_{E_2}: mechanical reflexes appear to be the main reflexes responsible for T_{PIIA} changes, while chemical reflexes are more likely to account for T_{E_2} behaviour.

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Le timing expiratoire dans les apnées obstructives du sommeil. F. Cibella, O. Marrone, S. Sanci, V. Bellia, G. Bonsignore.

RÉSUMÉ: Nous avons enregistré un électromyogramme diaphragmatique au cours du sommeil NREM chez 4 patients atteints du syndrome d'apnée obstructive du sommeil, afin d'évaluer le comportement du temps expiratoire (TE) dans le

décours du cycle de ventilation pendant l'apnée obstructive. Les deux composants de T_E, c'est-à-dire le temps d'activité inspiratoire aprés l'inspiration (T_{PIIA}) et le temps de phase expiratoire 2 (T_{E_2}) ont été analysés séparément. T_{PIIA} a montré une durée bréve, avec seulement de faibles variations pendant l'apnée, alors que sa durée s'avère plus variable et plus longue dans les périodes interapnéiques. Les valeurs les plus longues de T_{PIIA} sont associées aux volumes inspiratoires les plus élevés dans les mêmes respirations. Ce comportement semble réglé en fonction du besoin d'une interruption plus ou moins effective du débit expiratoire, probablement comme résultat d'une décharge des récepteurs de tension pulmonaire. Par ailleurs, T_{E_2} démontre une modulation graduelle continue, augmentant progressivement dans la période préapnéique, diminuant durant l'apnée et augmentant dans la période postapénique. Ces variations de T_{E_2} semblent en relation avec des oscillations de la stimulation chimique. Ces données montrent que T_{E_2} dans le cycle ventilation-apnée obstructive résulte d'une modulation différente dans ses deux composants, et suggèrent que des influences à la fois mécaniques et chimiques jouent un rôle dans sa durée totale.

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