Nocturnal evolution of respiratory effort in obstructive sleep apnoea syndrome: influence on arousal threshold

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ABSTRACT: It has been recently described that the overnight increase in maximal end-apnoeic oesophageal pressure (Poes,max), considered as an index of the arousal threshold to occlusion, mostly contributes to apnoea lengthening during the night. However, the rise in apnoea duration could also be caused by changes in hypoxaemia, chemosensitivity and upper airway resistance.

To better define the relative contributions of each of these factors, we examined the recordings of nine patients. Before apnoea, the mean pulmonary resistance at peak inspiratory flow (RPIF) was computed. During apnoea, all swings in oesophageal pressure (Poes) were measured to define the Poes,max, the increase from the minimum to the maximum (ΔPoes), the rate of increase in Poes (RΔPoes) and the Poes at the first occluded breath (Poes,1).

A gradual and significant increase in apnoea duration (p=0.02), Poes,max (p=0.02) and ΔPoes (p=0.006) was present across the night without any changes in oxygen saturation, RPIF, and Poes,1. The slope of increase in Poes,max, apnoea duration and ΔPoes was correlated with the apnoea/hypopnoea index.

We conclude that in obstructive sleep apnoea, the nocturnal rise in apnoea duration is attributable more to an increase in the arousal threshold related to apnoea recurrence than to changes in chemosensitivity and upper airway resistance.

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Resolution of obstructive apnoea during sleep is usually associated with a transient cortical arousal restoring upper airway patency and allowing resumption of ventilation. Hypoxaemia, hypercapnia, and increased respiratory effort [1, 2] may generate chemical and mechanical reflexes activating, directly or via central respiratory neurons, the reticular brainstem nervous system and allowing resumption of ventilation. Recent evidence in humans [3, 4] and in animals [5–7], has stressed that the progressive increase in the activity of respiratory muscles during an obstructive sleep apnoea (OSA) is the most important factor eliciting arousal and restoring upper airway patency. Thus, the maximum level of inspiratory effort (the maximal oesophageal pressure (Poes,max)) preceding arousal has been considered as an index of the arousal threshold to occlusion.

In patients with OSA, apnoea frequency and length increase in the second part of the night [8, 9] associated with an increase in Poes,max. This progressive rise in the index of the arousal threshold may occur throughout a night [10], as well as in the course of the disease [11]. Thus, we can hypothesize that the rise in apnoea length and in Poes,max in OSA patients may be determined by changes in arousability related to the effects of sleep fragmentation and sleep deprivation [12]. However, the reported studies did not investigate any potential effects of sleep fragmentation, changes in upper airway collapsibility and respiratory drive during the night, and the analysis were limited to selected apnoeas during the first and last hours of the night [10].

The current study was designed to determine whether the recurrence of obstructive apnoeas was associated with a progressive rise in the index of arousal threshold and in apnoea length across the night. If so, we analysed which diurnal or nocturnal variables (including indices of chemosensitivity and preapnoeic pulmonary resistance) affect the nocturnal rise in respiratory effort and in apnoea duration.

Patients and methods

Nine male patients, diagnosed as having OSA and chosen from our database, were examined. The patients were eligible if they had: 1) a nocturnal polysomnography performed using pneumotachograph and oesophageal pressure recordings without any technical problems during the monitoring; 2) a diagnostic study in the supine position throughout the night with repetitive apnoeas during all 1-h periods; 3) at least 7 h of nocturnal recording with periods of awake state lasting <30 min in each 1-h period; and 4) at least 10 obstructive apnoeas per hour eligible for analysis.

None of the patients suffered from acute lung disease at the time of the study, and none had received previous treatment with nasal continuous positive airway pressure.
(CPAP) or surgery. All patients had a full evaluation including polysomnography, blood-gas analysis and respiratory function tests for diagnostic purposes. They were informed that some of the collected data would be used for research purposes, and they gave written informed consent.

Nocturnal polysomnography was carried out between 22:00–23:00 h and at 06:00 h using an electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG) of chin muscles for conventional sleep staging. Breathing was analysed with a Fleisch #2 pneumotachograph and electronic integrator (Godart Statham, Bilt- hoven, the Netherlands) attached to a face mask. Oxygen saturation ($S_aO_2$) was measured continuously with an earlobe oximeter (Biox III; Ohmeda, Boulder, CO, USA). Oesophageal pressure was measured with a 10-cm latex balloon placed in the lower third of the oesophagus, inflated with 1 mL of air and connected to a pressure transducer (Validyne MW 45; Validyne, Northridge, CA, USA). The reference pressure for oesophageal pressure measurements was the atmospheric pressure and consequently all inspiratory pressures were negative. To facilitate analysis, all pressure values are given in absolute values, so that increases in the respiratory effort correspond to increases in the oesophageal pressure swings.

Sleep was scored using the criteria of RÉCHTSCHAFFEN and KALES [13] for 20-s periods, and the following variables were calculated: total sleep time, wake time after sleep onset (WASO), sleep efficiency (total sleep time/total recording time×100), and the percentage of stages 1, 2, 3, and 4 and rapid eye movement (REM) sleep. As indices of sleep fragmentation, we calculated the number of arousals, awakenings and sleep state changes. Arousal was defined as an EEG shift in the alpha or theta frequency having a duration of 3–10 s associated with an increase in chin EMG and awakening as a transition to at least one 20-s period of wakefulness. Respiratory events were defined using standard criteria. Hypopnoeas were defined as a $50\%$ reduction in tidal volume from the baseline value lasting at least 10 s. The apnoea index (AI) and the apnoea + hypopnoea index (AHI) were established as the ratio of the number of apnoeas and hypopnoeas per hour of sleep. The mean $S_aO_2$ during 10 min of quiet wakefulness prior to sleep onset, the minimal $S_aO_2$ and the mean of the minimal $S_aO_2$ after each event (mean lowest $S_aO_2$) were also computed.

Conventional spirography was performed with a 10-L closed spirograph, and static lung volumes were measured using the closed circuit helium dilution method.

Data analysis

Analyses were carried out for periods of 1 h from light-off to light-on for 7 h during non-REM (NREM) sleep. Oesophageal pressure was measured for all obstructive apnoeas with the following rejection criteria: 1) apnoeas with artifacts in oesophageal pressure or oxygen saturation tracings; and 2) apnoeas occurring during the 15-min periods before and after REM sleep periods. Obstructive apnoeas were defined as a cessation of airflow lasting at least 10 s with associated continuous inspiratory efforts. We considered for each apnoea two segments: the preapnoeic period and the obstructive period. These segments were defined using all polygraphic data to determine as accurately as possible the beginning and the end of apnoea. The analysis of some variables has been partially described in detail elsewhere [14].

During the three unoccluded breaths preceding the onset of apnoea, inspiratory peak oesophageal pressure ($P_{oes}$) and the peak inspiratory flow were measured. The mean preapnoeic oesophageal pressure was defined as the average of the single measured values. Resistance at peak inspiratory flow between apnoeic events was calculated as the ratio of each oesophageal pressure to peak inspiratory flow; the values obtained for each preapnoeic breath were averaged to obtain the mean resistance at peak inspiratory flow ($R_{PIF}$). As before the start of apnoea, the last unoccluded breath may show flow limitation, we also measured the $R_{PIF}$ before the apnoea ($R_{PIF,pre}$) in the second and third-last breaths preceding the apnoea, which were free from flow limitation as judged from the shape of the inspiratory flow curve.

During apnoea, the swings in oesophageal pressure during all occluded efforts were measured, and the following indices were calculated: the number of occluded respiratory cycles (cycles), the minimum of oesophageal pressure swings recorded at the start of apnoea, the maximum of the final swings ($P_{oes,max}$) recorded at the end of apnoea, the difference between the minimum and the maximum ($\Delta P_{oes}$) of the oesophageal pressure swings, and the rate of increase in intrathoracic pressure ($R_{Poes}$), defined as the ratio of $\Delta P_{oes}$ to the duration of apnoea. We also measured the lowest $S_aO_2$ value recorded after each apnoea and the value before occlusion in order to determine for each apnoea the decrease in oxygen saturation ($\Delta S_aO_2$) and its rate of decrease ($R_{S_aO_2}$), defined as the ratio of $\Delta S_aO_2$ to the apnoea duration. As indices of respiratory drive, we considered the value of $R_{Poes}$ and the $P_{oes}$ at the first occluded breath ($P_{oes,1}$).

During quiet wakefulness prior to sleep onset and in supine position, we defined for each patient the awake $S_aO_2$, the mean peak inspiratory flow and the mean peak inspiratory oesophageal pressure taken from the average of five consecutive breaths; their ratio was used as an awake resistance at peak inspiratory flow ($R_{PIF,w}$).

Results are given as means±SD. Data for each 1 h period obtained from each subject were averaged, and the slope of variation of ventilatory variables for the 1 h sample was determined with regression analysis over time. Values of ventilatory variables at each time point were compared by repeated measure analysis of variance. Pearson's correlation and multiple regression analysis were used to determine the relationship between changes in ventilatory variables and nocturnal and diurnal parameters. Statistical significance was assumed at p-value <0.05.

Results

Clinical, anthropometric and nocturnal respiratory findings of the patient group are listed in table 1. The patients, aged 52.8±3.0 yrs with a mean body mass index (BMI) of 30.8±1.4 kg·m$^{-2}$, had severe OSA syndrome, with a mean AHI of 85.9±6.8 ranging 55–128 and a mean AI of 82.9±6.8. The apnoeas were predominantly obstructive (94%) with a small number of central apnoeas (1%) and mixed apnoeas (5%). A wide range of nocturnal
hypoxaemia severity was present with a mean lowest \( S_aO_2 \) of 87.0±1.5% and a minimal \( S_aO_2 \) of 66.0±3.6%.

As a group, the patients had normal blood gases, forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity (FVC)%. Two patients were hypoxaemic (arterial oxygen tension \( \left( P_aO_2 \right) \) 8.6 kPa (65 mmHg)) and one hypercapnic (arterial carbon dioxide tension \( \left( P_aCO_2 \right) \) 6.0 kPa (\( \cong \) 45 mmHg)). None of the patients showed any restrictive or obstructive lung disease.

Nocturnal sleep structure was disrupted in all patients with a mean total sleep time of 318.6±25 min, a mean sleep efficiency of 70.1±5.3%, a mean WASO of 135.9±23.5 min, and a mean number of arousals, awakenings, and sleep state changes of 220.7±40.1, 221.9±37.4 and 327±98.5, respectively. Sleep architecture showed in all patients a sleep efficiency of 70.1±5.3%, a mean W ASO of 135.9±6.0 kPa, with a mean total sleep time of 318.6±25 min, a mean

### Table 2. – Mean values of ventilatory variables for each 1 h period during nonrapid eye movement (NREM) sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hour 1</th>
<th>Hour 2</th>
<th>Hour 3</th>
<th>Hour 4</th>
<th>Hour 5</th>
<th>Hour 6</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>( NREM ) sleep min</td>
<td>41.2</td>
<td>38.7</td>
<td>39.6</td>
<td>42.0</td>
<td>38.12</td>
<td>46.6</td>
<td>43.32</td>
</tr>
<tr>
<td>REM sleep min</td>
<td>0</td>
<td>2.6</td>
<td>1.9</td>
<td>2.9</td>
<td>4.5</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Number of recorded apnoeas</td>
<td>381</td>
<td>474</td>
<td>509</td>
<td>421</td>
<td>485</td>
<td>532</td>
<td>441</td>
</tr>
<tr>
<td>Number of analysed apnoeas</td>
<td>304</td>
<td>271</td>
<td>345</td>
<td>234</td>
<td>247</td>
<td>170</td>
<td>154</td>
</tr>
<tr>
<td>Duration s</td>
<td>25.7</td>
<td>29.7</td>
<td>28.4</td>
<td>29.9</td>
<td>31.1</td>
<td>31.2</td>
<td>31.3</td>
</tr>
<tr>
<td>( S_aO_2 ) after %</td>
<td>89.2</td>
<td>86.6</td>
<td>87.6</td>
<td>87.6</td>
<td>87.0</td>
<td>87.2</td>
<td>88.1</td>
</tr>
<tr>
<td>( \Delta S_aO_2 ) %</td>
<td>-7.5</td>
<td>-9.9</td>
<td>-8.8</td>
<td>-9.1</td>
<td>-9.7</td>
<td>-9.6</td>
<td>-8.4</td>
</tr>
<tr>
<td>( R_{PIF} ) cmH 2O·L-1·s</td>
<td>15.5</td>
<td>16.4</td>
<td>17.3</td>
<td>17.6</td>
<td>16.5</td>
<td>15.2</td>
<td>15.0</td>
</tr>
<tr>
<td>( R_{PIF,pre} ) cmH 2O·L-1·s</td>
<td>12.2</td>
<td>12.7</td>
<td>13.7</td>
<td>13.7</td>
<td>13.9</td>
<td>12.1</td>
<td>12.5</td>
</tr>
<tr>
<td>( P_{oes,1} ) cmH 2O</td>
<td>19.7</td>
<td>24.0</td>
<td>22.2</td>
<td>22.3</td>
<td>24.0</td>
<td>23.7</td>
<td>18.7</td>
</tr>
<tr>
<td>( P_{oes,max} ) cmH 2O</td>
<td>39.5</td>
<td>51.2</td>
<td>50.6</td>
<td>52.9</td>
<td>55.4</td>
<td>57.1</td>
<td>51.8</td>
</tr>
<tr>
<td>( \Delta P_{oes} ) cmH 2O</td>
<td>21.5</td>
<td>29.6</td>
<td>30.3</td>
<td>32.7</td>
<td>33.8</td>
<td>36.7</td>
<td>34.9</td>
</tr>
<tr>
<td>( R_{Poes} ) cmH 2O·L-1·s</td>
<td>0.85</td>
<td>1.01</td>
<td>1.10</td>
<td>1.11</td>
<td>1.12</td>
<td>1.19</td>
<td>1.17</td>
</tr>
</tbody>
</table>

\( S_aO_2 \): arterial oxygen saturation; \( \Delta S_aO_2 \): decrease in arterial oxygen saturation; \( R_{oes,1} \): rate of decrease in arterial oxygen saturation; \( R_{PIF} \): pulmonary resistance at peak inspiratory flow; \( R_{PIF,pre} \): \( R_{PIF} \) during the second and third last breaths preceding the apnoea; \( P_{oes,max} \): maximum oesophageal pressure; \( \Delta P_{oes} \): increase from the minimum to the maximum oesophageal pressure; \( R_{Poes} \): rate of increase in oesophageal pressure.
A Pearson's correlation analysis including the slope of increase in inspiratory effort and indices of sleep fragmentation and diurnal and nocturnal variables showed that none of the variables considered was correlated with the changes in $P_{\text{oes, max}}$ during the night. A significant and positive correlation was found between the slope of increase in apnoea length ($r=0.67$, $p=0.05$) and $P_{\text{oes, max}}$ ($r=0.66$, $p=0.05$) and the AHI.

Discussion

The results of this study have demonstrated that throughout the night, the recurrence of apnoeas results in altered responses to airway occlusion, including prolongation of the apnoea duration and increased peak inspiratory effort, irrespective of changes in hypoxaemia, respiratory drive responsiveness and pulmonary resistance. Using the $P_{\text{oes, max}}$ as an index of arousal threshold, we also demonstrated that repetition of apnoeic stimulus results in similar changes in the arousal threshold to occlusion. This latter finding suggests that the overnight rise in apnoea duration can be attributed predominantly to the associated change in arousal threshold rather than to other factors, such as nocturnal hypoxaemia or changes in upper airway collapsibility and chemosensitivity.

Some concerns about the methodology that we employed should be discussed before the analysis of our results. The measurements of respiratory variables we made may be affected by the distribution of sleep periods during the night as well as by the degree of sleep alteration. To minimize the effect of prolonged awakenings, we selected patients for whom repetitive apnoeas were present for the entire night with wakefulness periods lasting <30 min. Moreover, since the rise in apnoea duration over the night might merely reflect the greater amount of REM sleep in the second part of the night, we limited the analysis to NREM sleep. An upward trend in apnoea length and in $P_{\text{oes, max}}$ can still be observed, suggesting that the results cannot be attributed to the effects of REM sleep in itself. Moreover, our laboratory [14] has previously demonstrated that all indices of respiratory effort are lower in REM sleep. Taken together, these data led us to exclude the interference of REM sleep on nocturnal respiratory effort changes. Secondly, we have used the resistance at peak inspiratory flow as an index of upper airway resistance, which does not address directly upper airway collapsibility and dimension. It is known that upper airway resistance constitutes most of $R_{\text{PIF}}$ during NREM sleep and changes in $R_{\text{PIF}}$ are correlated with changes in upper airway resistance [15]. The use of this index may be complicated by the fact that the airway resistance can vary within a breath because of the variable negative pressure applied during inspiration to the collapsible airway. To avoid the confounding effect of flow limitation occurring frequently at the last breath before the onset of apnoea, we measured the peak inspiratory resistance at the second and third breath before the apnea in which the relationship between flow rate and negative pressure is often linear [15]. Even though we considered values without flow limitation, the
Nocturnal trend of respiratory effort in OSA

The figure shows the evolution during the 7 h of sleep for inspiratory peak resistance ($R_S$). Fig. 3. – The figure shows the evolution during the 7 h of sleep for nocturnal hypoxaemia were found during the remaining hours. The new finding of our study is that there is a progressive increase in apnoea duration present across the night associated with a significant rise in $P_{oes,max}$ (i.e. the index of arousal response to occlusion), and that occurs irrespective of changes in nocturnal hypoxaemia, in respiratory drive response and in preapnoeic resistance. These results are in keeping with the clinical observation that in the OSA syndrome, a progressive increase in apnoea duration occurs across the night [17, 18] and with the data of Montserrat et al. [10] showing a concomitant increase in $P_{oes,max}$ and apnoea duration at the end of the night. However, these studies were limited to an analysis at the start and at the end of the night for a limited number of apnoeas. Using a 1-h analysis, we were able to demonstrate that the increase in $P_{oes,max}$ and apnoea duration was greater during the first 2 h of the night, followed by a plateau in the second half of the night. This later finding may suggest that the changes in arousal response to upper airway occlusion can be attributed either to overnight alterations in the arousal threshold of the central nervous system or as being secondary to sleep fragmentation and recurrent apnoeas.

The potential mechanisms underlying the nocturnal changes in apnoea duration and in the index of arousal threshold are still not clear. We know that the arousal at the end of an obstructive apnoea may be induced by afferent stimuli arising from chemoreceptors, upper airway mechanoreceptors as well as increased ventilatory effort. Thus, several mechanisms may be implicated in the apnoea lengthening and in the increase in $P_{oes,max}$ during the night: changes in central chemosensitivity and in upper airway collapsibility, a dysfunction of peripheral mechanoreceptors, or altered arousal mechanisms.

Though upper airway resistance is higher in OSA patients when awake, it is well established that sleep per se [19, 20] or sleep fragmentation [21] has an impact on the upper airway collapsibility. If the rise in respiratory effort found in our OSA patients is influenced by changes in preapnoeic collapsibility, we could expect that a progressive increase in $R_{PIF}$ over the night would be present and shorter apnoeas might be recorded at the end of the night since a shorter time is necessary to obtain the maximal value of $P_{oes}$ causing arousal [22]. Peak inspiratory resistance did not change across the night and thus proved against the possibility that increased upper airway resistance contributed to the $P_{oes,max}$ rise.

It is well known that the maximal intrathoracic pressure generated during occlusion is a measure of the respiratory drive activated by chemical and mechanical inputs [23]. As indices of respiratory drive influence, we consider the first value of oesophageal pressure at the start of occlusion [23] and the rate of increase of respiratory effort during the apnoea [4, 11]. When these variables were analysed for each hour of the night, $P_{oes,1}$ did not show significant changes whereas a significant increase in $R_{pes}$ was found. This suggests that the only effect of respiratory drive during sleep is to influence the rate at which inspiratory effort rises to provoke arousal. However, the possibility that the arousal responsiveness to occlusion depends on the alteration of hypercapnic respiratory drive response cannot be ruled out [5, 6, 23] since end-tidal CO$_2$ was not measured in this study.

Increased apnoea duration and $P_{oes,max}$ during the night may also reflect a blunted arousal response as an adaptation to repetition of apnoeic stimuli. The reduced arousability through the night could be related either to a progressive decline in peripheral sensitivity or to a decrease in central responsiveness to peripheral stimuli. The influence of a nocturnal decline in peripheral sensitivity is suggested by the study of Cala et al. [24], showing that anaesthesia of the upper airway resulted in an increased respiratory effort and apnoea length at the start of sleep without any effect in the second part of the night. This observation suggests that afferents arising from the upper airway mechanoreceptors may exert an inhibitory influence directly on the respiratory drive at the start of sleep. Although our results do not allow us to establish a causal relationship between sleep fragmentation and change in $P_{oes,max}$, an attractive theory is the lowering of arousal threshold in OSA induced by sleep fragmentation and recurrence of apnoeas. On the basis of the relationship between changes in $P_{oes,max}$, $\Delta P_{oes}$ and AHI, we can suppose...
that sleep deprivation and sleep fragmentation have an effect on arousal responsiveness to respiratory stimuli either throughout the night or in the natural course of the disease [11]. An increased amount of time to reach arousal and an increased tendency to upper airway collapse have been reported after short-term sleep fragmentation in animals [25, 26], in normals [22] and in OSA patients [8], ex-plaining the deleterious effect of benzodiazepines [27, 28] and alcohol [29]. The detrimental effects of chronic sleep fragmentation on arousal response are evident from the re-sults of Brooks et al. [9] who studied four dogs in an OSA and sleep fragmentation protocol, and did not find any differences in apnoea length, time of arousal and peak inspiratory pressure in both conditions. In our subjects, however, the number of arousals and awakenings does not influence the nocturnal trend in arousal threshold. This finding may be explained by the difficulty to assess sleep fragmentation visually. Since resolution of apnoea is not necessarily associated with a cortical arousal or a "microarousal" [30], more sophisticated EEG analysis may be useful to assess the role of sleep fragmentation on the arousal response to occlusion.

Using a 1-h analysis we tried to obtain a dynamic interpretation of the changes in arousal threshold in patients with OSAs. The scattergram of the changes in apnoea length and in \( P_{\text{oes,max}} \) against the hour of the night revealed a peculiar trend of evolution. Interestingly, the rise in the two variables was not linear, with a greatest rise recorded in the first hours of the night followed by a plateau after the third hour and a tendency to decrease in the last part of the night. One possible explanation of these results is the methodological bias related to the analysis of selected apnoeas during NREM sleep. Since, as shown in table 2, no changes in the recorded apnoeas were noted across the night, the trend in decrease in or plateau found in the second part of the night may be related to the small number of apnoeas analysed, which in turn is related to the greater amount of REM sleep recorded in the last hours of the night. A second and more interesting possibility is that arousability may be modulated by circadian factors and, as a result, change through the course of the night. This seems intuitively logical when we consider the relationship between the circadian rhythm of the sleep promoting system and the change in arousability. Using an ultra-short multiple naps protocol Lavie and Scherson [31] have shown that a rapid rise occurs in sleep propensity, beginning at about 20:00 h followed by a broad plateau from midnight to 06:00 h. Considering this model of circadian sleep propensity, the mechanical response necessary to provoke arousal may be proportionally greater at the start of sleep when the sleepiness level is higher, compared with that at higher levels of alertness. Although this hypothesis is purely speculative at the present time, an interference of circadian rhythm is provided by a recent report [32], demonstrating that \( P_{\text{oes,max}} \) parallels the decline of delta activity in OSA patients, reflecting the physiological decrease in sleep pressure during the night.

In summary, we have found in patients with obstructive sleep apnoea a nocturnal rise of respiratory effort and apnoea duration occurring without any changes in oxygen desaturation, in chemosensitivity and in preapnoeic upper airway resistance. The frequency of sleep-related breathing disorders appears to contribute to the increase in apnoea length and in maximal oesophageal pressure supporting the hypothesis of a resetting of arousal threshold in obstructive sleep apnoea syndrome. Since a time-dependent evolution in maximal oesophageal pressure was found, further investigations should be directed at establishing whether sleep fragmentation or circadian influence is implicated in arousal threshold change in obstructive sleep apnoea syndrome.

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References


