Response to inspiratory resistive loading during sleep in normal children and children with obstructive apnea

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Response to inspiratory resistive loading during sleep in normal children and children with obstructive apnea. J. Appl. Physiol. 87(4): 1448–1454, 1999.—The response to inspiratory resistance loading (IRL) of the upper airway during sleep in children is not known. We, therefore, evaluated the arousal responses to IRL during sleep in children with the obstructive sleep apnea syndrome (OSAS) compared with controls. Children with OSAS aroused at a higher load than did controls (23 ± 8 vs. 15 ± 7 cmH₂O·l⁻¹·s⁻¹; P < 0.05). Patients with OSAS had higher arousal thresholds during rapid eye movement (REM) vs. non-REM sleep (P < 0.001), whereas normal subjects had lower arousal thresholds during REM (P < 0.005). Ventilatory responses to IRL were evaluated in the controls. There was a marked decrease in tidal volume both immediately (56 ± 17% of baseline at an IRL of 15 cmH₂O·l⁻¹·min; P < 0.001) and after 3 min of IRL (67 ± 23%; P < 0.005). The duty cycle increased. We conclude that children with OSAS have impaired arousal responses to IRL. Despite compensatory changes in respiratory timing, normal children have a decrease in minute ventilation in response to IRL during sleep. However, arousal occurs before gas-exchange abnormalities.

Methods

Study Group

Normal children and children with OSAS were studied. Prepubertal children (Tanner stage 1) who were old enough to cooperate with testing (in general, those ≥ 5 yr of age) were eligible for the study. Normal children were recruited from the community by means of advertisements. All control children were nonsnorers without symptoms of OSAS and had not undergone adenoidectomy, tonsillectomy, or other upper airway surgery. OSAS subjects were recruited from the Pediatric Sleep Disorders Clinic of Johns Hopkins University. All had OSAS secondary to adenotonsillar hypertrophy. Children with craniofacial anomalies or neuromuscular disease were excluded from the study.

Informed consent was obtained from the parents or legal guardians of each child, and assent was obtained from the child. The study was approved by the Institutional Review Board of Johns Hopkins University.

Study Design

All children underwent baseline polysomnography to confirm their diagnosis. After this, on a separate night, the response to IRL during sleep was evaluated. In normal children, both the ventilatory and arousal responses to IRL were assessed. In children with OSAS, only the arousal response was evaluated, as the relative contribution of partial upper airway obstruction to hypoventilation could not be determined.

The obstructive sleep apnea syndrome (OSAS) is a common and serious cause of morbidity during childhood. Despite the prevalence and severity of this disease, little is known about its pathophysiology. Childhood OSAS differs from adult OSAS in its etiology, clinical manifestations, and polysomnographic characteristics. Nevertheless, children and adults with OSAS share some pathophysiological characteristics. It is probable that OSAS in both age groups results from abnormal neuromuscular compensation for structural narrowing of the upper airway. In children, the structural narrowing is usually due to adenotonsillar hypertrophy; in adults, it is attributed to adipose tissue. During wakefulness, patients compensate for this increased inspiratory load by augmenting their upper airway neuromuscular tone (20). However, during sleep this compensatory mechanism is lost, and obstructive apnea ensues. Because sleep is associated with an increase in upper airway resistance of more than 200% (14), load compensation during sleep assumes particular importance. However, the response to inspiratory resistance loading (IRL) of the upper airway during sleep has not been studied in either normal children or children with OSAS.

Children with OSAS frequently exhibit a pattern of persistent, partial upper airway obstruction associated with gas-exchange abnormalities rather than episodes of recurrent, discrete obstructions (1, 25). This breathing pattern has been termed "obstructive hypoventilation" (1). The reason for this differing pattern of obstruction between children and adults is unclear. It is possible that children with OSAS, unlike adult patients, have preserved upper airway reflexes (17). This allows them to partially compensate for increases in upper airway resistance, thereby preventing complete upper airway collapse. If they have an impaired arousal threshold to the increased upper airway load and to the resultant hypercapnia and hypoxemia (16), this may allow for persistent, uninterrupted partial upper airway obstruction.

We, therefore, evaluated the arousal response to incremental IRL in prepubertal children with OSAS compared with controls. In addition, the ventilatory response to IRL was determined in the control subjects.
Baseline Polysomnography

Polysomnographic studies were performed overnight. During polysomnography, the following parameters were measured and recorded continuously with the use of a computerized polysomnography system (Alice 3, Healthdyne, Marietta, GA): electroencephalogram (EEG) (C3/A2, O1/A2), right and left electrooculogram, submental electromyogram (EMG), tibial EMG, electrocardiogram, chest and abdominal wall motion (piezoelectric transducers), oral airflow (3-pronged thermistor), end-tidal PCO2 ($\text{PETCO}_2$) measured at the nose by infrared capnometry (N-1000, Nellcor, Van Nuys, CA), arterial oxygen saturation by pulse oximetry ($\text{SpO}_2$ (N-1000, Nellcor), and oximeter pulse waveform. Subjects were also monitored and recorded on videotape with the use of an infrared video camera and were continuously observed by a polysomnography technician. The following parameters were measured. 1) Sleep architecture was assessed by standard techniques (23). Arousal responses were defined as recommended by the American Sleep Disorders Association (26). 2) Obstructive apneas were defined as the presence of chest/abdominal wall motion in the absence of airflow. As children have a higher respiratory frequency than adults and frequently desaturate even with short apneas, all obstructive apneas $\geq$2 breaths in duration were counted (18). 3) Hypopneas were defined as a qualitative decrease in oronasal airflow $\geq$50%, associated with paradoxical respiration, a change in the $\text{PETCO}_2$ waveform, and desaturation $\geq$4%. The apnea hypopnea index was defined as the number of obstructive apneas, mixed apneas, and hypopneas per hour of sleep. 4) The $\text{SpO}_2$, nadir and mean $\text{SpO}_2$, were determined. $\text{SpO}_2$, measurements associated with a poor pulse waveform were discounted. 5) The mean and peak $\text{PETCO}_2$ were determined. $\text{PETCO}_2$ measurements associated with a poor waveform were discounted. Hypoventilation was defined as the percentage of total sleep time with $\text{PETCO}_2$ $\geq$50 Torr.

OSAS in children differs from that in adults, and, therefore, age-specific criteria must be used for diagnosis (1). Control subjects were confirmed as being normal if they had an apnea hypopnea index $<1$/h, $\text{SpO}_2$ nadir $\geq$92%, peak $\text{PETCO}_2$ $\leq$53 Torr, and hypventilation $\geq$10% (1, 18). Children were diagnosed with OSAS if they exceeded the above criteria. All children with OSAS met multiple criteria for diagnosis.

IRL

The response to IRL was assessed during a separate, overnight polysomnogram. EEGs, electrooculograms, EMG, chest wall motion, $\text{SpO}_2$, and oximeter pulse waveform were measured as previously described, except that measurements were recorded on a polygraph recorder (78E, Grass Instruments, Quincy, MA). Because many of the children with OSAS breathed through their mouth, subjects wore oronasal masks. We found that an adult continuous positive airway pressure mask (Respironics, Murrysville, PA; size large or large narrow, with a Comfort Flap) would cover the child's nose and mouth snugly. A two-way nonrebreathing valve (Hans Rudolph, Kansas City, MO) was attached to the mask inlet. A heated pneumotachometer (Hans Rudolph) and differential transducer (Validyne Engineering, Northridge, CA) were attached to the inspiratory limb of the circuit with the use of wide-bore (3.81-cm) respiratory tubing (Sensormedics, Yorba Linda, CA). The circuit was suspended by a pulley to decrease weight on the face. The baseline resistance of the circuit was 1.0 cmH$_2$O·l$^{-1}$·s$^{-1}$ at a flow of 0.5 l/s. End-tidal CO$_2$ was measured via a port in the mask by using an infrared capnometer (Ametek, Paoli, PA). Changes in $\text{PETCO}_2$ were confirmed with transcutaneous measurements (Radiometer, Paramus, NJ). Tidal volume ($V_t$) was obtained by integration of the flow signal.

IRL was measured by inserting mesh resistors of known resistances (Hans Rudolph) into the inspiratory limb of the circuit. Resistances were linear over flow rates of 0–2 l/s. Once the patient was asleep, a resistance of 5 cmH$_2$O·l$^{-1}$·s$_{-1}$ was placed in the inspiratory limb of the circuit until the patient aroused or for a maximum of 3 min. If the patient did not arouse, the resistance was removed for 1 min to allow the subject to return to baseline. The challenge was then repeated with a resistance of 10 cmH$_2$O·l$^{-1}$·s$_{-1}$ and continued to be increased in 5 cmH$_2$O·l$^{-1}$·s$_{-1}$ increments until a maximum resistance of 35 cmH$_2$O·l$^{-1}$·s$_{-1}$ was reached.

Challenges were attempted twice in slow-wave, stage 2, and rapid-eye-movement (REM) sleep. However, all challenges were not always possible because of patient arousal or obstructive apnea. The mean of the two trials was used to characterize each sleep state. Initially, attempts were made to perform challenges during wakefulness. However, these were unsuccessful because of the tendency of these young children to fidget and to play with the masks. Children with OSAS have fewer apneas than do adult patients (1, 25), and, therefore, periods of unobstructed breathing were present. Challenges were initiated during these unobstructed periods. However, some patients developed obstructive apnea during a challenge. Furthermore, it was not possible to avoid all periods of partial obstruction (as demonstrated by paradoxical breathing, hypercapnia, or oscillations in $V_t$), particularly in the patients with severe OSAS. This is demonstrated in Fig. 1. The normal subject (Fig. 1B) had an immediate drop in $V_t$ after the application of IRL, with little fluctuation. In contrast, the patient with OSAS (Fig. 1A) had wide fluctuations in $V_t$, both at baseline and after placement of the IRL. This was due to a cyclical pattern of partial obstruction, followed by gasps, that was independent of the IRL. In some cases, such as the one demonstrated, the pattern of partial upper airway obstruction was obvious; in others, more subtle oscillations were seen. Because these changes in $V_t$ were independent of the load applied and differed among patients with differing severities of OSAS, the ventilatory response to IRL could not be determined in the patients with OSAS. However, arousal responses could still be determined in these patients, as care was taken to avoid analyzing any arousal that was preceded by ventilatory oscillations.

Data Analysis

Arousal response to IRL. The inspiratory load at which arousal occurred was determined. If the subject did not arouse, a maximum value of 35 cmH$_2$O·l$^{-1}$·s$_{-1}$ was used. Although attempts were made to perform challenges during nonobstructed breathing, some obstructive apneas occurred during testing of the OSAS subjects. Therefore, arousals were excluded from analysis if arousal coincided with termination of an apnea, as it could not be determined whether the arousal was due to the inspiratory load or to the apnea.

Ventilatory response to IRL. The ventilatory response to IRL was determined in the normal subjects only. Heart rate, inspiratory airflow, $V_t$, inspiratory time (TI), total time (TT), $\text{PETCO}_2$, and $\text{SpO}_2$ were measured for each breath. From this, the instantaneous minute ventilation ($V_e$), mean inspiratory flow rate [ratio of $V_t$ to TI ($V_t$/TI)] and duty cycle [ratio of TI to TT ($V_t$/TT)] were calculated. Both the acute and the sustained changes in cardiorespiratory parameters in response to IRL were evaluated. The acute response was
RESULTS

Study Population

Details of the patient population are shown in Table 1. Nine normal children and nine children with OSAS were studied. All normal controls had polysomnographic parameters within normal limits for children (1, 18). The patients studied had moderate to severe OSAS by pediatric standards (1, 25). Three children with OSAS had a history of mild asthma requiring intermittent β-agonists. None was symptomatic at the time of study. Three of the children with OSAS were considered obese (weight >120% of ideal weight for height); no control subject was obese. All children (OSAS and controls) had similar amounts of tonsillar tissue on physical examination; however, formal quantification was not attempted.

Arousal Response to IRL

Overall, control subjects aroused at a mean inspiratory load of $15 \pm 7$ cmH$_2$O·l$^{-1}$·s, whereas OSAS subjects aroused at a significantly higher load ($23 \pm 8$ cmH$_2$O·l$^{-1}$·s, $P < 0.05$). When arousal was compared among different sleep states, patients with OSAS were found to have a higher arousal threshold during REM sleep ($P < 0.001$) (Fig. 2). The level of $\text{SpO}_2$ or $\text{PETCO}_2$ at which arousal occurred did not differ between the two groups. In both groups, the arousal threshold differed significantly during REM compared with non-REM sleep. However, patients with OSAS had higher arousal thresholds during REM sleep than non-REM sleep ($P < 0.001$), whereas normal subjects had lower arousal thresholds during REM than non-REM sleep ($P < 0.005$).

Four of the normal controls had participated in a previous study evaluating arousal responses to carbon dioxide (16). In these subjects, the correlation between the arousal response to hypercapnia and to IRL was 0.88 ($P = 0.059$).

Table 1. Population characteristics and polysomnography results

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>OSAS</th>
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<tbody>
<tr>
<td>$n$</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Age, yr</td>
<td>9±2</td>
<td>7±2</td>
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<td>Girls, no.</td>
<td>5</td>
<td>5</td>
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<tr>
<td>BMI, kg/m$^2$</td>
<td>17.4±2.8</td>
<td>19.5±5.1</td>
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<tr>
<td>AHI, no/h</td>
<td>0.1±0.2</td>
<td>19.5±22.6* (0–0.6) (4.0–73.4)</td>
</tr>
<tr>
<td>$\text{SpO}_2$ nadir, %</td>
<td>96±2</td>
<td>81±8</td>
</tr>
<tr>
<td>(93–98)</td>
<td>(67–91)</td>
<td>(45–55)</td>
</tr>
<tr>
<td>Peak $\text{PETCO}_2$, Torr</td>
<td>47±3</td>
<td>51±4*</td>
</tr>
<tr>
<td>(44–53)</td>
<td>(45–55)</td>
<td></td>
</tr>
<tr>
<td>Duration of hypoventilation ($\text{PETCO}_2 &gt; 50$ Torr) as % total sleep</td>
<td>0±0</td>
<td>6±9</td>
</tr>
<tr>
<td>(0)</td>
<td>(0–7)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; ranges are displayed in parentheses. OSAS, obstructive sleep apnea syndrome; BMI, body mass index; AHI, apnea hypopnea index; $\text{SpO}_2$, arterial O$_2$ saturation by pulse oximetry; $\text{PETCO}_2$, end-tidal P$_{CO_2}$. *$P < 0.05$, †$P < 0.001$ vs. controls.
Ventilatory responses to IRL were evaluated in the normal subjects only. Data from one subject were excluded because of a pneumotachometer calibration error. Therefore, data on the remaining eight subjects are presented.

A typical example of a response to IRL in a normal subject is shown in Fig. 1B. The normal subjects showed an immediate (second breath) and sustained (third minute) reduction in $V\dot{E}$ that was proportional to the degree of IRL (Fig. 3). The responses to an IRL of 15 cmH$_2$O·l$^{-1}$·min are shown in detail (Fig. 4). This load was chosen for representation, as it was the highest load attained before arousal for the majority of the normal subjects during non-REM sleep. After application of the load, the children had an acute reduction in VT, to $58 \pm 13\%$ of baseline ($P < 0.001$), with no change in respiratory rate. This resulted in a drop in $V\dot{E}$ of $60 \pm 13\%$ ($P < 0.001$). Although there was no significant change in $T_i$, $T_i/T_T$ increased to $107 \pm 3\%$ of baseline ($P < 0.002$), indicating that expiratory time decreased. Little recovery was noted after 3 min of sustained IRL (Fig. 4): VT was $67 \pm 22\%$ of baseline ($P < 0.02$), $V\dot{E}$ was $68 \pm 22\%$ ($P < 0.02$), $T_i$ was $107 \pm 8\%$ (not significant), and $T_i/T_T$ was $109 \pm 4\%$ ($P < 0.005$). Overall, there were no significant changes in heart rate, $\text{SpO}_2$, or $P_{\text{ETCO}_2}$ during any of the challenges. The exception was a statistically significant but very slight decrease in $\text{SpO}_2$ during the third minute of IRL of 15 cmH$_2$O·l$^{-1}$·min, to $99.7 \pm 0.2\%$ of baseline ($P < 0.01$).

The responses to IRL were compared for REM vs. non-REM sleep. Control subjects aroused at a lower load during REM than non-REM sleep, and thus fewer ventilatory response data were available. Results in REM sleep were similar to those during non-REM sleep but because of smaller numbers did not reach statistical significance. The only significant difference between the REM and non-REM ventilatory responses was the $T_i/T_T$ response, which tended to be greater during non-REM than REM sleep. All normal subjects aroused before a load of 35 cmH$_2$O·l$^{-1}$·min during REM sleep.

**DISCUSSION**

This study has shown that children with OSAS have blunted arousal thresholds to IRL compared with matched controls. Combined with previous data showing blunted arousal responses to hypercapnia (16), this suggests that children with OSAS have a generalized deficit of arousal in response to respiratory stimuli, which may be either a contributory factor to, or a result of, OSAS. In addition, the normal ventilatory responses to IRL in prepubertal children have been characterized. Children show a marked, sustained decrease in $V\dot{E}$ in response to IRL, resulting in a decreased $V\dot{E}$ despite a compensatory lengthening of $T_i/T_T$. However, arousal occurs before gas exchange is impaired.

Arousal to IRL

Children with OSAS aroused at a significantly higher IRL than did controls during REM sleep, which is the state of sleep when pediatric obstructive apneas predominate (9, 22). Control children had lower arousal thresholds during REM than non-REM sleep, which is consistent with previous findings of lower REM arousal thresholds to acoustic stimuli in both children (3, 4) and adults (4). In contrast, children with OSAS actually
had higher arousal thresholds during REM compared with non-REM sleep. This may be a protective response. Children with OSAS have normal sleep architecture, including normal amounts of REM sleep (7, 9, 15). REM sleep is thought to be important in young children (and other species) to facilitate growth and maturation (24). Thus it may be important for children to preserve REM sleep even in the face of increased upper airway obstruction.

In adults with OSAS, arousal occurs in conjunction with the termination of the majority of obstructive apneas. This limits gas-exchange abnormalities, at the expense of fragmented sleep and excessive daytime sleepiness. In contrast, children often do not have cortical arousals in response to obstructive apneas (19). This is illustrated by the fact that excessive daytime sleepiness is uncommon in children with OSAS compared with adults (5). In fact, children may manifest sustained periods of partial upper airway obstruction, associated with hypercapnia, without signs of arousal; this has been termed obstructive hypoventilation (1). In the present study, we elected to use the American Sleep Disorders Association criteria for arousal, as standard criteria for children have not been established (26). It is possible that shorter EEG arousals are significant, or that subcortical, autonomic arousals may be occurring (21). We evaluated cortical arousal only, i.e., arousals associated with EEG changes, as pathological effects of noncortical arousals have not been demonstrated.

Previously, our laboratory (16) showed that children with OSAS have blunted arousal responses to hypercapnia. This study shows that these children also have blunted arousal responses to IRL. This suggests that children with OSAS have a generalized arousal deficit in response to respiratory stimuli. Further studies are required to determine whether this deficit applies to all arousal stimuli or is limited to respiratory stimuli only. Furthermore, it is not known whether the arousal deficit to IRL is a primary contributing factor to OSAS or is secondary to the effort of continually breathing against an increased upper airway load. Although the arousal response of adults with OSAS to IRL has not been assessed, the awake response has been shown to be reversible after treatment of the OSAS (10).

There was a positive correlation between the arousal thresholds to IRL and to hypercapnia in the four normal subjects studied. This is consistent with the theory that, in normal subjects, arousal to any stimulus is dependent on the degree of respiratory effort invoked (8).

Ventilatory Response to IRL

The normal children showed an immediate, large decrease in VT, and hence V\dot{E}, in response to IRL. This was associated with a shortening of T I/TT during non-REM sleep due to a shortening of expiratory time. However, this compensatory change was not sufficient to normalize V\dot{E}. Because measurements of respiratory drive, such as changes in intrapleural pressure, were not made, it cannot be ascertained whether the decrease in V\dot{E} was due to inadequate central augmentation of ventilatory drive in response to the IRL or purely to mechanical effects. The acute changes noted in the pediatric subjects were similar to responses to IRL reported in normal adults (2, 11, 27). However, in contrast to the adult studies, little recovery was seen during prolonged (3-min) exposure to IRL. Although techniques were not directly comparable, studies in adults showed that V\dot{E} either approached baseline values (80% of baseline) (27) or even exceeded baseline values (2) after 3 min of IRL of 12 cmH\(_2\)O l \cdot s\(^{-1}\). In comparison, after 3 min of IRL of 15 cmH\(_2\)O l \cdot s\(^{-1}\), the V\dot{E} in the children was only 67% of baseline. The reason for this difference between children and adults is
increase in PCO₂ in the Wiegand et al. study (27), al-
though significant, was slight (−1 Torr), and our tech-
nique may not have been sensitive enough to detect
such small changes.

Limitation of Methods

This study was possible because of the unique pat-
tern of childhood obstructive sleep apnea. Children
with OSAS have fewer obstructive apneas than adults
(1, 25). Therefore, the response to IRL could be deter-
mined between runs of obstructive apneas. To prevent
obstruction from confounding the data, arousals that
were temporally associated with obstructive apneas
were discounted. However, in patients who obstructed
frequently, this resulted in a limitation in the number
of challenges that could successfully be performed. This
was a particular problem during REM sleep, when
obstructive apnea occurred most commonly. Neverthe-
less, sufficient data were obtained. Ventilatory re-
sponses could not be determined in the patients with
OSAS, as our methods did not allow us to distinguish
whether the decrement in Vₑ in response to IRL in
these patients was due to partial upper airway obstruc-
tion or the effects of the load itself. Hence, ventilatory
data are presented for the normal subjects only.

In this study, an initial IRL of 5 cmH₂O·l⁻¹·s was
applied. If the patient failed to arouse, the IRL was
increased incrementally to a maximum of 35 cmH₂O·
l⁻¹·s. These loads were chosen as they were similar to
those used previously in the study of adults (2, 27).
However, it is not known how the loads chosen relate to
the normal physiology of the child’s upper airway
during sleep. Studies in awake children of a similar
height suggest that the normal total respiratory resis-
tance during wakefulness is ~5–9 cmH₂O·l⁻¹·s (6).
However, the resistance of the upper airway during sleep
in either normal children or children with OSAS is
unknown. It is possible that the patients with OSAS had a
greater degree of adenotonsillar hypertrophy in relation
to their underlying upper airway size than did controls
and thus had a greater intrinsic load to their upper airway.
All subjects in our study had clinically apparent tonsillar tissue. We did not attempt to quanti-
tate the degree of adenotonsillar hypertrophy in our
subjects as it is difficult to measure accurately, and a
relationship between the degree of adenotonsillar hyper-
trophy and upper airway obstruction has not been
proven (13). However, if indeed the children with OSAS
had a greater intrinsic upper airway load, and yet
aroused at a higher IRL, it suggests an even greater
impairment of arousal mechanisms than suggested by
our study.

The peak prevalence of childhood OSAS is thought to
occur between 3–5 yr of age. Thus the children with
OSAS in this study were slightly older than the average
child with OSAS. The lower age limit for this study was
chosen to exclude children too young to cooperate with
testing.

Clinical Relevance

Adenotonsillar hypertrophy plays an important role
in childhood OSAS. Most children with OSAS have
large tonsils and adenoids and improve after tonsillec-
tomy and adenoidectomy. However, it is important to
note that children in general have large tonsils and
adenoids and a smaller underlying upper airway than
adults do (12). Despite this increased upper airway
load, the vast majority of children do not develop OSAS.
Indeed, the severity of OSAS is not proportional to the
degree of adenotonsillar hypertrophy (13). Possibly, it is
only those children with abnormal neuromuscular or
arousal responses to this load that proceed to develop
OSAS. Further studies are required to determine
whether the blunted arousal response to inspiratory
resistance in children with OSAS is primary or second-
ary to a chronically increased upper airway load.

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