Effect of testosterone on the apneic threshold in women during NREM sleep

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Zhou, X. S., J. A. Rowley, F. Demirovic, M. P. Diamond, and M. S. Badr. Effect of testosterone on the apneic threshold in women NREM sleep. J Appl Physiol 94: 101–107, 2003. First published September 13, 2002; 10.1152/japplphysiol.00264.2002.—The hypocapnic apneic threshold (AT) is lower in women relative to men. To test the hypothesis that the gender difference in AT was due to testosterone, we determined the AT during non-rapid eye movement sleep in eight healthy, nonsnorers, premenopausal women before and after 10–12 days of transdermal testosterone. Hypocapnia was induced via nasal mechanical ventilation (MV) for 3 min with tidal volumes ranging from 175 to 215% above eupneic tidal volume and respiratory frequency matched to eupneic frequency. Cessation of MV resulted in hypocapnic central apnea or hypopnea depending on the magnitude of hypocapnia. Nadir minute ventilation as a percentage of control (%V˙E) was plotted against the change in end-tidal CO2 (PETCO2); %V˙E was given a value of zero during central apnea. The AT was defined as the PETCO2 at which the apnea closest to the last hypopnea occurred; hypocapnic ventilatory response (HPVR) was defined as the slope of the linear regression V˙E vs. PETCO2, Both the AT (39.5 ± 2.9 vs. 42.1 ± 3.0 Torr; P = 0.002) and HPVR (0.20 ± 0.05 vs. 0.33 ± 0.11%V˙E/Torr; P = 0.016) increased with testosterone administration. We conclude that testosterone administration increases AT in premenopausal women, suggesting that the increased breathing instability during sleep in men is related to the presence of testosterone.

METHODS

The experimental protocol was approved by the Human Investigation Committee of the Wayne State University School of Medicine and the John D. Dingell Veterans Affairs Medical Center. Informed, written consent was obtained from all subjects. We studied eight regularly menstruating, premenopausal women. All subjects were healthy nonsnorers and were not receiving any medication; none of the women was on birth control pills. The mean age for the group was 29.1 ± 5.7 yr, whereas the mean body mass index was 24.7 ± 5.9 kg/m².

Measurements. Electroencephalograms (EEG), electrocorticograms (EOG), and chin electromyograms (EMG) were attached by using the international 10-20 system of electrode placement (EEG: C3-A2, C4-A1, Oz-A2; EOG: F7-A2 and F8-A1). Data were logged to a polygraph recorder (model 78, Grass, West Warwick, RI), and sleep stage was scored according to standard methods (22). An appropriate-sized, tight-fitting nasal continuous positive pressure airway mask (Respironics, Murrysville, PA) was glued to the face with liquid latex to prevent mask leaks and was connected to the ventilation circuit. Subjects were restricted to nasal breathing by placing tape over the mouth. Airflow was measured by a heated pneumotachometer (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by integrating the pneumotachograph flow signal (model FV-156 Integrator, Validyne, Northridge, CA). Inspiratory muscle activity was obtained by surface EMG electrodes (Medi-Trace, Buffalo, NY) placed 2–4 cm above the

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costal margin in the anterior axillary line. End-tidal Pco2 (PetCO2) was measured with a gas analyzer (AEI Technologies, Pittsburgh, PA).

To confirm the central etiology of apnea and to ascertain upper airway mechanics, supraglottic pressure was measured with a solid-state catheter (model MPC-500, Millar Instruments, Houston, TX). A 10% lidocaine spray was used before catheter insertion to provide topical anesthesia to one nostril and the pharynx. The catheter was threaded through a hole in the nasal mask, through the nose, and positioned in the hypopharynx just below the base of the tongue as determined by visual inspection of the tip. Airflow was measured by the pneumotachometer, and supraglottic pressure was recorded by using Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer.

MV protocol. Hyperventilation was achieved by using a pressure support ventilator (Quantum PSV, Healthdyne Technologies, Marietta, GA) as previously described (34). The nasal mask dead space was determined to be 110.5 ± 1.5 ml. Accumulation of CO2 in the circuit was prevented by the biased flow provided by the ventilator and from an expiratory mushroom valve in-line between the pneumotachometer and the ventilator tubing. No rebreathing of CO2 took place as shown by the PetCO2 at start of inspiration equivalent to room air values. It should be noted that during the control and recovery periods the ventilator was set at an expiratory positive airway pressure (EPAP) pressure of 2.0 cmH2O. This was the minimum EPAP pressure allowed by the device. During periods of hyperventilation, the ventilator was set in spontaneous timed mode with timing matched to each subject’s eupneic rate. Hyperventilation was achieved by increasing the inspiratory pressure of the ventilator, with adjustments made during expiration. For each successive trial, the inspiratory pressure was increased in 1.0-cmH2O increments from the initial level of 2.0 cmH2O, which resulted in increased VT (range = 160.6–297.6% of eupneic control). Spontaneous respiratory effort remained in most trials as evidenced by persistence of an initial negative deflection of supraglottic pressure signal and persistent, albeit reduced, diaphragmatic EMG activity. MV was continued for 3 min and was terminated during expiration to an EPAP of 2.0 cmH2O. Each trial was repeated twice with trials separated by a minimum of 3 min. The post-MV period, or recovery period, was observed for posthyperventilatory inhibition. The end-tidal PETCO2 (PETCO2) was measured in the control and hyperventilation periods. The control period was represented by the PETCO2 level during wakefulness at the beginning of the study. For each trial, PETCO2 was measured in the control and hyperventilation periods. The control period was represented by the average of five breaths immediately preceding the onset of MV. The hyperventilation data were the calculated average of the last five mechanically ventilated breaths before the ventilator being turned back to an EPAP of 2.0 cmH2O. The change in PTEtCO2 (ΔPETCO2) was calculated as the difference between the control period and the last five MV breaths. For trials with hypopnea, the minute ventilation (Ve) reported was from the first breath in the recovery period. This represented the nadir breath, which was defined as the breath with the lowest Ve after cessation of MV. The nadir breath occurred on the first recovery breath in the majority of trials and within the first three breaths in all trials. Ve was given a value of 0 during central apnea, and the apnea length was set at a minimum of 5.0 s. The change in Ve as a percentage of control were plotted against the changes in PETCO2 for each trial. Linear regression analysis was performed on these data to determine the hypocapnic ventilatory response (HPVR) and the ΔPETCO2 threshold associated with zero Ve (apnea). AT was defined as the measured PetCO2 at which the apnea closest to the last hypopnea occurred. The ΔPETCO2-AT was defined as the ΔPETCO2 between the control and hyperventilation periods associated with the first apnea. The HPVR was defined as the slope of the regression line. Apnea points were not included in the regression analysis used to determine HPVR.

Pressure-flow loops were used to confirm the absence of inspiratory flow limitation (IFL) and to determine upper airway resistance (Rua), as previously described (23). Rua was determined from the linear portion of the inspiratory arm of the pressure-flow loops. Rua throughout inspiration was determined from the slope of the pressure-flow curve and expressed in centimeters of H2O per liter per second. Satisfactory pressure-flow loops were obtained in seven subjects. Control Rua was calculated for the five control breaths before MV. The nadir breath for hypopnea trials was selected as a representative “low-drive” recovery breath.

Statistical analysis. Paired Student’s t-tests were performed to compare the AT, ΔPETCO2-AT and HPVR at baseline and on-testosterone. Two-factor repeated-measures ANOVA was used for comparisons of PetCO2 and Rua. The first factor was baseline vs. on-testosterone for both PetCO2 and Rua, whereas the second factor was wake vs. NREM sleep for PetCO2 and control vs. nadir breaths for Rua. Statistical analysis was performed with Sigma Stat 3.0 (Jandel Scientific, San Rafael, CA). P < 0.05 was chosen as the accepted level of significance. All data are expressed as means ± SD.

RESULTS

Mean total serum testosterone level for the eight subjects on the day of the baseline study was 20.2 ± 3.4 ng/dl and increased to 469.9 ± 384.7 ng/dl (P = 0.008) on the day of the on-testosterone study. Male levels of testosterone (>130 ng/dl) were achieved in all eight subjects. No adverse effects attributable to the testosterone were reported by the subjects.

A representative polygraph record of one hypopneic trial from the baseline study is shown in Fig. 1 (top).
MV was initiated during expiration in stable NREM sleep (Fig. 1B). VT increased to 150% of control and resulted in a mild hypocapnia (ΔPETCO2 = 3.4 Torr from control). Note the persistence of spontaneous inspiratory effort during MV as evidenced by initial negative deflection on mask pressure signal. Cessation of MV resulted in a decreased VT (43.5% of control) with no corresponding change in breathing frequency (Fig. 1C). Figure 1 (bottom) shows a representative polygraph from the same subject on the 10th day of testosterone administration. In this polygraph, VT was increased 160% from control (Fig. 1B) and a central apnea resulted despite a similar magnitude of hypocapnia (ΔPETCO2 = 3.2 Torr; Fig. 1C).

For the group of 8 subjects at baseline, there were 98 successful MVs (of 133 attempts) of which 70 produced hypopneas and 28 produced apneas. For the on-testosterone study, there were 79 successful trials (of 133 attempts), of which 54 resulted in hypopneas and 19 resulted in apneas. On average, the VT delivered to the subjects at baseline was 216 ± 59% above baseline eupneic breathing. On-testosterone, the VT delivered was 177 ± 14% above baseline eupneic breathing.

Representative plots of the nadir VT (percentage of control) vs. ΔPETCO2 from one subject are shown for the baseline (Fig. 2) and on-testosterone (Fig. 2) studies. The linear regression line was fitted to the data from the hypopneic trials only, and the slope of the linear regression line was used to calculate the ventilatory response to hypocapnia. Note that ΔPETCO2-AT decreased and HPVR (slope of the regression line) increased with testosterone administration in this subject.

The individual and group mean values for AT, ΔPETCO2-AT, and HPVR are presented in Fig. 3. The AT significantly increased (baseline, 38.5 ± 1.5 vs. on-testosterone, 42.1 ± 3.0; Torr; P = 0.011) and ΔPETCO2-AT significantly decreased (4.6 ± 0.5 vs. 2.9 ± 0.8 Torr; P < 0.001) with testosterone administration. HPVR also significantly increased during testosterone administration (0.20 ± 0.05 vs. 0.33 ± 0.11%Vs/Torr; P = 0.002).

To determine whether the changes in AT or ΔPETCO2-AT were secondary to differences in baseline PETCO2, we measured wake and NREM PETCO2 at baseline and on-testosterone. There were no differences in PETCO2 between the baseline and on-testosterone conditions for either wake (40.1 ± 1.6 vs. 39.7 ± 1.6 Torr, respectively) or NREM sleep (43.2 ± 1.6 vs. 45.1 ± 2.9 Torr), but the PETCO2 values were higher during NREM sleep for both conditions (P < 0.001). To determine whether ventilatory changes were due to changes in

Fig. 1. Top and bottom: polygraph records of a single trial. A: eupneic breathing. B: last several breaths during a period of mechanical hyperventilation. C: immediate posthyperventilation breaths. Top: a trial before the administration of testosterone. The mechanical ventilation decreased the end-tidal PCO2 (PETCO2) by 3.4 Torr (from 45.9 to 42.5 Torr), which resulted in a hypopnea after the termination of mechanical ventilation. Note the decrease in flow, tidal volume (VT), and mask pressure (P mask) during the hypopneic period. Bottom: a trial during administration of testosterone in the same subject. The mechanical ventilation decreased the PETCO2 by 3.2 Torr (from 40.9 to 37.7 Torr), which resulted in an apnea after the termination of mechanical ventilation. We would classify this event as a central apnea as evidenced by the decreased diaphragmatic electromyogram (EMG) signal. Psg, supraglottic pressure; ΔPETCO2, change in PETCO2.

Fig. 2. Data from 1 subject from the baseline (●) and on-testosterone (○) studies that was used to determine the apneic threshold (AT) and hypocapnic ventilatory response (HPVR). Arrows point to the apnea closest to the last hypopnea; the AT is defined as the PETCO2 that resulted in this apnea, whereas the ΔPETCO2-AT is defined as the change in PETCO2 from baseline at the AT. Lines are the linear regression of nadir minute ventilation (V˙E) vs. PETCO2, and include only the data from the hypopnea trials. HPVR is defined as the slope of the regression line.
to premenopausal women elevates the hypocapnic AT and facilitates the development of central apnea for a given ventilatory perturbation during NREM sleep.

We considered several explanations for the effect of testosterone on the hypocapnic AT. First, the difference in the AT cannot be explained by a difference in upper airway mechanics, because the short duration of therapy was not sufficient to induce anatomic changes in upper airway structure. In fact, Rua did not increase, nor did snoring and IFL develop after testosterone therapy. This is consistent with previous data from our laboratory in which no difference in Rua between men and women was found (23). Thus we would not have expected testosterone to change Rua in this study. Second, a decrease in baseline PETCO2 may lower eupneic PCO2 precariously close to the AT (32); thus minimal hyperpnea may induce central apnea. However, there was no change in baseline PETCO2 between the baseline study and the follow-up study during testosterone therapy. Third, decreased metabolic rate may also enhance the susceptibility to develop central apnea. Although we did not measure CO2 production, previous studies have shown that androgen administration is associated with increased (31) or unchanged (18) metabolic rate. Furthermore, there is no difference in metabolic rate between women and men during sleep (12, 30), suggesting that testosterone has no effect on metabolic rate. Fourth, sleep state instability cannot be invoked, because sleep state was stable before and during each MV trial. Thus none of the aforementioned mechanisms explained the effect of testosterone administration on the AT.

An alternative explanation is that the elevation of the hypocapnic AT after administration of testosterone indicates increased CO2 chemoresponsiveness after testosterone administration, at least in the hypocapnic range. Our findings corroborate previous findings demonstrating increased hypercapnic ventilation after testosterone administration in neutered male cats (27). Conversely, White et al. (31) found that HPVR was minimally affected by testosterone administration in awake hypogonadal men (31). There are multiple differences in the experimental paradigm between the present study and the study by White et al., including hormonal baseline (hypogonadal men vs. normal women), sleep state (awake vs. NREM sleep), and the method of testing chemoresponsiveness (hyperoxic hypocapnia vs. normoxic hypocapnia). Accordingly, we cannot compare the two studies directly. However, our study is the first to demonstrate that testosterone per se induces changes in CO2 chemoresponsiveness during NREM sleep.

We have shown an elevation of the AT with no change in eupneic PETCO2, resulting in a narrowing of the \( \Delta \text{PETCO}_2\)-AT required to induce central apnea. Our findings are in contrast to a recent study showing a narrowed \( \Delta \text{PETCO}_2\)-AT with no change in the AT in patients with congestive heart failure and central sleep apnea, owing to eupneic PETCO2 being closer to the AT (32). Another study in a canine model showed a change in the \( \Delta \text{PETCO}_2\)-AT under conditions of increased ventilatory drive with metabolic acidosis despite hypocapnia during eupneic breathing (20); thus increased drive decreased the susceptibility to the development of central apnea. Given the lack of change of ventilatory drive after testosterone administration, as indicated by a stable PETCO2, we believe that the change in AT represents a centrally mediated primary change in the AT.

**Mechanisms of testosterone influence on the AT.** The change in the AT and the ventilatory response to hypocapnia indicate that testosterone increased CO2 chemoresponsiveness. The occurrence of central apnea requires medullary hypocapnia at the level of central chemoreceptors (3, 8), which was achieved via sustained (3 min) mechanical hyperventilation. Thus al-

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**DISCUSSION**

We have shown that administration of testosterone to premenopausal women elevates the hypocapnic AT and facilitates the development of central apnea for a given ventilatory perturbation during NREM sleep.

We considered several explanations for the effect of testosterone on the hypocapnic AT. First, the difference in the AT cannot be explained by a difference in upper airway mechanics, because the short duration of therapy was not sufficient to induce anatomic changes in upper airway structure. In fact, Rua did not increase, nor did snoring and IFL develop after testosterone therapy. This is consistent with previous data from our laboratory in which no difference in Rua between men and women was found (23). Thus we would not have expected testosterone to change Rua in this study. Second, a decrease in baseline PETCO2 may lower eupneic PCO2 precariously close to the AT (32); thus minimal hyperpnea may induce central apnea. However, there was no change in baseline PETCO2 between the baseline study and the follow-up study during testosterone therapy. Third, decreased metabolic rate may also enhance the susceptibility to develop central apnea. Although we did not measure CO2 production, previous studies have shown that androgen administration is associated with increased (31) or unchanged (18) metabolic rate. Furthermore, there is no difference in metabolic rate between women and men during sleep (12, 30), suggesting that testosterone has no effect on metabolic rate. Fourth, sleep state instability cannot be invoked, because sleep state was stable before and during each MV trial. Thus none of the aforementioned mechanisms explained the effect of testosterone administration on the AT.

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**Fig. 3.** Individual and group mean data (mean ± SD) for the PETCO2 at the AT (A), \( \Delta \text{PETCO}_2\)-AT (B), and HPVR (C) at baseline and on-testosterone administration. *There was a significant increase in AT (P = 0.011), \( \Delta \text{PETCO}_2\)-AT (P < 0.001), and HPVR (P = 0.002) with testosterone administration.

Rua, the Rua was measured from the linear portion of the pressure-flow curve in seven of the subjects. There were no differences in Rua between the baseline and on-testosterone conditions for either control breaths (7.2 ± 3.3 vs. 9.1 ± 5.1 cmH2O·L⁻¹·s⁻¹, respectively) or nadir breaths (8.1 ± 2.9 vs. 8.3 ± 4.7 cmH2O·L⁻¹·s⁻¹). In addition, there was no change in Rua between the control and nadir breaths. Thus reduced ventilatory output was not associated with changes in Rua during testosterone administration.
tation of the hypocapnic AT with testosterone administration indicates that testosterone has influenced central medullary chemoreceptors. In fact, cells with large numbers of androgen receptors have been identified in the central nervous system of several species, including birds (1), amphibians (16), rats (26), and rhesus monkeys (25). Interestingly, the distribution of androgen concentrating cells is most extensive in the primate model; androgens are taken up by cells in the midbrain, pons, cerebellum, and medulla. Both sensory and motoneurons demonstrated uptake (25). On the basis of the aforementioned observations, we speculate that the human brain is likely to be rich in androgen-concentrating neurons, including sensory motoneurons in the medulla that perceive changes in medullary pH. However, our speculation awaits experimental proof.

Decreased ventilatory motor output after hyperventilation could also be due to hypocapnia at the peripheral chemoreceptors, which occurs within 30 s of initiation of MV (3, 8). Accordingly, hypocapnic disfacilitation of the carotid bodies would decrease ventilatory motor output and hence facilitate the development of central apnea with sustained hyperventilation. Evidence in the literature suggests that testosterone may influence the function of peripheral chemoreceptors. Tatsumi et al. (27) measured the ventilatory and carotid sinus response to hypoxia in neutered male cats after testosterone or placebo administration. Testosterone increased carotid sinus nerve response to hypoxia, suggesting that peripheral chemoreponsiveness was altered by testosterone. However, decreased hypoxic chemoreponsiveness after unilateral central nervous system section raised the possibility that central influences may also play a role in HVR. Thus our data do not allow us to ascertain the relative contributions of carotid and medullary hypocapnia to posthyperventilation apnea/hypopnea and whether testosterone therapy altered peripheral or central chemoreponsiveness or both. Hypoxia or a brief hyperventilation would be needed to ascertain whether alterations in chemoreponsiveness were after testosterone therapy were due to influences on the peripheral or central chemoreceptors.

Methodological considerations. There are several methodological considerations. First, we chose not to use a placebo or randomize the order of the on-testosterone test because our laboratory has previously shown there is no difference in the AT between the follicular and luteal phases of the menstrual cycle, indicating that there would not be an order or time effect in the measurement of the AT (34). Also, our baseline ATs are very similar to those of our laboratory’s previous study. In addition, we believed that testosterone should not be provided to a subject who could not sleep under the experimental conditions, necessitating a baseline study be performed first in all subjects. Second, we chose a 10- to 12-day duration of testosterone because a previous investigation has shown that this length of testosterone administration is associated with other physiological changes in premenopausal women (10). We were concerned that a interpretation of a negative response may be confounded by an insufficient exposure if we shortened the duration of therapy. However, it is possible that a shorter duration of testosterone would have resulted in a similar change in AT.

Finally, it should be noted that we chose to define an apnea as an absence of flow for 5 s, instead of the standard 10 s used in most clinical sleep laboratories. We chose this definition because 5 s represents a doubling of the expiratory time, which is commonly used in physiological studies.

Implications to sleep apnea. Our finding that testosterone administration to women elevates the hypocapnic AT indicates that androgens facilitate the development of central apnea for a given ventilatory perturbation during NREM sleep. Our findings are consistent with previous studies implicating testosterone as a destabilizer of respiration in sleeping humans (18, 24). In a case series of seven obese men, the only subject free of sleep-disordered breathing was hypogonadal, indirect evidence supporting the role of testosterone in destabilizing respiration (13). Similarly, exogenous testosterone has also been shown to contribute to the development of sleep-disordered breathing in women (9, 15).

The noted difference in the AT after testosterone administration provides a mechanistic explanation for our laboratory’s previous work demonstrating a significant difference in the hypocapnic AT between men and women after MV (34). In fact, we note that the on-testosterone values for ΔPETCO2-AT and HPVR in this study were remarkably similar to the values we observed for men (3.6 ± 0.3 Torr for the AT and 0.34 ± 0.09%V̇E/Torr for the HPVR). Similarly, our findings explain the reported paucity of central apnea in women (6) and the increased prevalence of sleep-disordered breathing in women with polycystic ovarian disease, who have a high serum androgen level (11, 28).

Enhanced susceptibility to develop central apnea with testosterone may contribute to the development of recurrent central apneas. The occurrence of periodic breathing and central apnea may initiate several processes that perpetuate breathing instability. The inertia of the ventilatory control system prevents the initiation of respiratory effort until arterial Pco2 is elevated by 4–6 Torr above eupneic baseline (17). The ensuing prolongation of central apnea results in hypoxia and transient arousal. The combination of both factors produce ventilatory overshoot and more pronounced hypocapnia after apnea relative to hypopnea. This leads to recurrent central apnea and perpetuation of breathing instability as has been shown in the Wisconsin Cohort Study (19).

The effect of testosterone on the hypocapnic AT may also influence the development of obstructive sleep apnea (OSA). Support for this notion comes from studies concluding that the mechanisms of central and obstructive sleep apnea are tightly intertwined. Specifically, there is evidence that patients with sleep apnea and snorers with evidence of IFL are dependent on ventilatory motor output to preserve upper airway.
patency (4, 14, 21, 29). In these individuals, pharyngeal obstruction occurs when ventilatory drive reaches a nadir during induced periodic breathing (14, 21, 29). Similarly, a study from our laboratory has demonstrated, by using fiber-optic nasopharyngoscopy, that central apnea is associated with pharyngeal narrowing or occlusion (5). Similarly, our laboratory has shown that upper airway patency is compromised during periods of reduced ventilatory motor output in individuals with susceptibility to upper airway collapse, as evidenced by the development of upper airway obstruction and worsening flow limitation during periodic breathing when ventilatory motor output reaches a nadir (4). Thus hypocapnia may cause a decrease in upper airway ventilatory output and subsequent upper airway narrowing.

The occurrence of central apnea may be the critical trigger initiating breathing instability and recurrent upper airway obstruction during sleep. Once central apnea develops, complete pharyngeal collapse may occur in patients with a collapsible upper airway (5). This, combined with the mucosal and gravitational factors, may impede pharyngeal opening and necessitate a substantial increase in drive, including transient arousal, hyperpnea, hypocapnia, and further breathing instability. By elevating the AT, not only does testosterone enhance the probability of developing central apnea, it may induce periodic breathing and obstructive sleep apnea as well.

In summary, we have shown that administration of testosterone alters central chemore sponsiveness and increases the likelihood of developing central apnea. The influence of testosterone on the AT may be an important determinant of the increased prevalence of sleep-disordered breathing in men. Testosterone may also destabilize ventilatory control in postmenopausal women given testosterone as part of the hormone replacement therapy. Understanding the cellular and molecular mechanisms of the effect of testosterone on control of breathing may provide critical insight into the pathogenesis of OSA.

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