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The Effect of Etomidate Pretreatment on Cerebral High Energy Metabolites, Lactate, and Glucose during Severe Hypoxia in the Rat

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Etomidate was compared with thiopental with respect to preventing loss of brain high energy metabolites and accumulation of lactate during 20 min of hypoxemia (P_{aO_2} of 16–19 mmHg) in rats with unilateral carotid artery ligation. Male Sprague-Dawley rats, anesthetized with halothane and nitrous oxide (N_2O) in oxygen were randomly assigned to one of six groups. A normoxic control group which received 70% N_2O in oxygen, a hypoxia group received no iv drug treatment (hypoxia-N_2O), and four iv drug treatment groups (N_2O was replaced by 70% nitrogen at the start of drug administration). The iv drug groups were treated as follows: hypoxia-etomidate low dose (1 $mg \cdot kg^{-1}$ iv followed by an infusion at 0.35 $mg \cdot kg^{-1} \cdot min^{-1}$); hypoxia-etomidate high dose (1 $mg \cdot kg^{-1}$ then 1.3 $mg \cdot kg^{-1} \cdot min^{-1}$); hypoxia-thiopental low dose (15 $mg \cdot kg^{-1}$, then 1.5 $mg \cdot kg^{-1} \cdot min^{-1}$); and hypoxia-thiopental high dose (15 $mg \cdot kg^{-1}$, then 5 $mg \cdot kg^{-1} \cdot min^{-1}$). After hypoxia or a corresponding period in the normoxic group, the brains were frozen *in situ* for later biochemical analysis. Blood was obtained prior to and at the end of hypoxia and analyzed for glucose. Brain metabolite concentrations on the side ipsilateral to the ligated carotid artery in the normoxia-N_2O group were adenosine triphosphate (ATP), 2.76 ± 0.1, phosphocreatione (PCr) 3.88 ± 0.12, lactate 2.34 ± 0.16, and glucose 3.56 ± 0.28 ($\mu mole \cdot g^{-1}$ wet weight, mean ± SE). There was no significant decrease in ATP in any of the hypoxia groups. PCr decreased by 45% (compared to normoxia-N_2O) in the hypoxia-N_2O group. In the iv drug treatment groups only the hypoxia-thiopental high-dose group had a significant decrease in PCr. Lactate significantly increased in all hypoxia groups, though it was highest in the hypoxia-N_2O group (24.3 ± 0.96). Brain glucose did not change as a function of drug treatment. In this model, both high- and low-dose etomidate and low-dose thiopental prevented the decrease in PCr that occurred when N_2O alone was given. Etomidate and thiopental also attenuated, but did not prevent the increase in brain lactate. The results suggest that etomidate may have some potential in preventing metabolic changes that lead to cell damage during hypoxemia. (Key words: Anesthetics, hypnotics: barbiturates. Anesthetics, intravenous: etomidate. Brain: hypoxia; metabolism.)

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THE RECENT SUGGESTION of clinically significant brain protection by a barbiturate raises the issue of brain protection during operations that might place a patient at risk for intraoperative hypoxia or ischemia.[1,2] EEG suppressant doses of barbiturates, however, extend the duration of trachial intubation (19 or more hours)[1] and produce hypotension that often requires vasopressor support.[1,3] In the following study, we examined the ability of etomidate to prevent the loss of brain high-energy metabolites and accumulation of lactate during a period of profound hypoxemia. This agent is similar to the barbiturates in that it causes a dose-related depression of cerebral oxygen metabolism and blood flow,[4,5] but it has a shorter duration of action, particularly after infusion and a less pronounced effect on blood pressure.[5,6]

Methods

The study was approved by the institutional Animal Care and Use Committee. Male Sprague-Dawley rats were anesthetized with 2–3% halothane and 70% nitrous oxide (N_2O) in oxygen (O_2). Following tracheostomy, mechanical ventilation was established. During surgical preparation anesthesia was maintained with 0.5–1.5% halothane and 70% N_2O in O_2. The left carotid artery was isolated and divided between silk ligatures. The femoral vessels on one side were cannulated for monitoring arterial blood gases and *p*H, continuous arterial blood pressure monitoring, and iv drug and blood infusion. The head was then immobilized in a stereotaxic holder. The skull was exposed through a midline incision and a plastic funnel was fixed to the skull. Bilateral fronto-occipital platinum needle electrodes were inserted in the scalp for continuous monitoring of the EEG. A rectal temperature probe was inserted and temperature was maintained at 37° C by means of a heat lamp and servocontrol unit. The animals were paralyzed with 0.1 $mg \cdot kg^{-1}$ iv pancuronium bromide and ventilation was adjusted to maintain Pa_{CO_2} between 35–40 mmHg. Upon completion of surgical preparation, the halothane was discontinued and the lungs were ventilated with 70% N_2O in O_2 for 90 min prior to the onset of the experiment.

The animals were randomly assigned to a normoxic control or five different hypoxia groups. The animals in the normoxia group received 70% N_2O in O_2 throughout the experiment. One hypoxia group received no drug

TABLE 1. Physiologic Variables Measured at the End of Hypoxia

Group	MABP mmHg	Pa_{O_2} mmHg	Pa_{CO_2} mmHg	pH_a
Normoxia-N_2O	110 ± 2.7	127 ± 3.2	39.5 ± 0.7	7.38 ± 0.02
Hypoxia-N_2O	113 ± 1.2	16.4 ± 0.2*	26.4 ± 0.3*	7.56 ± 0.01*
Hypoxia + ETM (LD)	106 ± 2.5	17.7 ± 0.5*	32.5 ± 2.4*	7.56 ± 0.04*
Hypoxia + TPL (LD)	109 ± 2.7	18.1 ± 0.4*	27.3 ± 1.1*	7.56 ± 0.03*
Hypoxia + ETM (HD)	111 ± 1.9	17.9 ± 0.6*	29.2 ± 1.3*	7.49 ± 0.04*
Hypoxia + TPL (HD)	99 ± 1.5	18.1 ± 0.2*	33.1 ± 1.7*	7.54 ± 0.02*

Values are given as mean ± SE.
ETM = etomidate; TPL = thiopental; LD = low dose; HD = high dose.
* Significantly different from the normoxia-N_2O group, $P < .05$.

infusion (hypoxia-N_2O group). In the four remaining hypoxia groups, the N_2O was replaced by 70% nitrogen (N_2) at the start of drug infusion. These groups were treated as follows: The hypoxia-etomidate low-dose group received etomidate, 1 $mg \cdot kg^{-1}$ iv followed by an infusion at 0.35 $mg \cdot kg^{-1} \cdot min^{-1}$. The hypoxia-etomidate high-dose group received etomidate, 1 $mg \cdot kg^{-1}$ iv followed by an infusion at 1.3 $mg \cdot kg^{-1} \cdot min^{-1}$. The hypoxia-thiopental low-dose group received thiopental, 15 $mg \cdot kg^{-1}$ iv followed by an infusion at 1.5 $mg \cdot kg^{-1} \cdot min^{-1}$. The hypoxia-thiopental high-dose group received thiopental, 15 $mg \cdot kg^{-1}$ iv followed by an infusion at 5 $mg \cdot kg^{-1} \cdot min^{-1}$. The initial dose and infusion rates were based on a small preliminary study that examined the relationship between EEG and drug dose with the purpose of producing burst suppression on EEG in the low-dose groups and complete EEG suppression in the high dose groups.

Hypoxia to a Pa_{O_2} between 16–19 mmHg was induced by replacing O_2 with appropriate amounts of N_2 45 min after the onset of drug infusion or a comparable period of time in the noninfused groups. Inspired gas concentrations were adjusted using flow meters and Pa_{O_2} was monitored by arterial blood gases obtained at 1, 5, 10, 15, and 20 min after O_2 reduction. Mean arterial pressure (MABP) was maintained near 100 mmHg by an iv infusion of epinephrine as needed, and acidosis was treated with an iv infusion of sodium bicarbonate. After 20 min of hypoxia or a corresponding period in the normoxia group, the brains were frozen *in situ* by pouring liquid N_2 into the funnel.[7] Mechanical ventilation was continued and MABP was maintained during the initial stages of freezing. Blood was obtained just prior to and at the end of hypoxia and stored in liquid nitrogen for later determination of glucose concentration.

The frozen brains were chiseled from the skull and stored in liquid N_2. Later, samples of cortical brain tissue were taken from each cerebral hemisphere for microfluorometric analysis of adenosine triphosphate (ATP), phosphocreatine (PCr), lactate, and glucose.[8] Blood glucose concentration was also measured with these microfluorometric techniques.

Statistical analysis of changes in brain ATP, PCr, lactate, and glucose were performed using two-way analysis of variance (ANOVA) and Tukey's test to test for significant differences between treatment groups. Blood glucose changes were evaluated using one-way ANOVA and the paired t test. Comparison of physiologic variables was done using one-way analysis of variance and t tests with correction for multiple comparisons using Bonferroni's inequality. $P < 0.05$ was considered to be statistically significant. All ATP, PCr, lactate, and glucose values (both brain and blood) are given as $\mu mole \cdot g^{-1}$ wet weight.

Results

The final data set had eight to ten animals per group. Table 1 shows the physiologic variables in the normoxia and hypoxia groups. MABP during the hypoxia period was unchanged compared to the preceding normoxia period. There was also no difference in MABP between normoxia and hypoxia groups. Pa_{CO_2} decreased significantly during hypoxia compared with that in the normoxia group, but there was no significant difference in Pa_{CO_2} or Pa_{O_2} among the hypoxia groups. The significant increase in pH in the hypoxia groups relative to the normoxic group was most likely the result of the sodium bicarbonate infusion.

Table 2 shows the values of brain ATP, PCr, lactate, and glucose from hemispheres ipsilateral and contralateral to the ligated carotid artery in normoxia and hypoxia groups. ATP did not decrease during hypoxia in any group relative to the normoxia group. PCr on the ipsilateral (left) side decreased significantly in the hypoxia-N_2O and hypoxia-thiopental high-dose groups compared to the normoxia group. PCr in both etomidate groups and the low-dose thiopental group did not decrease significantly relative to the normoxia group and, in fact, was significantly higher than PCr in the hypoxia-N_2O group. On the contralateral side, there was a significant decrease in PCr in the hypoxia-N_2O and low-dose thiopental groups compared with that in the normoxia group. Except for the low-dose thiopental group, all of the PCr values from the contralateral side treatment groups were significantly higher than the values in the hypoxia-N_2O group. Lactate

TABLE 2. Cerebral Cortical Tissue Concentration of ATP, PCr, Lactate, and Glucose Obtained at the End of Hypoxia from Hemispheres Ipsilateral (left) and Contralateral (right) to the Ligated Carotid Artery

Group	ATP		PCr		Lactate		Glucose	
	Left	Right	Left	Right	Left	Right	Left	Right
Normoxia-N_2O n = 10	2.76 ± 0.10	2.82 ± 0.14	3.88 ± 0.12	3.94 ± 0.11	2.34 ± 0.16	2.13 ± 0.12	3.56 ± 0.28	3.29 ± 0.22
Hypoxia-N_2O n = 9	2.59 ± 0.12	2.63 ± 0.10	1.75 ± 0.25*	1.94 ± 0.21*	24.23 ± 0.96*	22.21 ± 0.73*	4.14 ± 0.36	4.35 ± 0.39
Hypoxia-ETM (LD) n = 8	2.58 ± 0.16	2.60 ± 0.16	3.27 ± 0.32†	3.75 ± 0.32†	11.67 ± 1.30*†	10.57 ± 1.20*†	5.17 ± 0.76	5.31 ± 0.78
Hypoxia-TPL (LD) n = 8	2.52 ± 0.16	2.56 ± 0.13	2.93 ± 0.32†	2.87 ± 0.3*	14.13 ± 2.23*†	13.23 ± 2.12*†	4.13 ± 0.47	4.14 ± 0.50
Hypoxia-ETM (HD) n = 9	2.56 ± 0.16	2.58 ± 0.17	3.33 ± 0.29†	3.44 ± 0.34†	15.47 ± 1.48*†	13.41 ± 1.26*§	3.58 ± 0.62	3.68 ± 0.61
Hypoxia-TPL (HD) n = 10	2.60 ± 0.17	2.96 ± 0.27	2.43 ± 0.17*	3.40 ± 0.12†	14.50 ± 1.29*†	11.41 ± 0.94*†	3.50 ± 0.36	4.05 ± 0.35

For group abbreviations see Table 1.
Values are given as mole g^{-1} wet weight (mean ± SE).
n is the number of animals per group.

* $P < 0.05$ Significantly different from Normoxia-N_2O.
† $P < 0.05$ significantly different from Hypoxia-N_2O.

increased significantly in both hemispheres in all hypoxia groups compared with that in the normoxia group. The largest increase in lactate occurred in the hypoxia-N_2O group. Though the level of lactate increased significantly in the iv drug treatment groups, the values were significantly less than those in the hypoxia-N_2O group.

Metabolite concentrations in the hypoxia groups tended to decrease more on the ipsilateral than on the contralateral side, but these changes only reached statistical significance for PCr concentration in the hypoxia-N_2O, hypoxia low-dose etomidate, and hypoxia high-dose thiopental groups; and for lactate concentration in the hypoxia-N_2O, hypoxia low- and high-dose etomidate, and hypoxia high-dose thiopental groups. Brain glucose concentration did not change in the hypoxia group compared with that in the normoxia group. There were no ipsilateral (compared to contralateral) side differences in glucose, except in the high-dose thiopental group where glucose was significantly higher on the contralateral side than on the ipsilateral side.

TABLE 3. Blood Glucose Concentrations before and at the End of Hypoxia

Group	Before Hypoxia	End of Hypoxia
Normoxia-N_2O	9.7 ± 0.6 (8)	11.8 ± 1.7 (8)
Hypoxia-N_2O	9.1 ± 0.6 (7)	14.0 ± 1.1* (8)
Hypoxia-ETM (LD)	8.7 ± 1.0 (6)	12.3 ± 2.1 (6)
Hypoxia-TPL (LD)	11.0 ± 1.0 (8)	10.2 ± 1.3 (7)
Hypoxia-ETM (HD)	9.4 ± 1.4 (7)	10.1 ± 1.6 (7)
Hypoxia-TPL (HD)	8.0 ± 0.8 (5)	9.6 ± 0.9 (8)

For group abbreviations see Table 1.
Values are $\mu mole \cdot g^{-1}$ wt weight (mean ± SE).
Values in parentheses are the number of samples.
* $P = .004$ (paired t test).

Blood samples for glucose were obtained before and at the end of the hypoxia period (table 3) or an equivalent period of time in the normoxia group. For technical reasons, some of these samples were not usable. In the normoxia group, the initial blood glucose was 9.7 ± 0.6 ($\mu mole \cdot g^{-1}$ wet weight, mean ± SE), and this showed a tendency to increase during the experimental period. There were no significant differences in blood glucose as a function of iv drug treatment either before or at the end of hypoxia. Paired t tests revealed a significant difference in the value of blood glucose before and at the end of hypoxia for the hypoxia-N_2O group. This increase of 55% was not seen in any of the other groups.

All iv drug treatment groups required epinephrine infusion during the hypoxia period to maintain MABP near 100 mmHg. The total dose of epinephrine was 72 ± 10 μg (mean ± SE) in the high dose etomidate group and 140 ± 6 μg in the high dose thiopental group. This latter group received significantly larger amounts of epinephrine than the other hypoxia groups, and some of these animals required epinephrine support prior to the onset of hypoxia.

Figure 1 shows representative EEG traces just prior to the onset of and at the end of hypoxia. Initially, the EEG from animals given N_2O showed a typical sedated high-

amplitude, low-frequency type pattern. At the end of the hypoxia period, however, there was virtually complete loss of the EEG with only occasional spikes. Both low-dose infusion groups showed marked depression of the EEG (burst suppression), and both high dose groups showed no EEG activity prior to the onset of hypoxia. EEGs in the iv drug treatment groups were virtually isoelectric at the end of the hypoxia period.

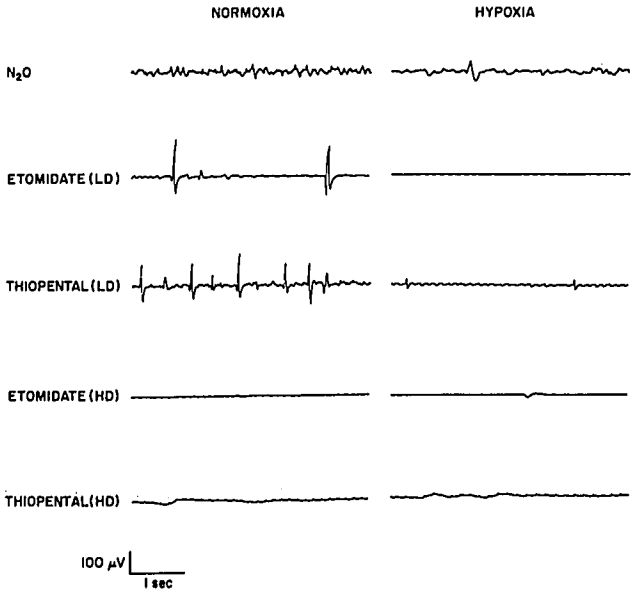

FIG. 1. Examples of the EEG changes before and at the end of the hypoxia period for the various treatment groups. The abbreviations are given in Table 1.

Discussion

Our results demonstrate that doses of etomidate producing burst suppression or complete suppression of the EEG have effects similar to doses of thiopental producing burst suppression in preventing the loss of PCr and attenuating the accumulation of lactate during 20 min of severe hypoxia in rats with unilateral carotid ligation. Both doses of etomidate were equally effective. In view of the relatively long period between the end of surgical preparation and the start of the experiment and the use of a high flow nonrebreathing gas delivery system, it is unlikely that the findings were related to residual halothane or N_2O.

The modified Levine model[9] of unilateral carotid artery ligation and hypoxia was used for this study because the degree of hypoxia (when used alone) needed to produce brain damage in rats often produces hypotension, arrhythmias, and death. Earlier studies with the same model showed that acute occlusion of one carotid artery decreased CBF by only 10% on the side of the occlusion, and that this mild reduction in CBF did not change the concentration of ATP, PCr, or lactate between the hemispheres ipsilateral and contralateral to the ligated carotid artery. During hypoxia, however, CBF increased by only twofold on the side with the carotid artery occlusion compared to fivefold on the side with the nonoccluded artery.[10]

It is important to differentiate studies attempting to define agents that may provide brain protection from those concerning brain resuscitation.[11] With resuscitation, an insult occurs prior to institution of therapy, and the agent must either prevent or reverse the events leading to neurologic damage. For protection, one goal is to prevent the deterioration in cell function that initiates events leading to brain damage. Several investigators have hypothesized that the onset of irreversible damage occurs just after hypoxia-induced neuronal depolarization.[12,13] Since high-energy metabolic depletion is associated with neuronal depolarization, prevention of this event might prevent damage from occurring. A drug that produces a better match between energy supply and demand may thus act to prevent brain damage. Though this is a more limited goal than resuscitation, for the anesthesiologist caring for a patient who might be subjected to an episode of intraoperative hypoxia or ischemia, an agent that confers protection without causing hypotension or unduly prolonging emergence from anesthesia would have definite benefits.

With respect to thiopental, its long duration of action and profound effects on blood pressure limit its usefulness. In the study by Nussmeier *et al.*[1] the time to extubation averaged 19 h after doses of thiopental that were required to maintain an isoelectric EEG. Though acceptable for patients undergoing cardiopulmonary bypass, these times are excessive for most other operations. Although our study did not evaluate the time to extubation, pharmacokinetic data of etomidate elimination,[14] and the experience of Batjer *et al.*,[15] would suggest that tracheal extubation can occur significantly earlier after etomidate than after thiopental. With respect to effects on cardiac function, the animals in our study receiving high-dose etomidate required half the dose of vasopressor, compared to those receiving thiopental, to maintain MABP above 100 mmHg during hypoxia, and several of the animals given thiopental required epinephrine prior to hypoxia. This is consistent with previous work showing that the cardiac depressant effects of etomidate are less than those of thiopental.[5,6] It is also interesting to note that the high-dose thiopental group had poorer preservation of PCr than the other drug treatment groups. Whether or not this was related to the higher dose of epinephrine cannot be determined from our study.

Though our data suggest that both etomidate and thiopental have similar effects on preserving brain PCr and decreasing lactate production, the hypoxic insult in

our model is primarily cortical and only metabolite concentrations in the cortex were measured. Studies of regional cerebral glucose metabolism suggest that with the barbiturates, the glucose cerebral metabolic rate in all areas of the brain is depressed, while with etomidate, the effect is primarily cortical and many subcortical structures show little effect.[16,17] We used relatively large doses of etomidate, however, so that the probability of widespread brain metabolic depression is higher, though regional differences are not ruled out by our study.

In our study, only PCr fell while ATP remained constant, suggesting that the insult was relatively mild. The pronounced increase in lactate is consistent, however, with an increase in anaerobic glycolysis. This, together with the fall in PCr, suggests that oxygen delivery in the groups not receiving thiopental or etomidate had reached a critical level and that the changes seen were related to hypoxic stress. Studies of the time course of high-energy metabolite changes during hypoxia in the dog brain have clearly demonstrated initial depletion of PCr and that ATP fall is a late event.[18,19]

Milde and Milde[20] demonstrated retardation of PCr loss and lactate production after etomidate in dogs subjected to 9 min of severe hypotension (a MABP of 31 mmHg). Their control group showed a loss of ATP (about 40%) that was greater than the loss seen in the etomidate group. The reported changes in PCr in their control group were similar to ours, about 50%; however, the changes in lactate were much greater in our study. The greater lactic acidosis in our animals may reflect better glucose delivery during hypoxia than during ischemia.[21,22] The 50% PCr fall, despite marked preservation of ATP, in our study may reflect the fact that hypoxia produces a less heterogeneous insult than ischemia, and is consistent with the hypothesis of marked oxygen gradients with markedly varying neuronal oxygen environments.[23]

Van Reempts and associates[24] examined the effects of subcutaneous etomidate on histologic change in the cortex of rats with unilateral carotid ligation 24 h after intermittent nitrogen exposure. They noted that the lesions were fewer and less severe in the etomidate group compared with controls. More recently, Baughman *et al.*[25] examined neurologic outcome after a period of regional ischemia. Animals receiving etomidate showed a tendency toward greater mortality and neurologic damage than those treated with methohexital or midazolam, but less than animals given only N_2O. Further work will be needed to reconcile the findings of Baughman *et al.*[25] with ours and those of Milde and Milde,[20] considering the differing hypoxic/ischemic insults and doses of etomidate.

Our prehypoxic values for blood glucose were similar in all treatment groups. There was a tendency toward an increase in blood glucose in the normoxia-N_2O group with time, but this increase did not reach statistical significance. A paired *t* test between the pre and post hypoxia blood glucose concentration, however, revealed a significant increase in blood glucose in the hypoxia-N_2O group. No significant change in blood glucose was noted in any of the iv drug treatment groups. It is interesting to speculate that high doses of anesthetics in a stressful situation may, in fact, decrease the increase in blood glucose that might otherwise occur, though the effects that this may have on an outcome cannot be determined from the present experiments.

It is clear that even single doses of etomidate can produce adrenal cortical suppression lasting 24 h or more in normal patients undergoing elective surgery[26,27] and that this effect is more pronounced as the dose is increased or if infusions are used.[28,29] The effect on adrenal cortical function, however, is relative in that rats receiving a single dose of etomidate (3 $mg \cdot kg^{-1}$) prior to 60 min of hemorrhagic shock had significantly less mortality than adrenalectomized rats.[30] Of particular importance, with respect to the current studies, is the fact that the initial reports of etomidate-induced adrenal cortical suppression and death were in intensive care patients receiving long term infusions of relatively low-dose etomidate for sedation.[31] Etomidate appears to affect the synthesis of cortisol, 17 alpha-hydroxyprogesterone, aldosterone, and corticosterone[29,32] and not the response of the receptors so that supplementation with exogenous steroids should prevent the adverse effects of adrenal cortical suppression and allow clinical use of etomidate for brain protection if further studies justify its use.

In summary, doses of etomidate, sufficient to produce burst suppression or an isoelectric EEG, prevent the loss of PCr and decrease the increases in lactate that otherwise occur during 20 min of severe hypoxemia in rats with unilateral carotid ligation. The effects of etomidate are similar to those of burst-suppression doses of thiopental, suggesting that etomidate has the potential to prevent the onset of brain damage that occurs with brain high-energy metabolic depletion.

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