Intracranial elastance in isoflurane-anesthetized horses

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Objective—To determine whether high intracranial pressure (ICP) during spontaneous ventilation (SV) in anesthetized horses coincides with an increase in intracranial elastance (ie, change in ICP per unit change of intracranial volume).

Animals—6 adult horses.

Procedure—Anesthesia was induced and maintained in each horse for 5 hours with isoflurane at a constant dose equal to 1.2 times the minimum alveolar concentration. Direct ICP measurements were obtained by use of a strain gauge transducer inserted in the subarachnoid space, and arterial blood pressure was measured from a carotid artery. Physiologic responses were recorded after 15 minutes of normocapnic controlled ventilation (CV) and then after 10 minutes of SV. Aliquots (3 mL) of CSF were removed from each horse during SV until ICP returned to CV values. Slopes of pressure-volume curves yielded intracranial elastance.

Results—Intracranial elastance ranged from 0.2 to 3.7 mm Hg/mL after removal of the first aliquot of CSF. Slopes of pressure-volume curves were largest following removal of the initial CSF aliquot, but shallow portions of curves were detected at relatively high ICPs (25 to 35 mm Hg). A second-order relationship between SV ICP and initial intracranial elastance was found.

Conclusions and Clinical Relevance—In horses anesthetized with isoflurane, small changes in intracranial volume can cause large changes in ICP. Increased intracranial elastance could further exacerbate preexisting intracranial hypertension. However, removal of small volumes of CSF may cause rapid compensatory replacement from other intracranial compartments, which suggests steady-state maintenance of an increase in intracranial volume during isoflurane anesthesia in horses. (*Am J Vet Res* 2004;65:1042–1046)

The Monro-Kellie doctrine[1] states that 3 nearly incompressible volumes (ie, blood, CSF, and brain parenchyma) exist within the rigid cranial vault. Consequently, an increase in volume of 1 of those compartments must increase **intracranial pressure (ICP)** unless it is compensated by an equivalent decrease within other compartment volumes. This change in ICP per unit change of intracranial volume defines intracranial elastance. Increases in intracranial pressure, in turn, decrease **cerebral perfusion pressure (CPP)**, a determinant of cerebral blood flow. When severe, the development of cerebral ischemia within the brainstem[2,3] initiates a reflex during which systemic arterial pressure increases to preserve CPP and cerebral blood flow.[4,5] This systemic pressor response to intracranial hypertension is termed a Cushing reflex.

Although ICP in standing, awake horses is similar to values measured in other healthy animals,[6] ICP in laterally recumbent, isoflurane-anesthetized horses is generally much higher than for other species under similar conditions.[7–9] Larger changes in hydrostatic gradients related to body size may cause larger increases in intracranial volumes (eg, a result of venous congestion or edema) in anesthetized horses, resulting in a higher ICP. However, another explanation for this difference could be that the intracranial compartment is less compliant in horses, thereby causing large increases in ICP as a result of small increases in volume.

It is also unknown whether increases in ICP associated with anesthesia in horses could cause a compensatory increase in systemic blood pressure. Support for this phenomenon was suggested by a pilot evaluation conducted by 1 of the authors (RJB) of 1 laterally recumbent, isoflurane-anesthetized horse that had an inadequate craniotomy seal following placement of a transducer in the subarachnoid space. In that horse, overt aliquorrhea was evident from the craniotomy site during hypercapnic **spontaneous ventilation (SV)** but not during normocapnic **controlled ventilation (CV)**. As a result, SV was associated with relatively modest increases in ICP, compared with ICP during CV. Furthermore, there was no increase in arterial blood pressure during SV, which is typically associated with respiratory acidosis. When an adequate craniotomy seal was finally obtained, the ICP change between CV and SV increased 3-fold and SV was likewise accompanied by increases in systemic arterial pressure of similar magnitude. It is possible that increased blood pressure during hypercapnia in that horse may have been involved in the vasopressor response to intracranial hypertension. The study reported here was designed to test the hypothesis that increases in ICP during SV in isoflurane-anesthetized horses accompany an increase in intracranial elastance and, in part, mediates the systemic pressor response.

Materials and Methods

Animals—Four geldings and 2 mares (1 Holsteiner, 1 Quarter Horse, 3 Thoroughbreds, and 1 Warmblood) were

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used in the study. Horses were between 3 and 13 years of age (mean ± SD; 7 ± 3 years) and weighed between 506 and 630 kg (mean, 552 ± 50 kg). The study was approved by the Animal Use and Care Committee of the University of California, Davis.

Anesthesia—Food (but not water) was withheld from horses for 12 hours prior to the onset of the study. Anesthesia was induced in unmedicated horses with isoflurane-oxygen delivered via a face mask by use of a technique that has been described elsewhere.[10-12] Horses were positioned in left lateral recumbency with the head in the sagittal plane, and each horse was intubated with a 30-mm cuffed endotracheal tube that was then connected to a semiclosed large-animal anesthetic circuit. Following induction, anesthesia was maintained for 1 hour in spontaneously breathing horses with 1.7% to 2.0% isoflurane in oxygen to prevent gross purposeful movement of horses during insertion of instruments. For the next 5 hours, anesthesia was maintained at a constant isoflurane concentration of 1.57%, corresponding to 1.2 times the **minimum alveolar concentration (MAC)** for this species[13]; this period of anesthesia was part of a separate and unrelated study. During this time, breathing in 3 horses was controlled with intermittent positive-pressure ventilation, whereas breathing in the remaining horses was via SV. Isotonic polyionic fluids were administered IV at the rate of 3 mL/kg/h to replace estimated fluid losses. Blankets and heat lamps were used as necessary to maintain normothermia.

After completion of that portion of the study, maintenance of anesthesia was continued at 1.2 MAC of isoflurane. Baseline intracranial and cardiorespiratory responses were measured in all horses after 15 minutes of normocapnic CV, with a mean peak inspiratory pressure of 21 ± 0.8 cm H_2O and mean end-expiratory pressure of 1.3 ± 0.7 cm H_2O. Physiologic responses after this equilibration period varied minimally. Next, SV in all horses was permitted at the same end-tidal concentration of isoflurane, with physiologic measurements made 10 minutes following the first breath; responses were essentially constant at 10 minutes after the first SV breath.

Skin over the occiput and atlas was shaved and aseptically prepared. By moderate flexion of the neck, cisternocentesis was accomplished by use of an 18-gauge, 5.6-cm spinal needle inserted percutaneously through the atlanto-occipital interarticular space into the cisterna magna. An aliquot (3 mL) of CSF was removed during a 3- to 5-second interval, and physiologic measurements were collected 90 seconds after each removal of CSF; physiologic measurements were essentially constant by 90 seconds after removal of each aliquot of CSF. Removal of CSF was repeated until ICP during SV was equal to or less than the baseline ICP value during CV.

Measurement of variables—Systemic arterial pressure was recorded by use of a 14-gauge, 11.6-cm polytetrafluoroethylene catheter inserted percutaneously in the right carotid artery; **mean arterial pressure (MAP)** was obtained from the electronic signal mean. **Central venous pressure (CVP)** was recorded by use of a 6.5-F, 110-cm polyethylene catheter inserted percutaneously into the right jugular vein and advanced into the right atrium, as confirmed by characteristic pressure waveform patterns. Both catheters inserted in the right jugular vein were connected to strain gauge transducers[a] that were calibrated against a manometer before each experiment. **Heart rate (HR)** was obtained from a single-axis (base-apex) ECG. Airway pressures and **respiratory rate (RR)** were measured from the endotracheal tube by use of a differential pressure transducer[b] that was calibrated against a water manometer before each experiment. Signal outputs from all transducers were recorded by use of a multiple-channel polygraph.[c] Values for Pa_{O_2}, Pa_{CO_2}, and **pH of arterial blood (pHa)** were measured by use of an automated blood gas analyzer[d] with values corrected by use of standard curves derived from tonometry of horse blood with certified gas mixtures. **Partial pressure of oxygen in the final CSF sample ($P_{CSF}O_2$)**, **partial pressure of carbon dioxide in the final CSF sample ($P_{CSF}CO_2$)**, and pH in the final CSF sample removed from each horse were analyzed. In addition, blood samples were collected by use of venipuncture of the cranial part of the external jugular vein, and **partial pressure of oxygen in venous blood (Pv_{O_2})**, **partial pressure of carbon dioxide in venous blood (Pv_{CO_2})**, and pH of venous blood were similarly analyzed. End-tidal carbon dioxide and isoflurane concentrations were measured by use of infrared analyzers,[e] and fraction of inspired oxygen was measured by use of a polarigraphic oxygen sensor.[f] All gas analyzers were calibrated with multiple certified gases from which linear regression curves were calculated. Body temperature was determined by use of a nasopharyngeal probe[g] that was calibrated against a thermometer of certified accuracy.

Direct ICP measurements were obtained from the subarachnoid space by use of a catheter-tip strain gauge transducer[h] inserted during the first hour of anesthesia via a right temporal craniotomy by use of a procedure described elsewhere.[6] All transducers were electronically calibrated before surgical placement, and accuracy was confirmed after each experiment via calibration in a graduated water column. Values for CPP were calculated as MAP minus ICP. Intracranial elastance was calculated as the **change in intracranial pressure (ΔICP)** divided by the **change in CSF volume (ΔV_{CSF})**, where ΔV_{CSF} was the amount of CSF removed.

Statistical analysis—Descriptive statistics were reported as mean ± SD. Inferential statistics for physiologic responses before and after removal of CSF were accomplished by use of a 1-way repeated-measures ANOVA with Tukey post hoc comparisons. Values of $P < 0.05$ were considered significant. Polynomial regression analysis was used to characterize the relationship between initial intracranial elastance and measurements of ICP during SV.

Results

Cardiorespiratory and ICP measurements were summarized (**Table 1**). During SV before removal of CSF, values for ICP, MAP, and Pa_{CO_2} were all significantly higher and values for Pa_{O_2} and pHa were significantly lower, compared with corresponding values for CV (**Table 2**). However, significant differences were not observed for CPP, CVP, or HR. By the time the experiment was conducted after the prolonged anesthesia, 2 horses had become hypoxemic, although exclusion of data from these horses in a separate ANOVA did not alter statistical results.

Removal of CSF caused a gradual reduction of ICP in all horses (**Figure 1**), resulting in a new pressure equilibrium within 30 to 45 seconds after fluid withdrawal. Intracranial elastance, as determined by the slope of the curve (ie, $\Delta ICP/\Delta V_{CSF}$), was generally largest following removal of the intial volume of CSF and ranged from 0.2 to 3.7 mm Hg/mL. Horses with higher ICP during SV also tended to have higher intracranial elastance; conversely, horses with lower ICP during SV tended to have lower intracranial elastance. However, at extremely high ICP, elastance actu-

ally decreased (**Figure 2**). This suggested a parabolic relationship, as defined by the following regression equation:

$$\text{Elastance} = (-0.011 \times [\text{ICP}]^2) + (1.07 \times \text{ICP}) - 22.29$$

The coefficient of determination for that equation was 0.99. This relationship predicts that intracranial elastance is equal to 0 when SV ICP is 30 or 67 mm Hg and maximum elastance is 3.7 mm Hg/mL at an ICP of 49 mm Hg.

The MAP decreased in 4 of 6 horses concomitant with cisternocentesis-mediated decreases in ICP (Table 1). However, in the horses that did not respond, a common cause (eg, hypoxemia or low initial ICP) was not apparent. Hence, analysis of the data does not support a consistent decrease in MAP with decreasing ICP (ie, an inverse Cushing reflex).

Values for $P_{CSF}O_2$ were always less than values for PaO_2 and greater than values for PvO_2 (Table 1). Moreover, $P_{CSF}O_2$ appeared to approximate PaO_2 much more closely in hypoxemic horses than in normoxemic horses. Values for $P_{CSF}CO_2$ were between $PaCO_2$ and $PvCO_2$ values or slightly less than $PaCO_2$ and $PvCO_2$ values, suggesting that $PaCO_2$ or $PvCO_2$ can serve as a reasonable estimator of $P_{CSF}CO_2$. Negative carbon dioxide gradients between CSF and venous blood may reflect differences in the respiratory cycle or minute ventilation during which removal of CSF was performed because there was a delay of up to 3 minutes between collection of blood and CSF samples.

Table 1—Cardiorespiratory responses during normocapnic controlled ventilation (CV) and during spontaneous ventilation (SV) before and after removal of the first 3 mL of CSF in 6 horses anesthetized with 1.57% isoflurane.

Time of measurements	Variable	Horse 1	Horse 2	Horse 3	Horse 4	Horse 5	Horse 6	Mean ± SD
CV	Arterial pressure (mm Hg)							
	Systolic	112	81	136	121	71	113	106 ± 25
	Diastolic	74	50	86	73	41	76	66 ± 17
	Mean	89	60	106	92	50	91	81 ± 22
	ICP (mm Hg)	38	27	34	6	23	29	30 ± 5
	CPP (mm Hg)	52	33	72	66	27	62	52 ± 18
	CVP (mm Hg)	15	9	9	8	17	7	11 ± 4
	HR (beats/min)	28	33	31	43	14	41	32 ± 10
	RR (breaths/min)	8	8	6	11	12	7	9 ± 2
	Pa_{O_2} (mm Hg)	248	57	324	154	70	362	202 ± 129
	Pa_{CO_2} (mm Hg)	45	43	44	43	40	46	44 ± 2
	pHa	7.38	7.46	7.41	7.45	7.37	7.36	7.40 ± 0.04
SV before initial CSF removal	Arterial pressure (mm Hg)							
	Systolic	122	102	141	136	81	121	117 ± 22
	Diastolic	76	64	82	89	51	79	74 ± 14
	Mean	97	82	113	108	67	96	94 ± 17
	ICP (mm Hg)	60	42	53	31	34	39	43 ± 11
	CPP (mm Hg)	38	40	60	77	33	58	51 ± 17
	CVP (mm Hg)	13	10	8	7	18	–0.3	9 ± 6
	HR (beats/min)	32	33	32	40	23	42	34 ± 7
	RR (breaths/min)	4	4	2	11	3	6	5 ± 3
	Pa_{O_2} (mmHg)	121	51	81	118	60	236	111 ± 68
	Pa_{CO_2} (mm Hg)	60	65	61	50	68	59	61 ± 6
	pHa	7.29	7.32	7.31	7.39	7.23	7.28	7.30 ± 0.05
SV after initial CSF removal	Arterial pressure (mm Hg)							
	Systolic	112	126	147	131	81	112	118 ± 23
	Diastolic	67	79	89	83	49	73	73 ± 14
	Mean	86	92	115	102	60	92	91 ± 18
	ICP (mm Hg)	38	28	33	25	24	27	29 ± 5
	CPP (mm Hg)	49	64	82	77	37	64	62 ± 17
	CVP (mm Hg)	9	0	6	1	22	–3	6 ± 9
	HR (beats/min)	34	32	33	45	21	36	34 ± 8
	RR (breaths/min)	3	5	3	7	3	6	4 ± 2
	Pa_{O_2} (mm Hg)	145	61	82	80	62	241	114 ± 72
	Pa_{CO_2} (mm Hg)	64	77	62	55	69	61	65 ± 8
	pHa	7.27	7.27	7.30	7.36	7.22	7.27	7.28 ± 0.05
	$P_{CSF}O_2$ (mm Hg)	81	60	68	64	57	105	72 ± 18
	$P_{CSF}CO_2$ (mm Hg)	63	63	58	54	71	62	62 ± 6
	pH_{CSF}	7.29	7.25	7.24	7.28	7.25	7.22	7.24 ± 0.03
	Pv_{O_2} (mm Hg)	NA	39	63	52	38	73	53 ± 15
	Pv_{CO_2} (mm Hg)	NA	70	64	55	77	63	66 ± 8
	pHv	NA	7.29	7.28	7.36	7.20	7.26	7.29 ± 0.06
Spontaneous ventilation	Volume of CSF removed (mL)*	21	21	12	12	18	9	16 ± 5

*Represents the volume of CSF removed until intracranial pressure (ICP) during SV was equal to or less than the ICP during CV.
CPP = Cerebral perfusion pressure. CVP = Central venous pressure. HR = Heart rate. RR = Respiratory rate. pHa = The pH in arterial blood. $P_{CSF}O_2$ = Partial pressure of oxygen in CSF. $P_{CSF}CO_2$ = Partial pressure of carbon dioxide in CSF. pH_{CSF} = The pH of CSF. Pv_{O_2} = Partial pressure of oxygen in venous blood. Pv_{CO_2} = Partial pressure of carbon dioxide in venous blood. pHv = The pH of venous blood. NA = Not available.

Table 2—Significant differences (mean ± SEM) between physiologic responses during CV and before and after removal of the initial 3 mL of CSF during SV in 6 horses anesthetized with isoflurane.

Variable	CV – SV(before)	CV – SV(after)	SV (before) – SV (after)
MAP (mm Hg)	–12 ± 3	ND	ND
ICP (mm Hg)	–13 ± 3	ND	14 ± 3
CPP (mm Hg)	ND	ND	ND
CVP (mm Hg)	ND	ND	ND
HR (beats/min)	ND	ND	ND
RR (breaths/min)	4 ± 1	4 ± 1	ND
Pao_2 (mm Hg)	91 ± 38	91 ± 36	ND
$Paco_2$ (mm Hg)	–17 ± 3	–21 ± 3	ND
pHa	0.10 ± 0.01	0.12 ± 0.02	ND

Reported differences were significant ($P < 0.05$; repeated-measures ANOVA with Tukey post hoc test). ND = Not determined because the comparisons were not significantly different.

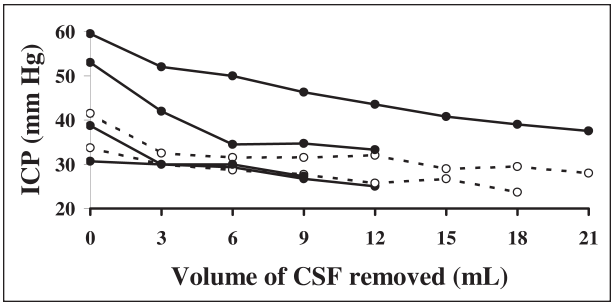

Figure 1—Graph of intracranial pressure (ICP) versus the volume of CSF removed during a period of spontaneous ventilation in 6 horses anesthetized with 1.57% isoflurane. Each set of points represents datum for 1 horse. Data for hypoxemic horses are indicated (open circles).

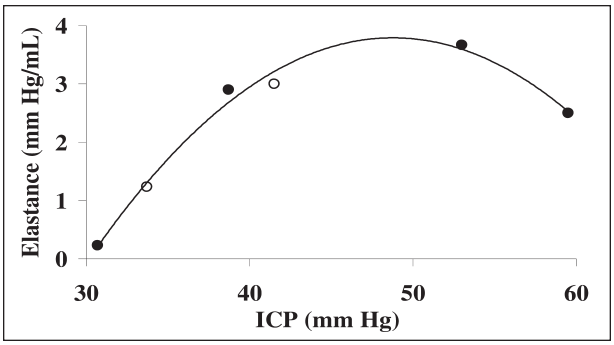

Figure 2—Graph of ICP versus intracranial elastance after removal of the first 3 mL of CSF during a period of spontaneous ventilation in horses anesthetized with 1.57% isoflurane. Each circle represents data for 1 horse. Data for hypoxemic horses are indicated (open circles). The equation for the polynomial regression curve ($r^2 = 0.99$) is as follows: elastance = (–0.011 × $[ICP]^2$) + (1.07 × ICP) – 22.29.

Discussion

To our knowledge, the study reported here is the first to document relationships between ICP and intracranial volume in horses. During isoflurane-induced anesthesia, horses typically have much higher ICP values than has been reported for other species, suggesting that intracranial elastance may be increased. Indeed, steeper elastance curves after removal of the initial volume of CSF revealed that even small changes in intracranial volume can cause large changes in ICP in horses during SV (Figure 1). During subsequent removals of CSF, elastance curves were more shallow, particularly at ICPs < 35 mm Hg, thereby manifesting augmented capacity for the intracranial compartment to accommodate changes in volume with minimal changes in pressure. These pressure-volume relationships appear similar in shape to exponential curves for barbiturate-anesthetized cats,[14,15] except that the shallow segment of the intracranial elastance curve for horses was evident at higher ICPs.

In our study, changes in intracranial volume were not compared to instantaneous changes in ICP; rather, they were compared to the new steady-state ICP obtained 90 seconds after CSF removal. As a result, possible increases in other intracranial compartment volumes following CSF removal could have offset potentially larger changes in ICP. Accordingly, the flattened portion of the pressure-volume curve represents the ICP at which a decrease in CSF volume approximates compensatory increases in blood or parenchymal volume. For example, as ICP decreases, there is less compression of thin-walled cerebral veins,[16] which may increase venous blood volume. Decreases in ICP may also lower interstitial hydrostatic pressure of the brain to favor increases in the volume of parenchymal extracellular fluid volume. Finally, lower CSF pressure can reduce the rate of CSF reabsorbtion[17] from arachnoid villi and extracranial lymphatics[18] and subsequently accelerate replacement of volumes that were removed.

Volume compensation may also have accounted for the quadratic relationship between initial SV ICP and elastance measurements (Figure 2). As ICP increases, instantaneous elastance will tend to increase exponentially. However, forces that increase volumes of the intracranial compartments (ie, vasodilation without deceased CPP or positional edema from diminished lymphatic drainage) are probably also increased at higher ICPs. Consequently, greater capacity for intracranial volume compensation during intracranial hypertension would reduce the actual net change in intracranial volume following CSF removal and thus decrease elastance values.

Various anesthetic agents appear to have similar effects on ICP-volume relationships. A comparison between etomidate and thiopental in normocapnic dogs anesthetized with halothane and nitrous oxide revealed[19] similar intracranial compliances. Moreover, intracranial compliance in dogs anesthetized with isoflurane and nitrous oxide; desflurane and nitrous oxide; or thiopental, halothane, and nitrous oxide did not have differences attributable to the various anesthetic agents during normoventilation, hyperventilation, a period of normal ICP, or a period of artificially induced intracranial hypertension.[20] In fact, anesthetic agents do not appear to alter structural relationships between pressure and volume at a given ICP (ie, by affecting the meninges or calvarium), but anesthesia does alter the volume of intracranial compartments that, in turn, affects an animal's position on the intracranial elastance curve. Therefore, it is likely through effects on intracranial compartment volumes, and not inherent viscoelastic properties, that new steady-state ICPs are achieved during anesthesia.

Low CPP that compromises cerebral blood flow triggers a Cushing reflex[21,22] that increases MAP to prevent cerebral ischemia. Conversely, for systemic hypertension secondary to intracranial hypertension, MAP should decrease as ICP decreases (inverse Cushing reflex). As reported in other studies,[8,9] ICP and MAP were significantly higher during SV in the horses of our study, compared with ICP and MAP during CV. However, CSF withdrawal during SV that returned ICP to values measured during CV caused a decrease in MAP in only 4 horses. On the basis of these responses, a consistent Cushing reflex associated with SV cannot be documented in horses. However, hypoxemia in 2 horses and nonconstant Pa_{CO_2} during SV may have confounded the response.[23-25] In addition, cerebral blood flow may not have become a linear function of MAP in all horses during SV, despite increases in ICP, because of changes in resting cerebrovascular tone that could have shifted the cerebrovascular autoregulation curve. Therefore, an inverse Cushing reflex would not have been expected in those horses. Given the design of our study, it was not possible to determine the extent to which the systemic pressor response during SV was mediated by intracranial hypertension versus respiratory acidosis.[26] Evaluation of horses during normoxemia and constant Pa_{CO_2}, in addition to quantification of cerebral blood flow, may be necessary to adequately address this mechanism.

The study reported here documented that isoflurane-anesthetized horses during SV have increased ICP, resulting in increased intracranial elastance. Moreover, intracranial elastance approaches 0 at ICP values between 25 and 35 mm Hg, suggesting that ICP during SV may be regulated at a much higher set point in anesthetized horses than in awake horses.

[a]Model P P23D, Statham Division of Mark IV Industries, Oxnard, Calif.
[b]Model PM131TC, Statham Division of Mark IV Industries, Oxnard, Calif.
[c]Grass model 7D, Statham Medical Instruments, Hato Rey, Puerto Rico.
[d]ABL5, Radiometer America Inc, Westlake, Ohio.
[e]LB2, Sensormedics Corp, Anaheim, Calif.
[f]OM-11, Sensormedics Corp, Anaheim, Calif.
[g]Yellow Springs Instruments Inc, Yellow Springs, Ohio.
[h]Codman Microsensor, Codman & Shurtleff Inc, Raynham, Mass.

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