Anesthesiology
61:703–707, 1984

Lung Water Increases with Fluid Administration during CPPV after Pulmonary Microembolization

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Hypoxemia created by pulmonary microemboli is improved by continuous positive-pressure ventilation (CPPV) but at a cost of reducing cardiac output ($\dot{Q}$). In this high pulmonary vascular resistance (PVR), pulmonary edema setting, the authors attempted to increase the $\dot{Q}$, which had been reduced by CPPV, with an infusion of dextran. In 14 dogs, 0.125 g/kg of starch microemboli (63–74 μm in diameter) were infused. CPPV at 15 cm H_2O then was applied and Pa_{O_2} increased from 53 ± 4 to 69 ± 3 mmHg, but $\dot{Q}$ decreased from 2.9 ± 0.2 to 1.7 ± 0.2 l/min. Seven of these dogs (control group) were monitored for 3 h. In the remaining seven dogs (volume group), dextran 40 was infused until $\dot{Q}$ returned to pre-CPPV values, and monitoring was continued for 3 h. With return of $\dot{Q}$ to pre-CPPV levels, indices of tissue oxygenation (O_2 transport, $P\bar{v}_{O_2}$, O_2 consumption and metabolic acidosis) were significantly improved. However lung water was increased significantly by the volume infusion, so that at 3 h lung water in the volume group was double the value in the control group. The authors conclude that volume infusion in the face of a high PVR may correct the reduced $\dot{Q}$ of CPPV and improve tissue oxygenation, but it also may increase pulmonary edema. (Key words: Fluid balance. Heart: cardiac output. Lung: edema; microemboli. Ventilation: continuous positive pressure.)

THE ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) is associated with an increase in pulmonary vascular resistance (PVR), pulmonary edema, and arterial hypoxemia. Pulmonary microemboli can create an increased PVR, pulmonary edema, and arterial hypoxemia[1] and have been suggested as a cause of ARDS.[2] Continuous positive-pressure ventilation (CPPV) is being used to improve the arterial hypoxemia of ARDS, however, we found that CPPV after pulmonary microemboli in dogs improves arterial oxygenation but reduces cardiac output ($\dot{Q}$) (unpublished data). The combination of an improved Pa_{O_2} and reduced $\dot{Q}$ resulted in decreased O_2 transport to and O_2 consumption of tissues and a developing metabolic acidosis. These observations are interesting because they indicate the possibility that patients with a high PVR (ARDS) who require ventilation with high levels of CPPV to improve arterial oxygenation may be improved additionally by increasing cardiac output and therefore oxygen transport and consumption.

It is important to determine whether, in a high PVR setting and with pulmonary edema present (*i.e.* ARDS), $\dot{Q}$ can be improved after CPPV by infusing fluid volume intravenously and whether there are any deleterious effects of this increased intravascular volume. The purpose of this study was to determine the effect of infusing intravenous fluid on gas exchange and hemodynamics after the hypoxemia of pulmonary microembolization had been treated with CPPV in dogs.

Methods

Animal Preparation and Measurements

Fourteen mongrel dogs weighing between 16 and 36 kg were studied. Anaesthesia was induced with pentobarbital 30 mg/kg iv and maintained with additional boluses of 50 mg as required. The animals breathed or were ventilated with air throughout the experiment.

The femoral artery and pulmonary artery were catheterized in order to monitor pressure continuously. The left atrium was catheterized from the internal carotid artery to monitor pressure.[3] Mean pressures were taken

Abbreviations

$\overline{BP}$ = mean arterial blood pressure (mmHg)
$P_{\overline{PA}}$ = mean pulmonary artery pressure (mmHg)
$P_{\overline{LA}}$ = mean left atrial pressure (mmHg)
P_{MV} = pulmonary microvascular pressure (mmHg)
PVR = pulmonary vascular resistance
$\dot{Q}$ = cardiac output (l/min)
CBV = central blood volume (ml/kg)
Pa_{O_2} = arterial partial pressure of oxygen (mmHg)
Pa_{CO_2} = arterial partial pressure of carbon dioxide (mmHg)
pH_a = arterial pH
$P\bar{v}_{O_2}$ = mixed venous partial pressure of oxygen (mmHg)
Ca_{O_2} = arterial oxygen content (ml/dl)
$C\bar{v}_{O_2}$ = mixed venous oxygen content (ml/dl)
$\dot{Q}_S/\dot{Q}_t$ = shunt fraction
V_D/V_T = dead space to tidal volume ratio
O_2 CONS = oxygen consumption (ml/min)
O_2 TRANSP = oxygen transport (ml/min)
O_2 EXTR = oxygen consumption/oxygen transport
ETV_L = extravascular thermal volume of lung (lung water)
PETW = pulmonary extravascular tissue weight

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Received from the Department of Anaesthesia, St. Michael's Hospital, Toronto, Canada. Accepted for publication May 24, 1984. Funding was provided by the Medical Research Council of Canada.

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TABLE 1. Control Group of Dogs

	Control	Pulmonary Embolism	CPPV	Early	Late
$P_{\overline{PA}}$ (mmHg)	18 ± 2	35 ± 4*	32 ± 3	34 ± 2	35 ± 3
$P_{\overline{LA}}$ (mmHg)	4 ± 1	1 ± 1*	10 ± 1*	9 ± 2	10 ± 2
Pmv (mmHg)	10 ± 1	15 ± 3*	19 ± 1*	19 ± 2	20 ± 1
$\overline{BP}$ (mmHg)	160 ± 8	138 ± 6*	115 ± 9*	121 ± 9	132 ± 8
CBV (ml/kg)	20 ± 2	14 ± 2*	12 ± 2	11 ± 1	10 ± 1
Pa_{O_2} (mmHg)	81 ± 3	52 ± 6*	71 ± 4*	73 ± 5	80 ± 6
Pa_{CO_2} (mmHg)	41 ± 2	37 ± 4	41 ± 2	40 ± 1	38 ± 2
pH_a	7.32 ± 0.01	7.31 ± 0.02	7.24 ± 0.01*	7.25 ± 0.01	7.25 ± 0.01
BE (mEq/l)	−5 ± 1	−6 ± 1*	−9 ± 1*	−9 ± 1	−11 ± 1
Ca_{O_2} (ml/dl)	16 ± 1	14 ± 1	17 ± 1*	17 ± 1	18 ± 1
$P\bar{v}_{O_2}$ (mmHg)	48 ± 2	35 ± 4*	37 ± 2	37 ± 2	38 ± 2
$C\bar{v}_{O_2}$ (ml/dl)	13 ± 1	10 ± 1	10 ± 1	11 ± 1	11 ± 1
$\dot{Q}_S/\dot{Q}_t$ (%)	14 ± 2	42 ± 6*	16 ± 3*	14 ± 3	12 ± 4
V_D/V_T (%)	45 ± 2	66 ± 5*	70 ± 4	68 ± 4	65 ± 3
Hb (g/dl)	12.7 ± 0.5	13.8 ± 0.6*	13.6 ± 0.7	14 ± 0.9	14.7 ± 0.8
O_2 CONS (ml/min)	126 ± 15	103 ± 6	96 ± 8	98 ± 7	105 ± 7
O_2 EXTR (%)	24 ± 3	28 ± 2	42 ± 4*	45 ± 6	46 ± 6

* Significantly different from preceeding value (analysis of variance).

over several respiratory cycles. No correction was made for increases in pleural pressure once CPPV was applied. Pulmonary microvascular pressure (P_{MV}) was calculated as $PMV = P_{\overline{LA}} + 0.4\,[P_{\overline{PA}} - P_{\overline{LA}}]$.[4] Arterial and mixed venous blood samples were analyzed for blood gases and hemoglobin (Hb). All values were corrected for body temperature. Oxygen content was calculated. Mixed expired gases, simultaneously collected through a tracheostomy, were analyzed for O_2 and CO_2 concentrations. Using this information venous admixture ($\dot{Q}_S/\dot{Q}_T$) and pulmonary deadspace (V_D/V_T) then were calculated using standard equations.[5] Oxygen consumption was calculated using the expired gas volume and expired oxygen and carbon dioxide concentrations. Cardiac output, central blood volume (CBV), and lung water (ETV_L) were measured using the thermodilution double indicator technique as previously described.[6–8] Oxygen transport was calculated as the product of cardiac output and arterial O_2 content. Oxygen extraction was calculated as O_2 consumption/O_2 transport. All catheters were kept open by flushing with normal saline, which resulted in an infusion of 150 ml/h in both groups.

Protocol

After control measurements, 0.125 g/kg of starch microemboli, 63–74 μm in diameter were infused as a single bolus through a large bore catheter inserted into the external jugular vein.

Thirty minutes after embolization, measurements were taken. The results of these measurements will be identified as "embolus."

CPPV at 15 cmH_2O end-tidal pressure then was applied, and measurements were repeated after 30 min and labeled "CPPV 15."

The animals then were divided into two groups:

1. Control—In seven dogs, while CPPV was applied, measurements were repeated every 30 min for 3 h.
2. Volume—In seven dogs, while CPPV was applied, 10% dextran 40 in normal saline (Rheomacrodex®) was infused until $\dot{Q}$ was returned to the "embolus value." The volume of dextran infused was 464 ± 24 ml. Measurements were repeated every 30 min for 3 h while CPPV was continued.

At the end of the experiment, the animals were killed with an intravenous injection of KCl and the lungs excised. The extravascular lung water was determined using a gravimetric method to measure pulmonary extravascular tissue weight (PETW).[7] This technique utilizes Hb to determine residual lung blood volume, which is subtracted from total lung weight.

Statistical analysis of the results was carried out using a two-way analysis of variance. Dunnett's and Tukey's test were used for multiple comparisons between means. Comparisons between groups were made using an unpaired t test. $P < 0.05$ was considered significant.[9] Only significant changes will be discussed. Data are reported as mean ± SEM.

Results

There were no significant differences between the two groups up to the time dextran 40 was infused. Thirty minutes after emboli, $P_{\overline{PA}}$ increased from 17 ± 1 to 33 ± 2 mmHg ($P < 0.001$); Pa_{O_2} decreased from 82 ± 2 to 53 ± 4 mmHg ($P < 0.001$); $\dot{Q}_S/\dot{Q}_t$ increased from 15 ± 2 to 41 ± 4% ($P < 0.001$); and $\dot{Q}$ decreased from 3.4 to 0.2 to 2.0 ± 0.2 l/min ($P < 0.025$). There was a small but significant increase in lung water from

TABLE 2. Volume Group of Dogs

	Control	Pulmonary Embolism	CPPV	Early	Late
$P_{\overline{PA}}$ (mmHg)	17 ± 2	31 ± 3*	34 ± 2	41 ± 3*	41 ± 3
$P_{\overline{LA}}$ (mmHg)	5 ± 1	3 ± 1*	9 ± 2*	14 ± 1*†	13 ± 2†
Pmv (mmHg)	10 ± 1	14 ± 2*	19 ± 2*	25 ± 1*†	24 ± 1†
$\overline{BP}$ (mmHg)	160 ± 4	138 ± 6*	124 ± 6	144 ± 9	160 ± 3†
CBV (ml/kg)	18 ± 2	14 ± 1*	13 ± 2	17 ± 2*†	15 ± 2†
Pa_{O_2} (mmHg)	82 ± 4	54 ± 5*	71 ± 2*	80 ± 2	72 ± 5
Pa_{CO_2} (mmHg)	41 ± 3	38 ± 3	38 ± 1	38 ± 1	37 ± 1
pH_a	7.34 ± 0.02	7.36 ± 0.04	7.31 ± 0.01	7.32 ± 0.01†	7.32 ± 0.02†
BE (mEq/l)	−4 ± 1	−4 ± 1	−7 ± 1*	−6 ± 1†	−6 ± 1†
Ca_{O_2} (ml/dl)	17 ± 1	17 ± 1	19 ± 1	14 ± 1*†	14 ± 1†
$P\bar{v}_{O_2}$ (mmHg)	53 ± 3	36 ± 3*	39 ± 1	46 ± 1*†	38 ± 1*
$C\bar{v}_{O_2}$ (ml/dl)	15 ± 1	13 ±1	14 ± 1	11 ± 1*	10 ± 1
$\dot{Q}s/\dot{Q}t$ (%)	16 ± 3	39 ± 6*	16 ± 2*	13 ± 2	17 ± 4
V_D/V_T (%)	38 ± 2	62 ± 5*	64 ± 3	58 ± 3	57 ± 4
Hb (g/dl)	13.3 ± 0.6	15.1 ± 0.6*	15.3 ± 0.8	10.9 ± 0.6*†	11.6 ± 0.6†
O_2 CONS (ml/min)	127 ± 11	119 ± 11	104 ± 18*	129 ± 12*†	123 ± 14
O_2 EXTR (%)	21 ± 2	26 ± 4	34 ± 4*	31 ± 4	36 ± 3

* Significantly different from preceeding value (analysis of variance).

† Significantly different from control dogs at the same time (unpaired *t* test).

13.2 ± 3.7 to 16.2 ± 5.1 ml/kg. CPPV at 15 cmH_2O after emboli increased Pa_{O_2} from 53 ± 4 to 69 ± 3 mmHg ($P < 0.001$) and reduced $\dot{Q}s/\dot{Q}t$ from 41.4 to 16.2% ($P < 0.001$); but because $\dot{Q}$ was reduced from 2.9 ± 0.2 to 1.7 ± 0.2 l/min ($P < 0.001$), O_2 transport decreased from 447 ± 37 to 310 ± 35 ml/min ($P < 0.001$). Other significant changes created by pulmonary emboli and then CPPV 15 cmH_2O are reported in tables 1 and 2.

The infusion of dextran 40 immediately increased CBV and $P_{\overline{LA}}$ (table 2). Dextran restored and maintained $\dot{Q}$ at the pre-CPPV value (fig. 1). $\dot{Q}$ was significantly greater after the volume infusion than in the control group. Hb was diluted by dextran 40, and arterial O_2 content (CaO_2) was reduced (tables 1 and 2). O_2 transport, $P\bar{v}_{O_2}$, and O_2 consumption were increased in the volume group. Base excess was less negative and *p*H less acidotic in the volume group (tables 1 and 2).

Lung water (ETV_L) was increased significantly immediately by the volume infusion and continued to increase over the remaining hours. By the last determination ETV_L in the volume group was double the value in the control dogs (fig. 2). The ratio of ETV_L/PETW was not significantly different between the two groups of dogs. It is greater than one because of thermal equilibrium with airways, pulmonary arteries and veins, the left heart, and a small portion of the inner chest wall,[6–8] which are not measured by the PETW technique.

Discussion

Our results indicate the following: 1) CPPV improves Pa_{O_2} and $\dot{Q}s/\dot{Q}t$ after pulmonary microemboli; 2) CPPV reduces $\dot{Q}$ in this high PVR setting; 3) the resultant effect of CPPV after pulmonary emboli is to reduce indices of tissue oxygenation (decreased O_2 transport and consumption, worsening metabolic acidosis).

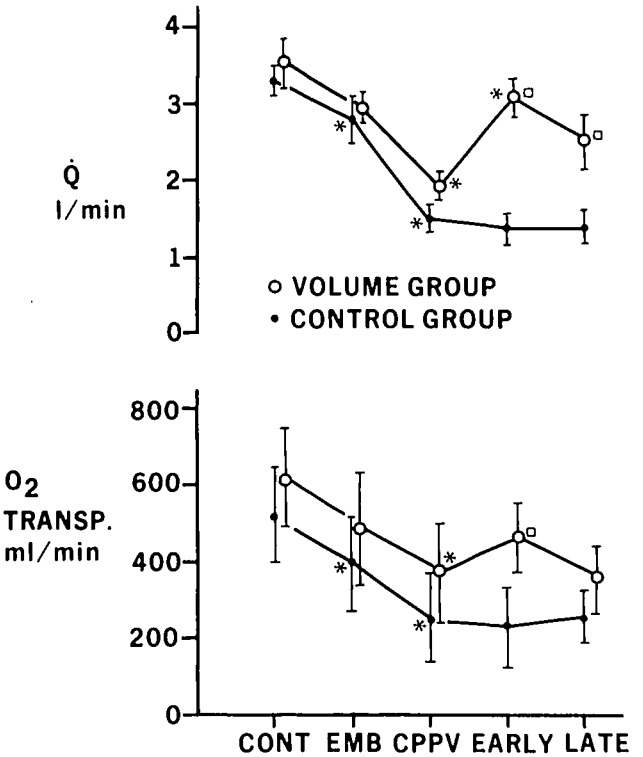

FIG. 1. Cardiac output and oxygen transport in the volume and control groups during the control period (CONT), after emboli (EMB), once CPPV was applied (CPPV), 30 min after treatment was applied (EARLY), and 3 h later (LATE). * indicates a significant difference from the preceding value. □ indicates a significant difference from the control group.

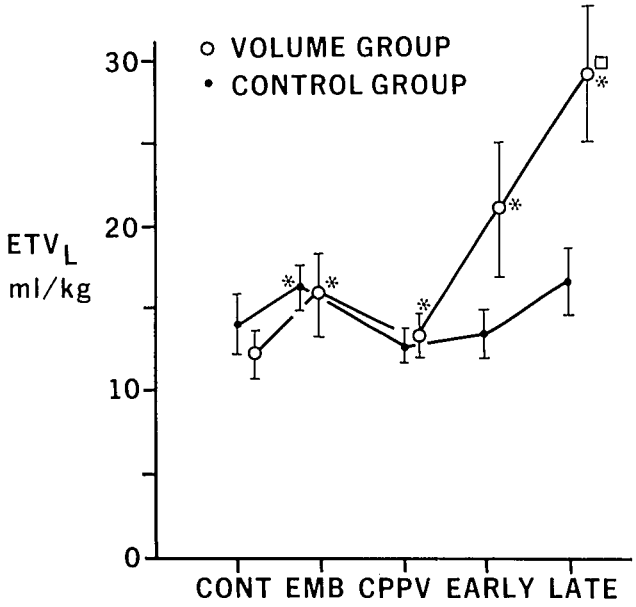

FIG. 2. Lung water measurements (ETV_L) in the volume and control groups at the indicated times. See figure 1 for abbreviations. * indicates a significant difference from previous value. □ indicates a significant difference from the control group.

CPPV has been shown to decrease $\dot{Q}$.[10-20] The mechanisms remain controversial and may include reduced left ventricular preload,[10-15] decreased myocardial contractility,[19,21] ventricular interdependence,[16-18,20] and ventricular compliance changes.[16] Most recent studies suggest CPPV reduces left ventricular preload, which reduces $\dot{Q}$.[10-15] A serious problem in these studies is the

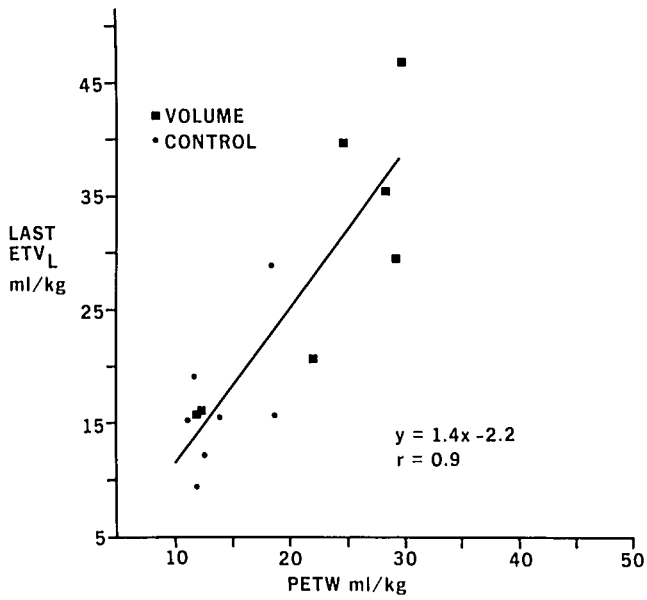

FIG. 3. Last ETV_L (lung water) measurement plotted against the post mortem weighing technique for lung water (PETW) in all dogs.

controversy over accurate measurement of transmural cardiac pressures during CPPV.[22,23] In view of this controversy we have not attempted to investigate the cause of the decreased $\dot{Q}$ after CPPV in this high PVR setting. We have, instead, attempted to return $\dot{Q}$ to pre-CPPV levels by infusing fluid volume and measured hemodynamic and gas exchange effects of this fluid volume intervention. We were successful in returning $\dot{Q}$ to pre-CPPV levels (fig. 1) when CBV was returned to control levels and $P_{\overline{LA}}$ was increased by infusing dextran. This is supportive of the large number of studies suggesting CPPV reduces $\dot{Q}$ by decreasing left ventricular preload.[10-15,22] There was a small increase in $P_{\overline{PA}}$; 34 ± 2 to 41 ± 3 mmHg ($P < 0.025$), $P_{\overline{LA}}$ 9 ± 2 to 14 ± 1 mmHg ($P < 0.05$), and P_{MV} 19 ± 2 to 25 ± 1 mmHg ($P < 0.025$) (table 2). Hb was diluted by the dextran 40 infused in the volume group, and this reduced Ca_{O_2} in these dogs. In spite of this the improved $\dot{Q}$ in the volume group, increased O_2 transport (fig. 1), O_2 consumption, and $P\bar{v}_{O_2}$ and reduced the metabolic acidosis (table 2), which was developing in the control dogs (table 1). These criteria of tissue oxygenation indicate the volume-induced increase in $\dot{Q}$ was beneficial after CPPV and pulmonary microemboli.

However, the volume group of dogs also demonstrated a large increase in lung water (ETV_L) of 13 ± 2 to 29 ± 5 ml/kg ($P < 0.001$), which was not found in the control group of dogs (ETV_L 13 ± 1 to 17 ± 2 ml/kg; NS [fig. 2]). It is conceivable that the control group of dogs had lung areas unperfused because of the microemboli and that these lung areas would not be measured by ETV_L. If this were so, ETV_L/PETW should be reduced in the control group. There was no significant difference between ETV_L/PETW in the volume and control dogs (fig. 3). Thus, by both measurement techniques (ETV_L and PETW) we measured a real increase in lung water in the dogs given volume to correct the CPPV reduced $\dot{Q}$. The cause of the increased lung water in the volume group of dogs must remain conjectural but may relate to higher pulmonary microvascular pressures in these dogs (P_{MV} increased from 19 ± 1 to 25 ± 1 mmHg, $P < 0.025$, with the infusion of volume). Pulmonary vascular pressures (measured without pleural pressure correction) were increased by the application of CPPV at 15 cmH_2O (tables 1 and 2), suggesting that transmural pressures were not as high as the absolute pressure would indicate. The volume infusion did not create large increases in pulmonary microvascular pressures (6 mmHg), but in the face of a lung lesion created by pulmonary microemboli (or ARDS in patients) any increase in pulmonary microvascular pressure may produce pulmonary edema. There are suggestions that changes in lung water become more sensitive to even small intravascular pressure changes when capillary per-

meability is increased.[24,25] This strongly suggests that the small increase in $P_{\overline{LA}}$ (5 mmHg) created by infusing the volume necessary to restore $\dot{Q}$ resulted in a dramatic increase in lung water.

The fact that lung water increased with the infusion of fluid volume supports previous evidence[26,27] that CPPV does not reduce lung water. CPPV does improve Pa_{O_2} and reduces $\dot{Q}_S/\dot{Q}_t$ in the face of large increases in lung water.[26,27] This presumably accounts for the fact that Pa_{O_2} and $\dot{Q}_S/\dot{Q}_T$ remained at control levels after CPPV was applied, even in the volume group of dogs when lung water was increased to alveolar edema levels[28] (tables 1 and 2). We would expect (but did not measure) a reduced Pa_{O_2} if CPPV were discontinued in the face of alveolar edema in the volume group of dogs.

The improved cardiac output and indices of tissue oxygenation are certainly desired effects of volume infusion (in a high PVR, pulmonary edema setting). However, they are obtained at a cost of more pulmonary edema. The clinical alternatives available when faced with high PVR, high CPPV, and low $\dot{Q}$ settings appear to be to reduce CPPV, infuse smaller volumes, and accept smaller increases in $\dot{Q}$, or improve Q with other techniques than volume infusion or combinations of these. It remains to be seen whether other techniques to improve $\dot{Q}$ after CPPV, in high PVR settings, can be successful without increasing lung water, *e.g.*, increasing myocardial contractility or decreasing left ventricular afterload.

The authors thank Gary Caskennette and E. Hobbs for their technical assistance and P. Slusarenko for preparing the manuscript.

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