Paraquat (PQ)-induced pulmonary fibrosis increases exercise metabolic cost, reducing aerobic performance in rats

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ABSTRACT — Rats exposed to the quaternary herbicide paraquat (PQ) exhibit oxidative stress and lung injury. In the present study, we investigated the effect of multiple exposures to PQ on aerobic performance during progressive exercise on a treadmill in rats. PQ was dissolved in saline (SAL) (10 mg/ml) and administered intraperitoneally 7 mg/kg body wt to Wistar rats (n = 5) once a week for one month. Control rats received SAL (0.7 ml/kg body wt., intraperitoneally, n = 5) over the same time period. The animals were submitted to aerobic evaluation on a treadmill using a progressive protocol until fatigue prior to the administration of the first dose of PQ or SAL and repeated at 1 week and 40 days following the last dose of the herbicide. Twenty-four hours after the last performance tests, the animals were sacrificed, lungs removed and divided in two groups: PQ and SAL for histopathological analysis. The animals exposed to PQ exhibited decrease in aerobic performance and mechanical efficiency (ME) as well as increase in oxygen consumption during exercise in comparison to the controls forty days after the last dose of PQ. Lung histologic changes included atelectasis, interstitial edema, and inflammation cells in PQ group. The collagen system fibers, fraction area of alveolar collapse and influx of polymorphonuclear (PMN) cells in lung parenchyma were higher in PQ compared to SAL. In conclusion, multiple exposures to PQ induce pulmonary fibrosis, reduce the aerobic performance and mechanical efficiency and increase the metabolic cost of exercise in rats.

Key words: Exercise, Oxygen consumption, Pulmonary fibrosis

INTRODUCTION

Paraquat (PQ) (1, 1’-dimethyl-4, 4’-bipyridinium dichloride) is a quaternary nitrogen herbicide. It is highly toxic to humans and animals, accumulating mainly in the lungs, liver, kidneys and heart. This herbicide has been widely used as an experimental model to study lung injury, especially diffuse alveolar damage, due to its low cost, rapid effect and simplicity of administration (Rocco et al., 2003; Silva and Saldiva, 1998). Moreover, the mechanism of pulmonary fibrosis induced by PQ in rats is similar to the fibrosis pathogenesis in humans exposed to this herbicide (Dasta, 1978).

The most common cause of death from PQ poisoning is respiratory failure due to an oxidative insult to the pulmonary parenchyma with subsequent pulmonary fibrosis (Tomita et al., 2007; Kim et al., 2006; Orito et al., 2004; Schenker et al., 2004). According to previous study (Heindl et al., 2001), there is marked sympathetic activation in patients with chronic respiratory failure associated with pulmonary fibrosis, which may have important consequences for respiratory muscle function.

Energy efficiency of the body becomes apparent during exercise when ~20 to 27% of the energy expended can be used for external work, whereas the remaining adenosine triphosphate (ATP) production is either used for homeo-
tasis or dissipated as heat (Brooks et al., 1984). Oxygen consumption is a significant parameter of physical exercise, reflecting both mechanical efficiency and physical performance until fatigue ensues (Lacerda et al., 2006). A high metabolic rate resulting from exercise drastically increases oxygen consumption in the exercising and inspiratory muscles as well as the heart and other tissues (Banerjee et al., 2003). During exercise, the oxygen consumption of the body is about 10 to 15 times greater than oxygen consumption at rest (Alessio, 1993). The capacity to perform physical exercise provides a wide variety of information used in the diagnosis of pulmonary disease as well as to evaluate the progression of diseases and therapeutic interventions (Miki et al., 2003). Dalvie et al. (1999) evaluated the possible effects of PQ spraying among workers on deciduous fruit farms in the Western Cape, South Africa and showed a significant relation between measures of long term exposure to PQ and arterial oxygen desaturation during exercise independent of short-term exposure. These findings indicate that working with PQ under usual field conditions is associated with abnormal exercise physiology in a dose dependent fashion independent of recent exposure and acute poisoning events. Furthermore, Schenker et al. (2004) studied pulmonary function and exercise-associated changes with chronic low-level PQ exposure and also observed the association of PQ exposure with oxygen desaturation suggesting that PQ may be associated with subclinical gas exchange abnormalities.

In the present study, four weekly administrations of PQ intraperitoneally were used to evaluate the respiratory effects of long term and to verify the relation between pulmonary injury and physical exercise performance. Therefore, we hypothesized that pulmonary fibrosis induced by multiple PQ exposures may reduce aerobic performance, thereby influencing oxygen consumption, i.e., energetic cost, and mechanical efficiency during incremental treadmill exercise until fatigue. The aim of the present study was to evaluate the effect of multiple PQ exposures on the physical performance (total exercise time and workload), energetic cost (oxygen consumption) and mechanical efficiency in untrained rats during progressive exercise until fatigue on a treadmill.

**MATERIALS AND METHODS**

Male Wistar rats with an initial weight of approximately 200 g were obtained from the Institute of Biological Sciences of the Federal University of Minas Gerais (Brazil) and kept in a controlled temperature of 22 ± 2°C with 14 hr of light daily (5 am - 7 pm). The animals had free access to rat chow and water.

The animals were randomly divided into two groups - an experimental group (PQ, n = 5) and a control group (SAL, n = 5). All animals were submitted to aerobic evaluation on a treadmill (Columbus Instruments, Columbus, OH, USA), with a progressive protocol (starting at 10 m/min and increasing 1 m/min every 3 min until fatigue, at 5% inclination). Aerobic evaluations were carried out prior to administration of the first dose of PQ or saline (SAL) and repeated at 1 week and 40 days following the last dose of the herbicide. Oxygen consumption was measured at rest and throughout the exercise protocol in both groups.

**Treatments**

PQ (Product: gramoxone® 200; Fabricant: Syngenta®; Composition: 1,1′-dimetil-4,4′-bipridilio dicloreto, ion (200 g/l) and inerts ingredients (876 g/l)) was dissolved in 0.9% NaCl SAL solution (10 mg/ml) and administrated intraperitoneally (i.p.) to PQ group (7 mg/kg body wt) once a week for four weeks. SAL rats were concurrently treated with SAL solution (0.7 ml/kg body wt, i.p.).

**Familiarization**

All animals underwent a familiarization procedure with the treadmill (5% inclination) for 5 min/day for 4 consecutive days prior to the experiment. On the first day of familiarization the rats exercised on the treadmill at a speed of 10 m.min⁻¹; on the following 3 days of familiarization, speed was progressively increased to 11, 13 and 15 m.min⁻¹. The objective of allowing the animals to familiarize themselves with the procedure was to minimize their stress levels without promoting the adaptations inherent to physical training (Lacerda et al., 2006).

All experiments were approved by the Ethics Committee of the Federal University of Minas Gerais for the Care and Use of Laboratory Animals (Approval 017/06).

**Experimental protocol**

Each animal remained on the metabolic treadmill for a 60-min resting period prior to exercise. A progressive exercise protocol was used in which the treadmill was maintained at 5% inclination (initial speed 10 m/min with a gradual increase of 1 m/min every 3 min until fatigue). Fatigue was defined as the point at which the animals were no longer able to accompany the treadmill pace (Lacerda et al., 2006; Hussain et al., 2001). Total exercise time (min) and workload (kgm) were considered running performance indexes. All the procedures were carried out between 6 pm and 10 pm, with room temperature maintained at 21 ± 1°C.
Oxygen consumption, which represents the energetic cost, was measured using an indirect open-circuit calorimeter (Columbus Instruments, Modular treadmill, series 96002-2) calibrated prior to each use with a standard mixture of gases containing 20.5% oxygen and 0.5% carbon dioxide (White Martins). Analysis of oxygen consumption was continuously recorded on-line both at rest and throughout progressive exercise until fatigue using a computerized system (Oxymax Apparatus, Columbus Instruments).

Workload (W; kgm) was calculated as W = body weight (kg) x TTF x treadmill speed (m.min⁻¹) x sine θ (treadmill inclination), where TTF is time to fatigue (min). Mechanical efficiency (ME) was calculated by the formula: ME = (W / energetic cost) x 100 (Brooks et al., 1984).

Lung histology

Twenty-four hr following the last aerobic evaluation (forty one days after the last dose of PQ) SAL and PQ animals were sedated (diazepam, 1 mg/kg, i.p.) and anesthetized (pentobarbital sodium, 20 mg/kg, i.p.). A laparotomy was done and heparin (1,000 IU) was injected in the vena cava. Abdominal aorta and vena cava were sectioned, yielding a massive hemorrhage that quickly killed the animals and the trachea was clamped at end expiration. Then, the lungs were removed en bloc and fixed in a solution of 10% formaldehyde in 0.1 M sodium phosphate buffer and pH 7.2. After fixation the tissue was embedded in paraffin; blocks were cut into 4-μm thick sections with a microtome and slices were stained with hematoxylin-eosin. The slides were coded and two investigators, who were unaware of the origin of the material, performed the microscopic examination. Morphometric analysis was performed using an integrated eyepiece and a coherent system consisting of a grid with 100-point and 50 lines of known length coupled to a conventional light microscope (Axioplan, Zeiss, Oberkochen, Germany). The volume fraction of the lung occupied by hyperinflated structures (alveolar ducts, alveolar sacs, or alveoli wider than 120 μm) (Silva et al., 1998), collapsed alveoli (alveoli with rough or plicate walls), or normal pulmonary areas (those not presenting overdistended or plicate walls) was determined by the point-counting technique (Weibel, 1990) at a magnification of 200 x across 10 random, non-coincident microscopic fields. Points falling on tissue area were counted and divided by the total number of points in each microscopic field. Thus, data are reported as the fractional area of pulmonary tissue.

Histomorphometry

Histopathologic changes were evaluated in all animals. Slices were stained with 1% alcian blue (8GX, Sigma, St. Louis, MO, USA) at pH 2.5 in a 0.1 M HCl solution for 30 min for mast cell staining; a modified Sirius red technique (Dolber and Spach, 1987, 1993) for collagen staining; and with Weigert’s resorcin fuchsin method modified with oxidation for elastic fiber staining. Histomorphometry was performed using an imaging analysis system consisting of a digital camera (Coolpix 990, Nikon, Tokyo, Japan) coupled to a light microscope (Eclipse 400, Nikon). Ten fields of lung parenchyma from sections stained with Sirius red and Weigert’s resorcin fuchsin were imaged for each animal using a 40 x magnification objective lens. Quantification was estimated on high quality images (buffer: 2,048 x 1,536 pixels) by considering the percentage of stained areas in the total histological field using the Image Pro Plus 4.5.1 (Media Cybernetics, Silver Spring, MD, USA). Results were expressed as surface area (μm²) (Pecly et al., 2006).

Statistical analysis

The data are reported as mean + S.E.M.. Analysis of variance (ANOVA) was used for the statistical analysis of physical performance (workload and total exercise time), oxygen consumption, mechanical efficiency and body weight. Differences between means were compared using the Tukey’s post-hoc test. Analysis of histological and histomorphometric data was performed using the Student’s t-test. The correlation between collapsed areas and physical performance at 40 days following the administration of the last dose of PQ or SAL treatment was assessed using Pearson’s correlation coefficient. Statistical significance for all variables analyzed was set at 5%.

RESULTS

Histologically PQ group had a significantly higher number of polymorphonuclear cells and collapsed alveoli in the lung parenchyma than SAL group. Mononuclear cell content was smaller in the PQ group than in the SAL group. Collagen fiber content was significantly greater in the PQ group than in the SAL group. On the other hand, elastic fiber content remained similar in both groups (Table 1).

Photomicrographs of lung sections stained with hema-
toxylin-eosin, obtained from rats after repeated administration of PQ (7 mg/kg body weight, i.p.) or 0.9% NaCl (SAL; 0.7 ml/kg body weight; i.p.) are shown in Fig. 1.

Physical performance (defined as the workload and total exercise time) was similar in the two groups prior to administration of the first dose of PQ or SAL solution as well as 1 week after administration of the last dose. However, 40 days after the last dose, PQ significantly reduced total exercise time and workload (Table 2). We also observed a close correlation between physical performance 40 days after the last dose of the herbicide and the fractional area of collapsed alveoli (p < 0.05) (Fig. 2).

Both prior to treatment and at 1 week after administration of the last dose, there was no difference in resting oxygen consumption between the two groups. Similar behavior in oxygen consumption occurred in both groups during exercise until fatigue; oxygen consumption increased rapidly during the first 9 min of exercise and at a slower rate after 9 min until fatigue. Forty days after the last dose, there was no difference in resting oxygen consumption between the groups; however, from 3 min after initiating exercise until fatigue, oxygen consumption at the point of fatigue was similar in both groups (PQ: 47.11 ± 1.82 ml O₂/kg/min vs SAL: 44.45 ± 1.01 ml O₂/kg/min, p = 0.32).

ME was calculated during the rapid phase of oxygen consumption (3 to 9 min after initiating exercise) and during the slow phase of oxygen consumption (9 to 12 min after initiating exercise) to compare the metabolic cost of exercise 40 days after the last dose of PQ or SAL solution (Fig. 4). ME was similar between groups during the rapid phase; however, the PQ group exhibited a lower ME than

### Table 1. Histological characteristics of lung tissue of rats injected with either PQ or SAL solution

<table>
<thead>
<tr>
<th>Analysed Parameters</th>
<th>SAL</th>
<th>PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Areas (%)</td>
<td>79.7 ± 1.6</td>
<td>63.9 ± 2.2*</td>
</tr>
<tr>
<td>Collapsed Areas (%)</td>
<td>20.3 ± 1.6</td>
<td>36.1 ± 2.2*</td>
</tr>
<tr>
<td>PMN (%)</td>
<td>1.3 ± 0.6</td>
<td>3.3 ± 0.3*</td>
</tr>
<tr>
<td>MN (%)</td>
<td>21.6 ± 2.4</td>
<td>12.3 ± 0.5*</td>
</tr>
<tr>
<td>Total Cells (%)</td>
<td>22.9 ± 2.6</td>
<td>15.6 ± 0.7*</td>
</tr>
<tr>
<td>Collagen Fiber (%)</td>
<td>6.8 ± 0.9</td>
<td>9.3 ± 0.7*</td>
</tr>
<tr>
<td>Elastic Fiber (%)</td>
<td>6.8 ± 0.4</td>
<td>6.8 ± 0.6</td>
</tr>
</tbody>
</table>

Data were gathered from ten random, non-coincident fields per rat. Rats were treated with 0.9% NaCl (SAL, 0.7 ml/kg body weight, i.p.) or PQ (7 mg/kg body weight, i.p.) once a week for four weeks and submitted to aerobic evaluation on a treadmill with a progressive protocol. The lungs were removed 24 hr after the last aerobic evaluation. Percentages of normal and collapsed alveoli, fraction area of PMN cells, fraction area of MN cells, total cellular fractional area (Total cells), collagen and elastic system fibers in alveolar septa. Values are mean ± S.E.M. of 5 animals in each group. *Significantly different from SAL group (p < 0.05).
Paraquat and aerobic performance in rats

the SAL group during the slow phase of exercise (PQ: 22 + 2 % vs SAL: 26 + 1 %, p < 0.05).

**DISCUSSION**

Our data are in agreement with the widely recognized premise that whole body oxygen consumption (i.e., metabolic oxygen demand) and work intensity (workload) are directly related during incremental exercise in such way that when maximal oxygen consumption is achieved, the sensation of fatigue occurs and the animal stops running or loses the cadency of the treadmill. In the present study there was higher oxygen consumption (i.e; total energetic cost of the physical work) by rats during exercise 40 days after administration of the last dose of PQ in comparison to the control group (Fig. 3). Furthermore, a reduction was found in mechanical efficiency during exercise as well as a poorer aerobic performance in these animals (Fig. 4 and Table 2). These results are consistent with the hypothesis that pulmonary fibrosis induced by multiple

**Table 2. Variables of physical performance in rats injected with either PQ or SAL solution**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Administration</th>
<th>Total duration of exercise (min)</th>
<th>Workload (kgm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAL</td>
<td>Before</td>
<td>40.1 ± 3.8</td>
<td>7.6 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>After (7)</td>
<td>26.3 ± 2.8*</td>
<td>6.5 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>After (40)</td>
<td>17.5 ± 0.9†</td>
<td>4.7 ± 0.6</td>
</tr>
<tr>
<td>PQ</td>
<td>Before</td>
<td>39.2 ± 2.5</td>
<td>7.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>After (7)</td>
<td>23.6 ± 2.3*</td>
<td>5.7 ± 0.5*</td>
</tr>
<tr>
<td></td>
<td>After (40)</td>
<td>12.0 ± 1.0††</td>
<td>3.0 ± 0.3††</td>
</tr>
</tbody>
</table>

Total exercise time and work performed during progressive exercise on a treadmill until fatigue in rats treated with PQ dissolved in physiological SAL (10 mg/ml) at a dose of 7 mg/kg body wt; intraperitoneally (i.p.) or 0.15 M NaCl (SAL; 0.7 ml/kg body wt.; i.p.). Values are mean ± S.E.M., n = 5 in each group. *p < 0.05 compared to pre-treatment. †p < 0.05 compared to 1 week after administration of the last dose of the treatment. ‡p < 0.05 compared to controls.

Before, i.e. prior to treatment.

After (7), i.e. 1 week after the last dose of the treatment.

After (40), i.e. 40 days after the last dose of the treatment.

**Fig. 2.** Correlation between lung collapsed areas (%) and workload (kgm) (A), and total duration of exercise (min) (B) 40 days after administration of the last dose of PQ (7 mg/kg body wt, intraperitoneally i.p.; PQ; filled circle) or 0.9% NaCl (SAL; open circle; 0.7 ml/kg body wt.; i.p.). n = 5 in each group.

Vol. 34 No. 6
exposures to PQ, promotes a larger metabolic cost during exercise. The decreased aerobic performance was associated with increased oxygen consumption and reduced mechanical efficiency. The experimental model used in this study has already been validated as a model of pulmonary fibrosis (Akahori and Oehme, 1983; Satomi et al., 2004, 2006, and 2007); in such way, the increase in collagen production in the intoxicated animals was to be expected. However, to the best of our knowledge, up to the present date no studies have been carried out to investigate the effect of pulmonary fibrosis induced by PQ on aerobic performance, energy expenditure and mechanical efficiency during physical exercise. Only four studies have investigated the effects of pulmonary fibrosis during exercise tests (Schenker et al., 2004; Dalvie et al., 1999; Castro-Gutiérrez et al., 1997; Howard et al., 1981) and these publications reported no changes in spirometric variables during the tests despite repeated exposure to PQ and the existence of a pulmonary lesion confirmed by imaging tests. Moreover, these studies were restricted to evaluating spirometric variables during physical effort and none investigated the impact of consecutive exposure to the herbicide or its consequent pulmonary fibrosis on aerobic performance, energy expenditure and mechanical efficiency.
efficiency during physical exercise. Therefore, there is a gap in scientific knowledge that requires further clarification.

The dose of PQ used in the present study (7 mg/kg) is currently the lowest dose used in studies to induce pulmonary fibrosis (Akahori and Oehme, 1983; Satomi et al., 2004, 2006 and 2007), and is in accordance with data published by Rocco et al. (2004). These authors evaluated the time course of in vivo and in vitro respiratory mechanics and examined whether these parameters were able to reflect the temporal changes in lung parenchyma remodelling in PQ-induced lung injury. Measurements were performed 1, 3 and 8 weeks after the intraperitoneal (i.p.) injection of a single dose of SAL (control) or PQ (7 mg/kg) in rats. The authors observed that viscoelastic/inhomogeneous pressure, tissue elastance, the number of polymorphonuclear cells, and collagen fiber content in lung parenchyma increased at PQ1 and remained elevated at PQ3 and PQ8. In the present study four doses were used at weekly intervals (7 mg/kg) to ensure that PQ would indeed induce alterations.

The primary PQ-induced lesion in mammalian systems occurs in the lungs, where the substance accumulates due to a process of active transport in type I and II alveolar epithelial cells (Nakayama et al., 1992; Serra et al., 2003; Skillrud and Martin, 1984). PQ-induced lung injury is morphologically characterized by a destructive phase in which type I and II epithelial cells are damaged, leading to the release of cytokines and growth factors that induce a proliferation process characterized by alveolitis, pulmonary edema and the infiltration of inflammatory cells (Kim et al., 2006; Schoenberger et al., 1984). This occurs due to inhibition of the neural regulation of fluid reabsorption in the pulmonary interstitium. Inhibition of this regulation may cause pulmonary hemorrhage and interstitial edema in the acute stage. In the chronic phase fibroblastic proliferation occurs, along with an increase in collagen synthesis with the development of pulmonary fibrosis (Kim et al., 2006; Satomi et al., 2004; Adachi et al., 2003). Alveolar insult and onset of pulmonary fibrosis induced by a single dose of PQ have been reported at seven days after its administration (Chen et al., 2005). This process is associated with a progressive increase in the expression of genes responsible for collagen synthesis as well as the production of neutrophil and macrophage chemotactic factors and fibroblast growth factors (Akahori and Oehme, 1983; Satomi et al., 2004, 2006; Schoenberger et al., 1984; Chen et al., 2005).

Fig. 4. Mechanical efficiency during progressive exercise on a treadmill until fatigue in rats chronically treated with PQ (7 mg/kg body wt, intraperitoneally, i.p.) or 0.9% NaCl (SAL; 0.7 ml/kg body wt, i.p.). Values are expressed as mean ± S.E.M.; n = 5 in each group; *p < 0.05 compared to controls.
as multiple administrations of the herbicide provokes successive lesions in the pulmonary parenchyma (among other effects), it eventually results in a model of pulmonary fibrosis. Similar to other interstitial lung diseases, pulmonary fibrosis is considered as the consequence of a chronic, unresolved inflammatory process resulting from a pulmonary insult (Selman and Pardo, 2002). In the present study, the pulmonary histological analyses demonstrated that multiple PQ treatments induced pulmonary fibrosis (Table 1). This confirms previous described findings (Akahori and Oehme, 1983; Satomi et al., 2004, 2006, and 2007), that consecutive administration of PQ (7 mg/kg body wt., i.p.) can be used as a model to study fibrosis in rats.

The dose used in the present study (7 mg/kg of body weight, i.p.) may be classified as mild exposure to PQ (14% of the LD50) in rats (LD50 = 50 mg/kg, ip.), corresponding to mild exposure in humans, considering 14% of the estimated human LD50 (LD50 = 35 mg/kg) (Nwabisi and Nwanze, 1997).

In this study a close correlation was found between physical performance 40 days after the last dose of the herbicide and the fractional area of collapsed alveoli (Fig. 2). In other studies (Rocco et al., 2003; Silva et al. 1998), data from the area of lung collapse were used as an indicator of the degree of pulmonary injury. In the chronic phase of PQ intoxication the development of fibrosis maintains the alveolar collapse, thereby reducing lung ventilation and decreasing gas exchange. The reduced lung volume and compliance result in hypoxemia and increased work of breathing (Silva and Saldiva, 1998; Kao et al., 1999), impairing physical performance during exercise (Hansen and Wasserman, 1996).

During exercise, the fatigue of inspiratory muscles, together with an increase in the neural impulse to motor areas of the central nervous system (CNS), causes reflex sympathetic activation (Croix et al., 2000). According to previous study (Heindl et al., 2001), patients with chronic respiratory failure associated with lung fibrosis have a marked sympathetic activation, partially explained by the arterial chemoreflex activation that interferes with the function of the respiratory muscles. In these patients, the increased sympathetic activity is related to impaired exercise tolerance and a high mortality rate (Swedberg et al., 1990). Our results are in agreement with the general idea that pulmonary fibrosis plays a role in increasing sympathetic tonus more importantly during exercise. The increased sympathetic activity reduces mechanical efficiency and increases oxygen consumption (metabolic cost) during physical exercise, contributing to earlier fatigue (St Croix et al., 2000).

In conclusion, pulmonary fibrosis resulting from multiple exposures to PQ intraperitoneally may affect the metabolic demand of inspiratory and exercising muscles, increasing metabolic cost during exercise, reducing mechanical efficiency and decreasing physical performance (approximately 32% in exercise time until fatigue and approximately 36% in work performed) during physical exercise in rats.

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Paraquat and aerobic performance in rats

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