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3 **Physiological determinants of the increase in oxygen consumption during exercise**
 4 **in individuals with stroke**

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6 **Short title:** Determinants of the increase in oxygen consumption

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22

23 **Abstract**

24 **Background:** Understanding the physiological limitations of the increase in oxygen
 25 consumption ($\dot{V}O_2$) during exercise is essential to improve cardiorespiratory fitness in
 26 individuals with stroke. However, the physiological determinants of the increase in $\dot{V}O_2$
 27 during exercise have not been examined using multivariate analysis in individuals with
 28 stroke. This study aimed to identify the physiological determinants of the increase in
 29 $\dot{V}O_2$ during a graded exercise in terms of the respiratory function, cardiac function, and
 30 ability of skeletal muscles to extract oxygen.

31 **Methods:** Eighteen individuals with stroke (60.1 ± 9.4 years of age, 67.1 ± 30.8 days
 32 poststroke) underwent a graded exercise test for the assessment of cardiorespiratory
 33 response to exercise. The increase in $\dot{V}O_2$ from rest to ventilatory threshold and that
 34 from rest to peak exercise were measured as a dependent variable. The increases in
 35 respiratory rate, tidal volume, heart rate, stroke volume, and arterial-venous oxygen
 36 difference from rest to ventilatory threshold and those from rest to peak exercise were
 37 measured as independent variables.

38 **Results:** From rest to ventilatory threshold, the increases in heart rate ($\beta = 0.546$) and
 39 arterial-venous oxygen difference ($\beta = 0.398$) were significant determinants of the
 40 increase in $\dot{V}O_2$ (adjusted $R^2 = 0.703$, $p < 0.001$). From rest to peak exercise, the

41 increases in tidal volume ($\beta = 0.611$) and heart rate ($\beta = 0.353$) were significant
 42 determinants of the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.702$, $p < 0.001$).
 43 **Conclusion:** $\dot{V}O_2$ is well-known to increase nearly linearly with increasing heart rate;
 44 however, our results suggest that arterial-venous oxygen difference and tidal volume are
 45 also significant physiological determinants of the increase in $\dot{V}O_2$ from rest to
 46 ventilatory threshold and that from rest to peak exercise, respectively. Our findings
 47 could potentially contribute to the development of appropriate therapies to improve
 48 cardiorespiratory fitness in individuals with stroke.

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Introduction

Individuals with stroke have reduced cardiorespiratory fitness compared with age- and sex-matched healthy individuals [1, 2]. Cardiorespiratory fitness reduction is potentially related to walking disability [3, 4], poor cognitive performance [5], and limitations in activities of daily living in individuals with stroke [6-8]. Low levels of cardiorespiratory fitness following stroke may lead to avoidance of physical activity, which causes further deconditioning [9, 10]. Therefore, understanding the physiological limitations of cardiorespiratory fitness in individuals with stroke is essential for the development of appropriate therapies to improve physical activity levels and to prevent further deconditioning.

Oxygen consumption ($\dot{V}O_2$) at ventilatory threshold and that at peak exercise measured during a graded exercise test are used to assess cardiorespiratory fitness in individuals with stroke [1, 11-13]. The physiological factors that potentially limit $\dot{V}O_2$ at peak exercise are respiratory and cardiac functions to supply oxygen and the ability of skeletal muscles to extract oxygen [12, 14, 15]. In healthy adults, $\dot{V}O_2$ at peak exercise seems to be limited primarily by cardiac function [14, 15]. Previous studies [12, 16-18] reported that tidal volume, heart rate, and arterial-venous oxygen difference at peak exercise are significantly lower in individuals with stroke than those in age- and

68 sex-matched healthy adults, which may lead to the deterioration of cardiorespiratory
 69 fitness after stroke. Tomczak et al. [18] reported a significant difference between
 70 individuals with stroke and healthy adults in $\dot{V}O_2$ at peak exercise, but not in $\dot{V}O_2$ at
 71 rest. Thus, identifying the determinants of the increase in $\dot{V}O_2$ during exercise
 72 contributes to understanding the physiological limitations of cardiorespiratory fitness in
 73 individuals with stroke. However, the physiological determinants of the increase in $\dot{V}O_2$
 74 during exercise have not been examined using multivariate analysis in individuals with
 75 stroke.

76 Cross-sectional and longitudinal studies found the relationship between $\dot{V}O_2$
 77 and arterial-venous oxygen difference at peak exercise in individuals with stroke [17,
 78 19]. Therefore, we hypothesized that arterial-venous oxygen difference is a primary
 79 physiological determinant of the increase in $\dot{V}O_2$ during exercise in these individuals. In
 80 this study, we aimed to explore the physiological determinants of the increase in $\dot{V}O_2$
 81 from rest to ventilatory threshold and that from rest to peak exercise in individuals with
 82 stroke.

83

84 **Methods**

85 **Study design**

86 This study used a cross-sectional observational design. The study protocol was
87 approved by the appropriate ethics committees of the Tokyo Bay Rehabilitation Hospital
88 (approval number: 172-2) and the Shinshu University (approval number: 3813). All
89 participants provided written informed consent prior to study enrollment. The study was
90 conducted according to the Declaration of Helsinki of 1964, as revised in 2013.

91

92 **Participants**

93 Participants were recruited from a convalescent rehabilitation hospital between
94 November 2017 and November 2018. The inclusion criteria for the study were as
95 follows: (1) age 40–80 years, (2) being within 180 days after first-ever stroke, (3) ability
96 to maintain a target cadence of 50 rpm during exercise, and (4) a Mini-Mental State
97 Examination score [20] of 24 or more. The exclusion criteria were as follows: (1)
98 limited range of motion and/or pain that could affect the exercise test, (2) unstable
99 medical conditions such as unstable angina, uncontrolled hypertension, and tachycardia,
100 (3) use of beta-blocker, and (4) any comorbid neurological disorder.

101

102 **Exercise testing**

103 Participants were instructed to refrain from eating for 3 hours and to avoid
104 caffeine and vigorous physical activity for at least 6 and 24 hours, respectively, before
105 the exercise test [21]. All participants performed a symptom-limited graded exercise test
106 on a recumbent cycle ergometer (Strength Ergo 240; Mitsubishi Electric Engineering
107 Co., Ltd., Tokyo, Japan) that can be precisely load-controlled (coefficient of variation,
108 5%) over a wide range of pedaling resistance (0-400 W). The distance from the seat
109 edge to pedal axis was adjusted so that the participant's knee flexion angle was 20°
110 when extended maximally. The backrest was set at 20° reclined from the vertical
111 position. Additional strapping was attached to secure the paretic foot to the pedal as
112 needed. Following a 3-min of rest period (in sitting position) on the recumbent cycle
113 ergometer to establish a steady state, a warm-up was performed at 0 W for 3 min
114 followed by 10 W increments every minute [21, 22]. Participants were instructed to
115 maintain a target cadence of 50 rpm throughout the exercise [21, 22]. Blood pressure
116 was monitored every minute from the non-paretic arm using an automated system
117 (Tango; Sun Tech Medical Inc., NC, USA). The test was terminated if the participants
118 showed signs of angina, dyspnea, inability to maintain cycling cadence more than 40
119 rpm, hypertension (more than 250 mmHg systolic or more than 115 mmHg diastolic), or

120 drop in systolic blood pressure more than 10 mmHg despite an increase in work load
 121 [22, 23]. Participants provided their ratings of perceived exertion (6 = no exertion at all,
 122 20 = maximal exertion) [24] for dyspnea and leg effort at the end of the test. Work rate
 123 at peak exercise was defined as the peak wattage on test termination [19]. To identify
 124 whether maximal effort was reached during the exercise test, at least 1 of the following
 125 criteria had to be met: (1) $\dot{V}O_2$ increased less than 150 mL·min⁻¹ for more than 1 min
 126 despite increased work rate, (2) respiratory exchange ratio achieved greater than 1.10,
 127 (3) or heart rate achieved 85% of the age-predicted maximal heart rate (220 minus age)
 128 [23, 25].

129 Physiological variables were measured at rest and continuously during exercise
 130 test. $\dot{V}O_2$, respiratory rate, and tidal volume were measured on a breath-by-breath basis
 131 using an expired gas analyzer (Aerosonic AT-1100; ANIMA Corp., Tokyo, Japan).
 132 Carbon dioxide output, the ventilatory equivalents of oxygen and carbon dioxide, and
 133 the end-tidal oxygen and carbon dioxide fractions were also measured using the expired
 134 gas analyzer to determine the ventilatory threshold. Heart rate and stroke volume were
 135 measured on a beat-by-beat basis using a noninvasive impedance cardiography device
 136 (Task Force Monitor model 3040i; CN Systems Medizintechnik GmbH., Graz, Austria)
 137 [26-28]. For calculating arterial-venous oxygen difference, measurement values of

138 physiological variables were interpolated to 1-s intervals, time-aligned, and averaged
139 into 5-s bins [18]. Arterial-venous oxygen difference was calculated as the ratio between
140 $\dot{V}O_2$ and the product of heart rate and stroke volume.

141 Physiological variables at rest were defined as the average value obtained
142 during 1 min before exercise onset, and those at peak exercise were defined as the
143 average value obtained during the last 30 s of exercise test [18, 21]. The ventilatory
144 threshold was determined using a combination of the following criteria: (1) the point
145 where the ventilatory equivalent of oxygen reaches its minimum or starts to increase,
146 without an increase in the ventilatory equivalent of carbon dioxide; (2) the point at
147 which the end-tidal oxygen fraction reaches a minimum or starts to increase, without a
148 decline in the end-tidal carbon dioxide fraction; and (3) the point of deflection of carbon
149 dioxide output versus $\dot{V}O_2$ [29]. The first two methods were prioritized in case the three
150 methods presented different results [30, 31]. The ventilatory threshold was determined
151 as an average based on the values provided by two independent raters (NI and YS),
152 when the difference in the $\dot{V}O_2$ values of the corresponding points as determined by the
153 two raters was less than 100 mL·min⁻¹ [31, 32]. In case of any discrepancy, a third
154 experienced rater (KO) judged the point, and the ventilatory threshold was taken as the
155 average of the two closest values [30, 31].

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157 **Statistical analysis**

158 The G Power computer program version 3.1.9.2 (Heinrich Heine University,
159 Dusseldorf, Germany) [33] was used to calculate the sample size required for multiple
160 regression analysis. For multiple regression analyses, if up to five variables (respiratory
161 rate, tidal volume, heart rate, stroke volume, and arterial-venous oxygen difference) are
162 modeled at an effect size of 0.49 (very large) at an α level of 0.05 and power of 0.80, a
163 minimum of 12 participants are required [33, 34].

164 Normality of distribution was tested using the Shapiro-Wilk test. One-way
165 repeated-measures analysis of variance or Friedman test with exercise period as a factor
166 was used to examine whether physiological variables change during exercise. Post hoc
167 analyses were performed using the Bonferroni multiple comparison test.

168 The increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to
169 peak exercise were calculated as the dependent variables. Pearson's product moment
170 correlation coefficient or Spearman's rank correlation coefficient was used to test the
171 correlations between the increases from rest to ventilatory threshold in $\dot{V}O_2$ and other
172 physiological variables and between the increases from rest to peak exercise in $\dot{V}O_2$ and
173 other physiological variables. Those variables that were significantly correlated with the

174 increase in $\dot{V}O_2$ during exercise testing were then entered into the stepwise multiple
 175 regression analysis to determine the physiological limitations of the increase in $\dot{V}O_2$
 176 with considering multicollinearity. Statistical analyses were performed using the
 177 Statistical Package for the Social Sciences software version 24.0 (International Business
 178 Machines Corp., NY, USA). Any p values less than 0.05 were considered statistically
 179 significant.

180

181 **Results**

182 A flow diagram of study participants is shown in Fig 1. Eighteen individuals
 183 with stroke participated in the study. Table 1 shows the characteristics of the
 184 participants.

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186 **Fig 1. Flow diagram of study participants.**

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195 Table 1. Characteristics of participants

Variable	Value
Age, years	60.1 ± 9.4
Sex, male/female	14 (78)/4 (22)
Body mass index, kg·m ⁻²	23.0 ± 3.3
Type of stroke, ischemic/hemorrhage	11 (61)/7 (39)
Side of motor paresis, right/left	8 (44)/10 (56)
Time since stroke, days	67.1 ± 30.8
Fugl-Meyer lower extremity motor scores, points	28.8 ± 7.7
Antihypertensive medications	
Angiotensin II receptor blocker	2 (11)
Calcium channel blocker	4 (22)
Comorbidities	
Hypertension	6 (33)
Diabetes mellitus	4 (22)

Hyperlipidemia

3 (17)

196 Values are presented as mean $\pm$ SD or number (%).

197

198 No significant adverse events occurred during or after exercise test. All
199 participants stopped their exercise test due to inability to maintain cycling cadence more
200 than 40 rpm. In addition, all participants met at least one of the criteria for reaching
201 maximal effort. Median (interquartile range) values of the ratings of perceived exertion
202 for dyspnea and leg effort at the end of the test were 13 (13–15) and 15 (13–15),
203 respectively. Mean $\pm$ standard deviation of work rate at peak exercise was 69.4 ± 30.6
204 W.

205 Measurement values at rest, ventilatory threshold, and peak exercise are shown
206 in Table 2. We observed a main effect of exercise period on all physiological variables
207 ($p < 0.001$). All physiological variables at ventilatory threshold were significantly
208 higher than those at rest ($p < 0.001$). From ventilatory threshold to peak exercise, $\dot{V}O_2$,
209 respiratory rate, tidal volume, and heart rate significantly increased (mean difference =
210 198.6, 95% confidence interval [CI] = 95.4, 301.7, and $p < 0.001$; mean difference = 7.5,
211 95% CI = 3.2, 11.7, and $p < 0.001$; mean difference = 0.21, 95% CI = 0.08, 0.33, and p
212 = 0.002; mean difference = 18.7, 95% CI = 10.2, 21.3, and $p < 0.001$, respectively),

213 whereas no significant changes in stroke volume and arterial-venous oxygen difference
214 were found (mean difference = -1.9, 95% CI = -6.9, 3.0, and $p = 0.945$; mean difference
215 = 0.74, 95% CI = -0.22, 1.70, and $p = 0.172$, respectively).

216 Table 2. Physiological variables at rest, ventilatory threshold, and peak exercise

Variable	Rest	Ventilatory threshold	Peak exercise	p value
$\dot{V}O_2$, mL·min ⁻¹	253.1 ± 57.7	899.7 ± 224.8 [*]	1098.3 ± 330.3 ^{†, ‡}	< 0.001
Respiratory rate, breaths·min ⁻¹	18.5 ± 2.8	25.2 ± 4.5 [*]	32.6 ± 8.5 ^{†, ‡}	< 0.001
Tidal volume, L	0.46 ± 0.11	1.07 ± 0.23 [*]	1.28 ± 0.30 ^{†, ‡}	< 0.001
Heart rate, bpm	76.0 ± 9.2	109.9 ± 13.6 [*]	128.6 ± 17.5 ^{†, ‡}	< 0.001
Stroke volume, mL	55.0 ± 7.6	73.0 ± 10.4 [*]	71.0 ± 9.4 [†]	< 0.001
Arterial-venous oxygen difference, mL·100 mL ⁻¹	6.2 ± 1.6	11.2 ± 1.8 [*]	12.0 ± 2.4 [†]	< 0.001

217 Values are presented as mean ± SD.

218 A p value represents a significant main effect of exercise period.

219 ^{*}, a significant difference between ventilatory threshold and rest (p < 0.001).

220 [†], a significant difference between peak exercise and rest (p < 0.001).

221 [‡], a significant difference between peak exercise and ventilatory threshold ($p < 0.001$).

From rest to ventilatory threshold, correlations between the increases in $\dot{V}O_2$ and other physiological variables are shown in Fig 2. The increase in $\dot{V}O_2$ was significantly correlated with the increases in tidal volume ($r = 0.620$; 95% CI = 0.215, 0.843; and $p = 0.006$) (Fig 2b), heart rate ($r = 0.804$; 95% CI = 0.540, 0.924; and $p < 0.001$) (Fig 2c), and arterial-venous oxygen difference ($r = 0.752$; 95% CI = 0.440, 0.902; and $p < 0.001$) (Fig 2e). Stepwise multiple regression analysis revealed that the increases in heart rate ($\beta = 0.546$) and arterial-venous oxygen difference ($\beta = 0.398$) were the significant determinants for the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.703$, $p < 0.001$) (Table 3).

Fig 2. Correlations between the increases in $\dot{V}O_2$ and respiratory rate (a), $\dot{V}O_2$ and tidal volume (b), $\dot{V}O_2$ and heart rate (c), $\dot{V}O_2$ and stroke volume (d), and $\dot{V}O_2$ and arterial-venous oxygen difference (e) from rest to ventilatory threshold.

241 Table 3. Stepwise multiple regression analysis for identifying the determinants of the increase in $\dot{V}O_2$ from rest to ventilatory threshold

Variable	β	Coefficient	SE	t value	p value
Increase in heart rate from rest to ventilatory threshold	0.546	8.73	2.78	3.14	0.007
Increase in arterial-venous oxygen difference from rest to ventilatory threshold	0.398	43.03	18.82	2.29	0.037
Constant		133.20	83.61	1.59	0.132
F (2, 15) = 21.12, p < 0.001, R ² = 0.738, Adjusted R ² = 0.703					

242 β , standard coefficient; SE, standard error.

From rest to peak exercise, correlations between the increases in $\dot{V}O_2$ and other physiological variables are shown in Fig 3. The increase in $\dot{V}O_2$ was significantly correlated with the increases in tidal volume ($r = 0.806$; 95% CI = 0.544, 0.925; and $p < 0.001$) (Fig 3b), heart rate ($r = 0.691$; 95% CI = 0.330, 0.875; and $p = 0.002$) (Fig 3c), and arterial-venous oxygen difference ($r = 0.729$; 95% CI = 0.398, 0.892; and $p < 0.001$) (Fig 3e). Stepwise multiple regression analysis revealed that the increases in tidal volume ($\beta = 0.611$) and heart rate ($\beta = 0.353$) were significant determinants for the increase in $\dot{V}O_2$ (adjusted $R^2 = 0.702$, $p < 0.001$) (Table 4).

Fig 3. Correlations between the increases in $\dot{V}O_2$ and respiratory rate (a), $\dot{V}O_2$ and tidal volume (b), $\dot{V}O_2$ and heart rate (c), $\dot{V}O_2$ and stroke volume (d), and $\dot{V}O_2$ and arterial-venous oxygen difference (e) from rest to peak exercise.

262 Table 4. Stepwise multiple regression analysis for identifying the determinants of the increase in $\dot{V}O_2$ from rest to peak exercise

Variable	β	Coefficient	SE	t value	p value
Increase in tidal volume from rest to peak exercise	0.611	749.82	194.88	3.85	0.002
Increase in heart rate from rest to peak exercise	0.353	6.72	3.02	2.23	0.041
Constant		-117.65	155.12	0.76	0.460
F (2, 15) = 20.99, p < 0.001, $R^2 = 0.737$, Adjusted $R^2 = 0.702$					

263 β , standard coefficient: SE, standard error.

Discussion

This study is the first to explore the physiological determinants of the increase in $\dot{V}O_2$ during graded exercise in individuals with stroke. From rest to ventilatory threshold, the increases in heart rate and arterial-venous oxygen difference were the significant determinants of the increase in $\dot{V}O_2$. From rest to peak exercise, the increases in tidal volume and heart rate were the significant determinants of the increase in $\dot{V}O_2$. Physiological impairments in these variables may negatively affect cardiorespiratory fitness in individuals with stroke.

The results of correlation analyses may support previous studies suggesting that impaired tidal volume, heart rate, and arterial-venous oxygen difference at peak exercise limit cardiorespiratory fitness in individuals with stroke [12, 16-18, 31]. Contrary to our hypothesis, only the increase in heart rate was identified as one of the significant determinants of both the increases in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise, which can be explained by the fact that $\dot{V}O_2$ increases nearly linearly with increasing heart rate during exercise [35]. Tomczak et al. [18] indicated that the impaired increase in $\dot{V}O_2$ during exercise in individuals with stroke may be attributed to the impaired increase in heart rate. Our results suggest that cardiac function to supply oxygen rather than the ability of skeletal muscles to extract oxygen affects cardiorespiratory fitness in individuals with stroke. Conversely, Jakovljevic et al. [17] and Moore et al. [19] reported that oxygen extraction

rather than oxygen supply is related with cardiorespiratory fitness in individuals with chronic stroke. The discrepancy in results between the present and previous studies [17, 19] may be caused by the characteristics of participants such as time since stroke.

Skeletal muscle changes after stroke, such as muscle atrophy and shift of muscle fiber type (from type I slow-twitch muscle fibers to type II fast-twitch muscle fibers) particularly in the paretic lower extremity, are observed in individuals with stroke [36]. In addition, impaired vasodilatory function and reduction in blood flow in the paretic lower extremity have also been reported [37, 38]. These changes after stroke may reduce the ability of skeletal muscles to extract oxygen. Reduction in the ability of skeletal muscles to extract oxygen during exercise may increase the dependence of anaerobic glycolysis for energy output, thus increasing the output of lactic acid [39, 40]. Minute ventilation begins to increase exponentially relative to the increase in $\dot{V}O_2$ to eliminate the excess carbon dioxide produced from bicarbonate buffering of lactic acid, which is defined as ventilatory threshold [41]. These findings support our results that arterial-venous oxygen difference was identified as one of the physiological determinants of the increase in $\dot{V}O_2$ from rest to ventilatory threshold.

Although arterial-venous oxygen difference increases with incremental exercise, that is assumed to be relatively constant at a submaximal work rate [35]. We observed a significant increase in $\dot{V}O_2$ but not in arterial-venous oxygen difference from ventilatory

threshold to peak exercise. This may explain the reason why the increase in arterial-venous oxygen difference was not selected as the significant physiological determinant of the increase in $\dot{V}O_2$ from rest to peak exercise. Our stepwise regression analysis indicated that the increase in tidal volume was a major physiological determinant of the increase in $\dot{V}O_2$ from rest to peak exercise. Sisante et al. [16] and Tomczak et al. [18] reported that tidal volume and $\dot{V}O_2$ at peak exercise are significantly lower in individuals with stroke than in healthy controls. Their findings suggest that decreased tidal volume limits the increase in $\dot{V}O_2$ during exercise. The paralysis of the expiratory muscles on the affected side, decreased motion of the diaphragm, and reduced chest wall excursion may limit the increase in tidal volume during exercise [12, 42].

This study had several limitations. First, all participants were in the subacute stages of recovery from stroke. Therefore, generalization of the findings to individuals with chronic stroke should be made with caution. Second, we used a recumbent cycle ergometer. A treadmill [6], a total-body recumbent steppe [43], a robotics-assisted tilt table [30], and an arm crank ergometer [31] are also used to assess cardiorespiratory fitness in individuals with stroke. Further studies are warranted to examine whether the major physiological determinant of the increase in $\dot{V}O_2$ during exercise differs with the exercise devices. Finally, as this study used the cross-sectional observational design, the physiological determinants of the temporal changes in $\dot{V}O_2$ at ventilatory threshold and at peak exercise could not be examined. Further

longitudinal studies are needed to examine whether physiological impairments in tidal volume, heart rate, and arterial-venous oxygen difference affect the temporal changes in $\dot{V}O_2$ for the development of appropriate therapies to improve cardiorespiratory fitness in individuals with stroke.

Conclusions

$\dot{V}O_2$ is well-known to increase nearly linearly with increasing heart rate [35, 41]; however our results suggest that arterial-venous oxygen difference and tidal volume are also significant physiological determinants of increase in $\dot{V}O_2$ from rest to ventilatory threshold and that from rest to peak exercise, respectively. Our findings could potentially contribute to the development of appropriate therapies to improve cardiorespiratory fitness in individuals with stroke.

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