Non-uniform muscle oxygenation despite uniform neuromuscular activity within the vastus lateralis during fatiguing heavy resistance exercise

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Summary

Previous studies have reported for the vastus lateralis (VL) that the extent of muscle hypertrophy in response to resistance training is greater in the distal than in the middle region, despite uniform muscle fibre composition within VL along its length. In the present study, to investigate mechanism(s) for such non-uniform muscle hypertrophy, we simultaneously measured neuromuscular activity and muscle oxygenation state at the middle and distal regions of VL during fatiguing heavy resistance exercise. Twelve males performed unilateral knee extension exercise which consisted of 4 sets of 8 repetitions at intensity of 80% of the individual one repetition maximum. During the resistance exercise, neuromuscular activities and muscle oxygenation status at the middle and distal regions (50% and 70% of the thigh length, respectively) of VL were measured by using electromyography and near-infrared spectroscopy, respectively. Neuromuscular activities were similar between the distal and middle regions of VL, whereas muscle tissue oxygenation saturation was significantly lower at the distal than at the middle region of VL. These results suggest a possibility that the regional difference in muscle oxygenation but not in neuromuscular activity during fatiguing heavy resistance exercise is responsible for the regional difference in hypertrophy within a muscle.

Introduction

Previous studies have reported that the extent of hypertrophy in response to chronic resistance training is inhomogeneous even within a single muscle along its length (Narici *et al.*, 1989, 1996; Kawakami *et al.*, 1995; Kanehisa *et al.*, 2002; Wakahara *et al.*, 2012). For example, Narici *et al.* (1996) demonstrated that the extent of muscle hypertrophy of the vastus lateralis (VL), after knee extension training with 80% of one repetition maximum (1RM) for 6 months, was greater in the distal than in the middle region, despite uniform muscle fibre composition within VL along its length (Lexell *et al.*, 1983). As an explanation for such non-uniform muscle hypertrophy, Narici *et al.* (1996) proposed differences in neuromuscular activity during the resistance exercise. However, recently, we showed that there was no significant difference in the neuromuscular activation levels between the distal and middle regions in VL during maximal voluntary isometric contraction (MVC) of knee extension (Miyamoto *et al.*, 2012). Although the contraction mode and intensity of knee extension exercise

are different between the two studies (Narici *et al.*, 1996; Miyamoto *et al.*, 2012), it is likely that mechanism(s) other than difference in the neuromuscular activity is responsible for the non-uniform muscle hypertrophy within VL.

During heavy resistance exercise, blood flow to exercising muscles is restricted by increased intramuscular pressures, leading to muscle hypoxia (i.e. reduced muscle oxygenation) (Miura *et al.*, 2001; Quaresima *et al.*, 2001). Muscle hypoxia has been considered to act to trigger muscle hypertrophic responses (Loenneke *et al.*, 2012; Schoenfeld, 2012). A number of studies have reported by using near-infrared spatially resolved spectroscopy (NIRS) that muscle oxygenation during exercise is non-uniform within a muscle (Miura *et al.*, 2001; Mizuno *et al.*, 2003, 2004; Esaki *et al.*, 2005; Kime *et al.*, 2005; Crenshaw *et al.*, 2010). In the case of VL, the magnitude of muscle oxygenation changes is more prominent in the distal compared with in the middle region (Mizuno *et al.*, 2004; Kennedy *et al.*, 2006; Crenshaw *et al.*, 2010). However, it has also been suggested that such regional differences depend on exercise mode, intensity and duration (Kime *et al.*,

2005; Kennedy *et al.*, 2006; Crenshaw *et al.*, 2010). Most of the previous studies have used static contraction, light-to-moderate-intensity, and/or short-duration exercise, and it remains unclear whether regional differences in muscle oxygenation exist within VL during fatiguing heavy resistance exercise, and whether it is associated with regional differences in muscle hypertrophy. Therefore, in the present study, we aimed to investigate muscle tissue oxygen (de-)saturation as well as neuromuscular electrical activities at the distal and middle regions of VL during fatiguing heavy resistance exercise, by using NIRS and electromyography (EMG).

Methods

Subjects

Twelve healthy male subjects (26.5 ± 1.9 years, 1.73 ± 0.05 m, 67.3 ± 7.3 kg; mean $\pm$ SD) participated in this study. Before participation, all subjects were fully informed of the experimental procedures and possible risks as well as the purpose of the study. None of them had taken part in regular resistance training for at least 1 year. Written informed consent was obtained from all subjects. This study was approved by the local ethics committee on human research and performed in accordance with the Declaration of Helsinki.

Experiment set-up

Electromyography measurement

Surface EMG signals were obtained from the distal and middle regions of VL. After shaving, rubbing with sandpaper and cleaning with alcohol, pre-amplified bipolar surface electrodes (1×10 mm, 10-mm interelectrode distance; DE-2·1, DELSYS, Boston, MA, USA) with band-pass filtering between 20 and 450 Hz (Bagnoli 8 EMG System, DELSYS, Boston, MA, USA) were placed over at the level of 50% (middle) and 70% (distal) of the thigh length between the greater trochanter and the lateral condyle of the femur. These sites were chosen because it has been reported that the smallest (7%) and greatest (39%) extent of hypertrophy occurred in the former and latter regions, respectively, after 6 months knee extension training with 80% of 1RM (Narici *et al.*, 1996). The reference electrode was placed over the left patella for all EMG measurements.

Nerve stimulation

To assess M-wave amplitude of the distal and middle regions of VL, the femoral nerve was stimulated percutaneously by using the cathode (2×2 cm) placed on the femoral triangle. The anode (8×5 cm) was positioned midway between the superior aspect of the greater trochanter and the inferior border of the iliac crest. Single square-wave pulses of 1-ms duration were delivered from a custom-made constant-current stimulator (Atrjum, Saitama, Japan). Supramaximal stimulus

intensity was determined prior to the testing, by increasing the current intensity until the M-wave amplitude reached a plateau, and then set to 20% above the maximum for the experimental measurements.

Near-infrared spatially resolved spectroscopy measurement

Changes in VL muscle oxygenation were continuously monitored by using a multichannel NIRS apparatus (NIRO-200, Hamamatsu Photonics, Japan). In the present study, only tissue oxygenation (TOI) data were modelled similarly to previous studies for the following reasons. The NIRS apparatus was a three-wave length (775, 810 and 850 nm) continuous wave system, which simultaneously uses the modified Beer-Lambert and spatially resolved methods, and measured changes in tissue oxyhaemoglobin ([HbO2]), de-oxyhaemoglobin ([HHb]) and total haemoglobin ([tHb]) using the differences in absorption characteristics of each light. However, changes in [HHb] and corresponding [tHb] following exercise are difficult to model (Buchheit *et al.*, 2012), possibly due to the abrupt change in muscle blood flow at muscle contraction and relaxation (i.e. muscle pump effect). On the other hand, the NIRS apparatus provides a derived data termed the TOI, which is an index of average saturation of the haemoglobin volume present within the microvasculature. Because TOI is calculated independently using the spatially resolved spectroscopy method and multi-distance source-detector approach, TOI can provide a better indication of muscle oxygenation status than [tHb] and/or [HHb] when blood flow is not constant (Wolf *et al.*, 2007).

The optodes were housed in a plastic holder (A9782, Hamamatsu Photonics, Shizuoka, Japan), ensuring that the interoptode distance was maintained at 30 mm throughout all testing. The optode holders were located just medial to the EMG electrodes and secured on the cleaned skin surface with double-sided adhesive tape (A9342, Hamamatsu Photonics, Japan) in order to minimize the loss of infrared light and intrusion of extraneous light from the outside of the field of interrogation. Because skin and subcutaneous adipose tissue thickness affects the NIRS signal (van Beekvelt *et al.*, 2001), the thickness at each site of application of the NIRS optodes was measured before the testing session by using B-mode ultrasonography (SSD-6500, Aloka, Tokyo, Japan). Considering that the penetration depth of the NIRS signal is almost half of the source-detector separation (30 mm in this study) and that the calculated values of skin and subcutaneous adipose tissue thickness were relatively low (5.3 ± 2.0 and 5.3 ± 2.2 mm for the distal and middle regions, respectively), the changes in TOI were considered to reflect mainly hemodynamic changes in VL (Ferrari *et al.*, 2004).

Experimental procedure

The subjects sat on a standard training machine with dynamic constant external resistance for knee extension (Nitro S3LE,

Nautilus, Vancouver, WA, USA). A determination of 1RM of unilateral knee extension of the right leg began with several knee extensions at light-to-moderate load. Then, the load was increased until each subject could not perform a lift throughout a range of knee extension (approximately 110°–20°: 0°= full knee extension). Then, subjects performed an isometric MVC of knee extension at approximately 90° of knee joint angle on the training machine. Following a sufficient rest period, training exercise which consisted of four sets of eight repetitions of the right leg was performed at intensity of 80% of the individual 1RM, with a 90-s rest period between each set. Each repetition required approximately 2 s to lift and 2 s to lower the load through the range of motion, which was measured by an electronic goniometry (SG150, Biometrics, UK). Immediately before and after each set of training exercise, the responses to singlet for the measurement of M-wave amplitude were recorded. During training exercise, strong verbal encouragement was provided by the investigators throughout each set. The data were simultaneously stored by using a 16-bit analogue-to-digital converter (PowerLab/16SP, ADInstrument, Sydney, Australia) at a sampling frequency of 2 kHz for EMG and joint angle data and 6 Hz for NIRS data.

Data analysis and statistics

The root mean square values of EMG signals (RMS-EMG) and average values of TOI at each region were calculated separately in the shortening and lengthening phases of the training exercise, which were determined from the knee joint angle. The RMS-EMG values of each repetition at each region during the training exercise were normalized to those over a 1-s period during the MVC task. For M-wave data, the peak-to-peak amplitudes at each region were computed.

Tissue oxygenation data at rest immediately before the initiation of each set were analysed by two-way analyses of variance (ANOVAs) (Region × Set) with repeated measures. For RMS-EMG and TOI data in the shortening and lengthening phases at each set, separate two-way ANOVAs (Region × Rep) with repeated measures were used. When a significant interaction was observed, additional ANOVAs with post hoc test (paired t-tests) were performed. For the M-wave data of each region, separate one-way ANOVAs were used. The significance level for all comparisons was set at $P<0.05$. All data are expressed as means ± SD. The statistical analyses were performed by using statistical software (SPSS Statistics 20, IBM Japan, Japan).

Results

For the M-wave amplitude of each region, no significant main effect was observed, indicating that M-wave amplitude of each region remained unchanged throughout the measurement. Fig. 1 shows the changes in RMS-EMG during the shortening and lengthening phases. For each set, two-way ANOVAs revealed no significant Region × Rep interaction and a significant main effect of Rep. Also, when the RMS-EMG values of each region were normalized to the averaged M-wave amplitude for the respective regions, there were no significant Region × Rep interaction and a significant main effect of Rep (Fig. 2). These results indicate that the RMS-EMG were not different between the two regions.

For the TOI data at rest immediately before the initiation of each set, there was no significant main effect or interaction. This result indicates that TOI was not different at rest between the distal and middle regions. Regarding the shortening phase at each set, two-way ANOVAs showed a significant Region × Rep interaction ($P<0.05$). Follow-up analyses revealed that, at the all sets, TOI values at the distal region were significantly lower than those at the middle region during 3rd- or 4th-8th repetitions ($P<0.05$, Fig. 3). Similarly, for the lengthening phase, there were significant Region × Rep interactions ($P<0.05$). According to further analyses, significantly smaller TOI at the distal region
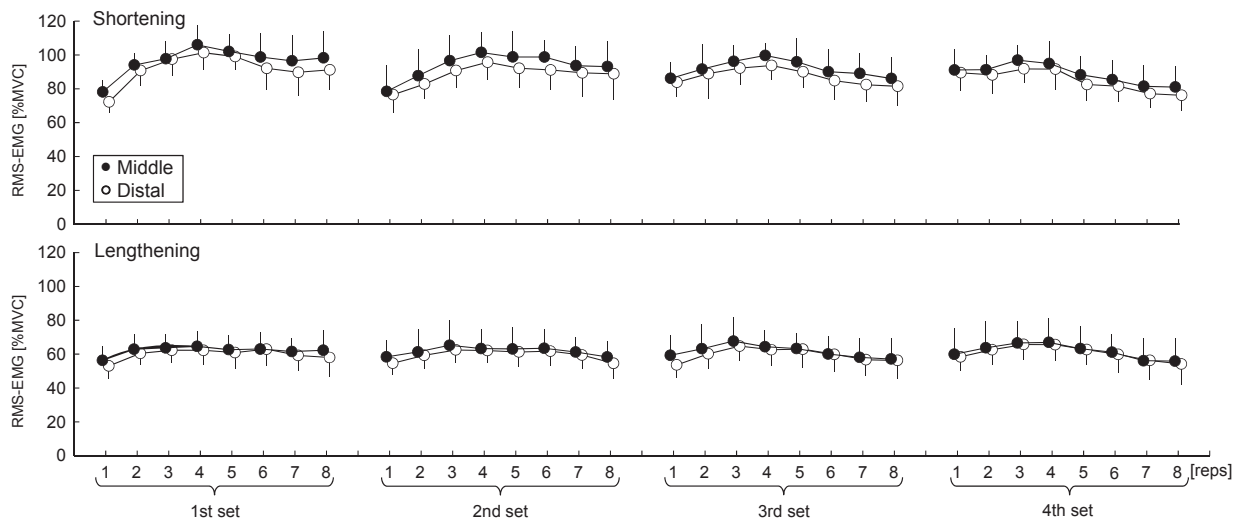

Figure 1 Changes in neuromuscular activity (root mean square value of electromyogram amplitude: RMS-EMG) at the middle (filled circle) and distal (open circle) regions of vastus lateralis during shortening (upper panel) and lengthening (lower panel) phases of resistance exercise.

Figure 2 Changes in normalized neuromuscular activity (RMS-EMG value normalized to peak-to-peak amplitude of M-wave of each region) at the middle (filled circle) and distal (open circle) regions of vastus lateralis during shortening (upper panel) and lengthening (lower panel) phases of resistance exercise.
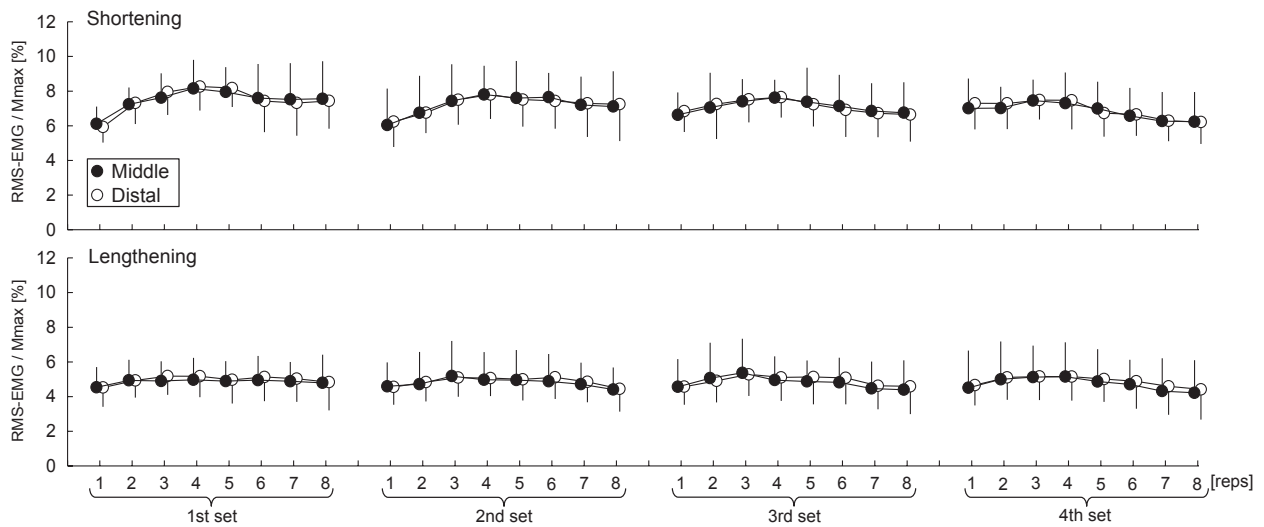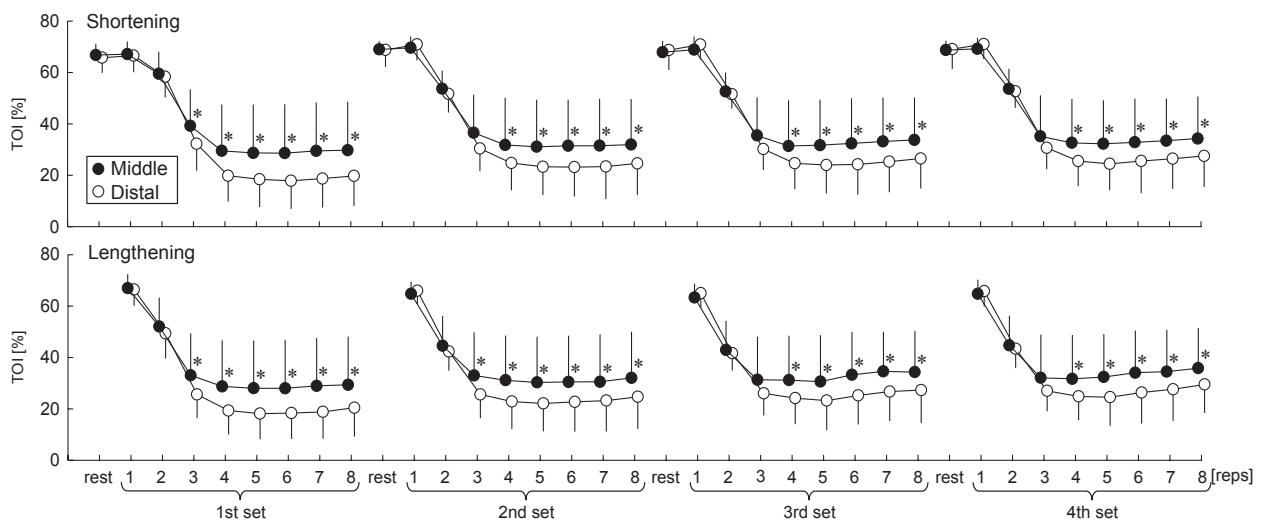

Figure 3 Changes in muscle oxygenation index (TOI) at the middle (filled circle) and distal (open circle) regions of vastus lateralis at rest and during shortening (upper panel) and lengthening (lower panel) phases of resistance exercise. *Significantly different ($P<0.05$) between middle and distal regions.

than at the middle region was observed during 3rd–8th, 3rd–8th, 4th–8th and 4th–8th for the 1st, 2nd, 3rd and 4th sets, respectively ($P<0.05$, Fig. 3).

Discussion

The major finding of this study is that neuromuscular (EMG) activities during fatiguing heavy resistance exercise were similar between the distal and middle regions of VL, whereas muscle tissue oxygenation saturation was significantly lower at the distal than at the middle region of VL. To the best of our knowledge, this is the first study to demonstrate the non-uniform muscle oxygenation within a single muscle during fatiguing heavy resistance exercise, despite uniform EMG activities.

The EMG activities during the exercise relative to those during MVC task were similar to the distal and middle regions of VL. This finding is in line with the previous studies that adopted light-to-moderate load intensities (Mizuno et al., 2004; Crenshaw et al., 2010). However, because the muscle activation level is not necessarily uniform within a muscle even during MVC (Miyamoto et al., 2012), the normalization procedure with MVC task may not accurately reflect the regionally non-uniform muscle activities. To elude this concern, we used not only surface EMG but also electrical stimulation to evaluate neuromuscular activation. In the present study, we normalized EMG amplitudes during voluntary contraction to the maximal M-wave amplitude for each muscle, which enables us to compare the muscle activation level

between regions (Millet & Lepers, 2004; Pasquet et al., 2005; Miyamoto et al., 2012). The present study did show that VL was activated at comparable levels along the longitudinal direction of the muscle during the resistance exercise with 80% of 1RM.

There has been an increasing number of attempts to combine NIRS with EMG to investigate changes in muscle oxygenation with varying neuromuscular activities (Yoshitake et al., 2001; Praagman et al., 2003; Mizuno et al., 2004; Felici et al., 2009; Crenshaw et al., 2010). Some of them have examined regional differences in neuromuscular activity and muscle tissue oxygenation status within a particular muscle (Mizuno et al., 2004; Crenshaw et al., 2010). For example, Mizuno et al. (2004) showed that EMG activity was similar between regions of VL over the range of contraction intensity from 5% to 55% MVC, while the distal region of VL exhibited greater de-oxygenation than did the middle region. Regarding the regional difference in VL muscle oxygenation, a consistent finding over studies is that the muscle de-oxygenation is more prominent in the distal compared with in the middle/proximal region (Mizuno et al., 2004; Kennedy et al., 2006; Crenshaw et al., 2010), although the contraction intensity can influence the magnitude of responses. The finding of the present study is in line with those of the previous studies. Theoretically, heterogeneity of TOI within a muscle despite the homogeneous neuromuscular activity can be explained by either one or a combination of the following factors: (i) variations in the distribution of capillary vessels and (ii) different local blood supply produced by differences in intramuscular pressure.

The circulation network within a muscle is surely an important factor that influences oxygen supply to the muscle; in particular, differences in microcirculation within a muscle affect muscle oxygenation. In the animal model, one of the causes for the regional differences in muscle oxygenation is suggested to be a shunt of blood flow selectively to oxidative muscle fibres (Laughlin & Schrage, 1999). In human in vivo studies, although it is not clear to what extent NIRS signals reflect information from arteries, veins and capillaries (McCully & Hamaoka, 2000), it is generally accepted that the NIRS signal stems from the small blood vessels (i.e. capillaries) and not from the larger blood vessels such as arteries and veins. It has been reported that capillary density depends on muscle fibre types (Hather et al., 1991; Kadi et al., 1999), but there is no difference in muscle fibre composition within the VL along its length (Lexell et al., 1983). Considering the present result that muscle oxygenation state during resting period was similar between both regions of VL, it is unlikely that distribution of circulation network is clearly different between distal and middle regions of VL.

It has been suggested that regional differences in muscle architecture and the resultant differences in intramuscular pressure during contraction cause variation in the regional muscle oxygenation state (Ameredes & Provenzano, 1997; Miura et al., 2004). Greater de-oxygenation in the distal than in the middle region might be attributable to the region-spe-cific inhomogeneity in intramuscular pressure that is related to the regional difference in muscle architecture within VL. If so, it is reasonable to assume that there was higher mechanical and/or metabolic stress in the distal region, where the muscle typically shows greater hypertrophy (Narici et al., 1989, 1996). Further research is needed to clarify the relationship among regional differences in muscle architecture, intramuscular pressure and hypertrophic responses.

A potential mechanism for the regional difference in hypertrophy within VL is the benefit of muscle hypoxia. Previous studies have shown that mechanical stimulus in muscle tissue causes local release of growth factors such as insulin-like growth factor-1 (IGF-1) (Goldspink, 1999; Miyazaki & Esser, 2009). IGF-1 expression has been demonstrated to be tissue-specific and dependent on the intensity of the muscle hypoxia/reoxygenation (Aravindan et al., 2005). Furthermore, (Yamaguchi et al., 2003) showed in rat plantaris muscle that the extent of hypertrophy of muscle fibres and IGF-1 mRNA expression level following overload were greater at the distal than at the proximal regions (Yamaguchi et al., 2003). Taken together, it is possible that the inhomogeneous hypertrophy observed in previous studies (Kawakami et al., 1995; Narici et al., 1996; Kanehisa et al., 2002; Wakahara et al., 2012) is caused by the difference in IGF-1 mRNA expression level within a muscle induced by inhomogeneous muscle oxygenation state during resistance training exercise.

A limitation associated with the present study was that the subjects participated in this study were restricted only to untrained young males. It was reported that the muscle fatigability could be influenced by the training status of the subjects (Miyamoto et al., 2013; Gacesa et al., 2010). In addition, the exercise mode and muscle used in the present study were also limited. Thus, further investigations are warranted to reveal whether similar findings could hold true for other populations (i.e. trained subjects), exercise modes (e.g. single-joint versus multi-joint exercises) and muscles.

In conclusion, this study revealed that during fatiguing heavy resistance exercise, neuromuscular activities were similar between the distal and middle regions of VL, whereas muscle tissue oxygenation saturation was lower at the distal than at the middle region of VL. Our results suggest that a possibility that the regional difference in muscle oxygenation but not in neuromuscular activity during fatiguing heavy resistance exercise is responsible for the regional difference in hypertrophy within a muscle.

Acknowledgment

Conflict of interest

The authors have no conflicts of interest.

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