Effects of swimming exercise on red blood cell rheology in trained and untrained rats

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Yalcin, Ozlem, Melek Bor-Kucukatay, Umit K. Senturk, and Oguz K. Baskurt. Effects of swimming exercise on red blood cell rheology in trained and untrained rats. J Appl Physiol 88: 2074–2080, 2000.—Red blood cell (RBC) mechanical properties were investigated after swimming exercise in trained and untrained rats. In the untrained rats, the RBC aggregation index decreased to 2.60 ± 0.4 immediately after exercise from a control value of 6.73 ± 0.18 (P < 0.01), whereas it increased to 13.13 ± 0.66 after 24 h (P < 0.01). RBC transit time through 5-µm pores increased to 3.53 ± 0.16 ms within 5 min after the exercise from a control value of 2.19 ± 0.07 ms (P < 0.005). A very significant enhancement (166%) in RBC lipid peroxidation was detected only after 24 h. In the trained group, the alterations in all these parameters were attenuated; there was a slight, transient impairment in RBC deformability (transit time = 2.64 ± 0.13 ms), and lipid peroxidation was found to be unchanged. These findings suggest that training can significantly limit the hemorheological alterations related to a given bout of exercise. Whether this effect is secondary to the training-induced reduction in the degree of relative metabolic and/or hormonal perturbation remains to be determined.

hemorheology; erythrocyte deformability; erythrocyte aggregation; oxidant stress

It is widely accepted that regular exercise reduces morbidity and mortality related to vascular diseases (42). The hypothesis about the mechanisms of this protective effect is mostly based on the metabolic alterations that affect cardiovascular risk factors (43). Alternatively, exercise-related sudden death is also a well-documented phenomenon and is accepted to have a cardiovascular origin in most cases (22). Ventricular fibrillation is the most common cause of exercise-induced sudden death; however, the exact mechanisms leading to this fatal arrhythmia are not clear (22). In many cases, an existing coronary disease process is found, but total occlusion of the coronary is not a frequent finding (22). Inadequate blood supply to the myocardium as a result of atherosclerotic narrowing or thrombus generation, in addition to exercise-induced coronary artery spasm, has been discussed as the underlying cause of myocardial ischemia leading to fatal arrhythmias (22). A frequently ignored factor that affects blood flow is its fluidity (31), and this property of blood might be altered dramatically during and/or after exercise (12, 18).

Besides increased whole blood and plasma viscosities (13), impaired red blood cell (RBC) deformability (19) and enhanced RBC aggregation (12) were found during and after heavy exercise. The mechanical properties of RBCs are important determinants of tissue perfusion (16, 31). Deformability of RBCs is one of the key factors in the perfusion of capillaries, whereas RBC aggregation affects the fluidity of blood in larger blood vessels. It is well known that blood flow in skeletal muscles is closely related to oxygen demand (29). Therefore, the above-mentioned alterations in hemorheological parameters may not be limiting factors for oxygen transport to exercising muscles, because the regulating mechanisms on the basis of oxygen demand would balance the extra hemorheological load. However, these alterations might affect the perfusion of other tissues (e.g., myocardium), especially if there is a vascular challenge (e.g., coronary stenosis).

RBC mechanical properties are closely related to the structure and physiological status of this unique cell and are sensitive to the alterations in their environment as well as to metabolic disturbances (16, 34). RBC mechanical properties were found to be altered in many physiological and/or pathophysiological processes (16–18, 34). Oxidant damage is one of the important common pathways of these processes, and there is a considerable amount of data in the literature indicating the direct relationship between the free radical attack and mechanical alterations in RBC (9, 10, 39). Strenuous muscular exercise is known to induce oxidant stress resulting from several different mechanisms (32, 41). Reaction to heavy exercise may even involve an inflammatory response (15), including the activation of leukocytes (44). Increased lactate influx to RBCs may also affect deformability (37). The effects of acute, strenuous muscular exercise on RBC mechanical properties can well be explained by either one of these mechanisms (6, 10, 37).

Alternatively, despite the expected deleterious circulatory effects of acute exercise-related RBC mechanical alterations, exercise training is known to reduce cardiac risk and improve hemorheological parameters (i.e., increase RBC deformability and decrease RBC aggregation, resulting in increased blood fluidity) (12, 26). It has been argued that exercise training may...
enhance antioxidant defense mechanisms (40). Circulatory adaptations in trained individuals may reduce tissue injury and related inflammatory responses due to strenuous exercise (24).

This study investigates the immediate and late effects of muscular exercise on RBC mechanical properties in untrained and trained rats. An animal model of exercise has been preferred to be able to achieve a high level of standardization in the baseline cardiovascular status of the subjects, although the same degree of standardization cannot be achieved in exercise intensity and the resulting metabolic challenge. However, the swimming exercise used in this study was thought to model the unexpected and unavoidable exercise episodes that are encountered by ordinary people during their everyday lives. It can be suggested that training can induce "adaptations" that will reduce the magnitude of the hemorheological effect and the extra load imposed on the circulatory system.

### MATERIALS AND METHODS

Animals, exercise protocol, and blood samples. Male albino rats, 8 wk old and weighing 200–250 g, were used in the experiments. The animals were divided into five groups of 12. The animals in the exercise groups were subjected to swimming exercise in groups of six in a swimming tank of 100 x 50 cm with a depth of 50 cm, filled with tap water. The water temperature was kept at 32 ± 2°C. The rats were kept in the swimming tank for 10 min on the first day, the swimming period was increased by 10 min each day, and the swimming exercise lasted 60 min on the sixth day. In the untrained-5m and untrained-24h groups, blood samples were obtained on the sixth day, within 5 min or 24 h, respectively, after this 60-min-long exercise. Animals in the trained-5m and trained-24h groups started swimming exercise as described for the untrained exercise groups, and after the sixth day they were subjected to swimming exercise 60 min/day, 5 days/wk, for 6 wk. They were also sampled within 5 min or 24 h, respectively, after the last exercise. Control animals were kept in the same environment, except that they were not subjected to swimming exercise. All animals were 14 wk old and weighed 250–300 g at the time of sampling.

Blood samples were obtained from the abdominal aorta of the rats under light ether anesthesia and were anticoagulated with heparin sodium (15 U/ml). These samples were used for the measurements of RBC aggregation, deformability, shape-recovery time constant, and lipid peroxidation.

Determination of RBC aggregation. RBC aggregation was assessed by using a custom-built photometric aggregometer interfaced to a digital computer (8). The shearing portion of the system consists of two parallel glass plates with a gap of 500 µm between them; a stepper motor, controlled by the computer, rotates one of these plates. An infrared light-emitting diode and a phototransistor, combined with an amplifier and an analog-to-digital converter, were used to record light transmission time data. The blood sample under study is placed between the glass plates and is first sheared at 500 s⁻¹ for 10 s to disperse RBC aggregates. After a sudden stop of the motor, the infrared light transmission through the blood sample is monitored for 10 s and recorded by the computer. The computer then calculates the area under the light transmission curve and reports a dimensionless index that reflects the extent of aggregation. Measurements were done in triplicate for each sample, and the mean of these three measurements was used as the result. Measurements were done at room temperature (20 ± 2°C). The instrument precision for aggregation index measurements, calculated as the coefficient of variation for 10 repeated measurements on the same sample, was 4.73% (8).

RBC aggregation was measured in autologous and standard plasma. The standard plasma was pooled from healthy, nonexercised rats, and the same suspending medium was used for control and exercised groups. The hematocrit of the samples was adjusted to 0.4 l/l by adding or removing autologous or standard plasma.

RBC deformability measurements. RBC deformability was estimated by measuring transit time (TT) through pores with 5-µm diameter and 15-µm length by using a cell transit analyzer (CTA) (2). The CTA consists of an oligopore filter with 30 cylindrical pores, mounted between two reservoirs and an alternating-current conductimeter. The conductimeter operates at 100 kHz and measures the electrical resistance between the electrodes placed in each reservoir. By adjusting the level of fluid in the reservoirs, a pressure gradient is created that forces the dilute RBC suspension (0.04%) in PBS (pH = 7.4) in one of the reservoirs to flow through the oligopore filter. The passage of a RBC through one of the 30 pores results in a resistance change between two reservoirs. A resistive pulse is generated at the output of the conductimeter circuit, which carries the information about the passage of that RBC through a 5-µm pore. This signal is then digitized and passed onto a digital computer for analysis. The computer determines the width of each valid pulse that corresponds to the TT of a RBC through a pore. TTs of 1,000 RBC for each specimen were determined, and their mean was used to represent the deformability of that RBC population. The pressure gradient used in this study was 3 cmH₂O. All measurements were conducted at 25°C. The instrument precision for RBC TT, calculated as the coefficient of variation for 10 repeated measurements on the same sample, was 2.01% (2).

The measurement of RBC TT by the CTA provides data directly relevant to passage of RBCs through capillary-size pores (i.e., 5-µm diameter) under constant pressure gradient, and it is a measure of the resistance encountered during the "flow" of this cell through the pore. Because the pore diameter is close to the cell dimensions, this parameter quantitatively reflects the deformability of RBCs.

RBC shape-recovery time constant measurement. RBCs were separated from whole blood by centrifugation and were suspended in a 15% solution of dextran with molecular weight of 40,000 (Sigma Chemical) in PBS at a hematocrit of 0.4 l/l (5). The RBC suspension was sheared at a shear rate of 500 s⁻¹ for 10 s in the plate-plate shearing system described above, after which the shear rate was abruptly reduced to zero. The light transmittance through the RBC suspension after this sudden stop of the rotating plate at time 0 (t₀) was measured by the phototransistor and digitized by computer at a sampling rate of 2,000 Hz. The first 200-ms portion of the data was transferred to data-analysis software (Statmost, Datamost, Salt Lake City, UT) for curve fitting. Light reflectance-time data (I₁) were fitted by use of an exponential equation

\[ I₁ = I₀ - (Iₐ - I₀) \cdot e^{-t/t₀} \]

where t is time, I₀ is light reflectance at the end of the 200-ms period (t₀), Iₐ is the difference in light reflectance between t₀ and the plateau level, and t₀ is the time of half-maximal recovery.

In summary, the swimming exercise used in this study was thought to model the unexpected and unavoidable exercise episodes that are encountered by ordinary people during their everyday lives. It can be suggested that training can induce "adaptations" that will reduce the magnitude of the hemorheological effect and the extra load imposed on the circulatory system.
and $t_{200}$, and $t_c$ is the time constant of RBC shape recovery after deformation by shear; a decreased $t_c$ indicates a faster rate of shape recovery. The program calculated $I_d$, $I_r$, and $t_c$ by using a least-square minimization technique. The correlation coefficients between the entered and calculated values were 0.98 or higher for all fitted equations. Coefficient of variation for 10 repeated measurements of the RBC shape-recovery time constant was 5.21% (5).

Measurement of thiobarbituric acid-reactive substances. The extent of lipid peroxidation of RBC membranes was estimated by measuring thiobarbituric acid-reactive substance (TBARS) levels according to the method of Stocks and Dormandy (36). TBARS levels were estimated by measuring absorbance at 532 nm after reaction with thiobarbituric acid; trichloroacetic acid extracts of RBC samples were used to avoid the interference of proteins with TBARS determinations. Results were expressed as nanomoles per gram Hb.

Statistics. Results are expressed as means ± SE. Statistical comparisons between groups were done by one-way ANOVA followed by Newman-Keuls post hoc test and paired t-test; P values <0.05 were accepted as statistically significant.

RESULTS

Effects of exercise in untrained rats. The rats could tolerate the swimming exercise for 60 min; however, it has been observed that this is an exhaustive exercise for rats, indicated by observations of submerged periods of the animals for 15–20 s (20). In the blood samples obtained immediately after this exercise period, RBC aggregation was found to be significantly decreased ($P < 0.01$) both in autologous and standard plasma (Fig. 1). However, in the blood samples obtained 24 h after this exhaustive exercise, RBC aggregation was found to be increased ($P < 0.01$) in both suspending media.

RBC TT increased significantly after the swimming exercise ($P < 0.005$) and remained longer 24 h after the exercise compared with the control value ($P < 0.001$; Fig. 2). RBC shape-recovery time constant decreased significantly after the exercise ($P < 0.001$) but returned to the control value after 24 h (Fig. 3). TBARS values, indicative of lipid peroxidation in RBC, were found to be increased only 24 h after the exercise ($P < 0.001$) (Fig. 4).

Effects of exercise in trained rats. The behavior of rats during the last swimming period at the end of the training was similar to that of untrained rats except that these animals exhibited very little evidence of exhaustion (i.e., very rare submerged periods longer than 15 s). RBC aggregation in autologous plasma was not affected in the trained rats immediately after the 60-min swimming exercise. The decrement in standard plasma was significant (Fig. 1), and the RBC aggregation in the standard plasma was significantly lower than the value measured in autologous plasma ($P < 0.001$). The late response of RBC aggregation to swimming exercise was again an increment; the value obtained in the blood samples obtained 24 h after the exercise was significantly higher than control values. However, the aggregation indexes did not reach the levels measured in the 24-h samples of the untrained rats; there was a significant difference between the 24 h RBC aggregation indexes of untrained and trained groups ($P < 0.01$).

RBC TT was increased ($P < 0.005$), suggesting a decreased deformability, in the samples obtained within 5 min after the exercise; however, the value was significantly lower than the TT measured in the untrained group within 5 min after the similar exercise ($P < 0.001$; Fig. 2). Unlike the results in the untrained group, the TT values returned to control values 24 h after the exercise and were significantly lower than the corresponding value (i.e., the TT measured in 24 h)
DISCUSSION

Swimming is frequently preferred as an exercise model for small laboratory animals, and it has several advantages over other types of exercise (23). The intensity of labor during exercise is greater than running for equal periods, and aversive stimulation used to promote running is not used in swimming (23). Running on a treadmill may also have an adverse effect on RBCs, as a result of the foot impact, that is not encountered in swimming (37). On the other hand, swimming exercise certainly includes some emotional factors (23). This is especially true in inexperienced animals, and the endocrine response to this mixture of emotional and physical stress was found to be different from that to exercise alone (23, 30). First-time swimming caused an enhanced release of epinephrine from the adrenal medulla and a reduced output of norepinephrine from sympathetic nerve endings (30). In contrast, physical exercise with less emotional component resulted in increased norepinephrine to epinephrine ratio (23). Corticosterone is also found to be increased in proportion to the level of emotional component of swimming exercise (e.g., decrement in water temperature) in rats as well as to the length of exercise (1). The rats in this study were not first-time swimmers, even in the untrained group. The swimming conditions were also set to reduce any possible emotional stress. However, despite all these efforts to minimize the emotional component of the swimming exercise, the results of this study should be accepted to reflect a mixture of emotional and physical components of the applied exercise.

One hour of swimming had been accepted as an exhaustive exercise for the untrained rats used in the study, on the basis of the observation of periods in which the animals were submerged for more than 15 s toward the end of the exercise period (20). The same length of swimming exercise was not exhaustive for the trained rats on the basis of the same criteria. It has been reported that training reduces the endocrine and metabolic alterations induced by acute exercise (38). Although there might be considerable heterogeneity among the rats in their response to exercise, it can be accepted that the work outputs in both groups were close to each other. However, the impact of this workload should be smaller in the trained animals. Comparing the effects of a given workload instead of comparing the effects of exhaustive exercise in trained and untrained animals seemed to be more realistic from a pathophysiological point of view.

This exhaustive exercise resulted in significant alterations in the mechanical properties of RBCs of untrained rats. RBC TTs were found to be 61% higher immediately after exhaustive exercise in untrained rats, implying a significant rigidification of RBCs. RBC deformability was still significantly impaired 24 h after the exercise period. RBC deformability can be impaired as a result of structural and metabolic alterations within the cell (16, 34). The cation content of RBCs might be altered during and after exercise (35). Osmotic alterations in the blood were reported during exercise; however, it seems to be unlikely that these alterations cause significant osmotic changes in RBCs (35). The alterations in the cation content might be the result of decreased RBC cation pump activities (33). Although sodium content of RBCs is the key determinant of cell hydration and volume, low cytosolic calcium concentration is critical for the maintenance of appropriate viscoelasticity of the RBC membrane, most probably by regulating the dynamic protein-protein associations in the membrane skeleton (25). However, both effects should be reversible by returning to the resting state (33), and these mechanisms cannot explain the impaired RBC deformability after 24 h.

The RBC shape-recovery time constant, which primarily reflects the membrane viscoelasticity (5), exhibited a different pattern of alterations; it was found to be decreased significantly immediately after exhaustive exercise in untrained rats, suggesting increased shear elastic modulus in the RBC membrane, but this effect was not seen after 24 h. This transient effect of exercise on RBC membrane shear elastic modulus probably reflects the alterations in membrane skeletal proteins that result from metabolic impairments within the RBC. Alternatively, in the untrained rats, RBC TBARS levels were found to be increased only after 24 h, being at the control levels right after the exercise period. Although TBARS measurements can be affected by many other biochemical alterations in the cells, it is generally accepted and widely used as a measure of the lipid peroxidation in RBC membranes (28). This late increment in lipid peroxidation should reflect the effects of mechanisms triggered by exercise, which continued afterward and may include the inflammatory response and leukocyte activation that are known to be associated with heavy, strenuous exercise protocols (15). These continuing effects seem to be responsible for the impaired deformability of RBCs 24 h after the exhaustive exercise.

These observations also underline the role of exercise-related oxidant stress in RBC mechanical alterations.
It has been previously shown that oxidant stress may have significant effects on both RBC deformability and aggregability (10). Acute effects of heavy exercise on RBC aggregation are not well documented, and there are conflicting data in the literature (12). Although unchanged intensity of aggregation was reported in several studies (14, 19), increased RBC aggregation was reported in other studies using different exercise protocols and techniques to assess RBC aggregation (11, 21). Additionally, Brun et al. (12) reported increased aggregate strength after exercise.

In this study, RBC aggregation was found to be inhibited during the early phase after the exhaustive exercise. A similar inhibition of RBC aggregation was observed in an in vitro model of oxidant stress on the basis of a xanthine-xanthine oxidase system (10). This inhibition might be due to the rigidification and alterations in surface properties of RBCs (34). Furthermore, in the same in vitro model of oxidant stress, an increased disaggregation shear rate was observed under the influence of oxidant stress, suggesting increased aggregate strength (10). Therefore, putting our data and the observations of Brun et al. (12) together, it can be stated that the effect of heavy, exhaustive exercise on RBC aggregation mimics the influence of oxidant attack on RBC.

However, the later effects of exercise on RBC aggregation are quite different; there was almost a 100% increase in the aggregation indexes 24 h after the exhaustive exercise in untrained rats. This late effect most likely reflects the acute-phase response related to the muscle damage and the accompanying inflammatory process (28). It should be noted that, in the untrained rats, RBC aggregation indexes in autologous and standard plasma were not different from each other, implying that the plasma factors in exercised rats were not primarily responsible for the altered aggregation in these groups. Surface alterations of RBCs under the influence of oxygen free radicals or other factors (e.g., proteolytic enzymes from activated neutrophils) may play role in this change of aggregability.

It is interesting to see a biphasic effect of exhaustive exercise on RBC aggregation. There might be two different explanations for this picture. 1) Some additional mechanisms may continue to be activated during the later phases of recovery, including the above-mentioned inflammatory process and related leukocyte activation. These activated leukocytes can well be the source of oxygen free radicals and proteolytic enzymes that affect RBC aggregability (6). It has been previously shown in vitro that activated neutrophils enhance the aggregability of neighboring RBCs (6). Furthermore, significantly increased TBARS levels after 24 h provide supportive evidence for this late-activated mechanism. 2) Oxygen free radicals may have a dose-dependent effect on RBC aggregability (7). However, detailed molecular mechanisms of these dose-dependent effects are not clearly known yet.

It is quite obvious that training has significantly changed the pattern and magnitude of the effects of the swimming exercise on RBC mechanical properties in this study. The effect on RBC deformability and membrane shear elastic modulus seems to be blunted. This was especially true for the late effects. In the trained rats, only a slight, transient increase in RBC TT was observed, and the RBC deformability was found to be at the control level after 24 h. The very significant increment in TBARS levels observed in the untrained rats after 24 h was also not seen in the trained rats. This observation provides additional indirect support for the above-mentioned two separate mechanisms for the altered RBC mechanics in untrained rats, the late effect being related to the processes that resulted in increased lipid peroxidation in RBC membranes. Obviously, this second part of the exercise-related effects was absent in trained rats.

RBC aggregation indexes measured in trained rats also reflect the attenuated effect of the swimming exercise: RBC aggregation in autologous plasma of the blood samples obtained immediately after the exercise protocol was found to be unchanged compared with the control value, and the index after 24 h was significantly lower than the corresponding value in untrained rats, although a significantly higher value than control was measured. It is interesting to note that RBC aggregation in autologous and standard plasma were significantly different in trained rats, whereas such a difference was not found in the untrained groups. These differences indicate that training may induce plasma composition changes that influence RBC aggregation (34).

The attenuation of the exercise-related effect on RBC mechanical properties by training should reflect the adaptation mechanisms. Such mechanisms include cardiovascular and metabolic alterations that contribute to the “fitness” of individuals (43). These adaptations may reduce the impact of the exercise bout, and 1 h of swimming, which has been characterized as a heavy exercise in untrained rats in this study, might be a moderate exercise for the trained rats. Therefore, the metabolic perturbations induced by the exercise might be attenuated in the trained animals, and the altered pattern of hemorheological disturbances may directly result from this reduced metabolic challenge. It should be noted that training did not induce an “improvement” in RBC deformability; TT and shape-recovery time constant of RBCs 24 h after the exercise were very close to the control levels, but the acute alteration was significantly smaller than that of untrained rats.

The smaller acute effect of exercise in the trained rats may also be related to the adaptive alterations in RBC. It is well documented that in trained individuals RBC turnover is increased and the RBC population in the circulation is “younger” (35). These younger RBCs should have a more effective antioxidant defense system. It has been observed that training enhances the antioxidant enzyme activities in RBCs (40). However, it is not possible to determine the exact mechanism of the attenuated hemorheological alterations in the trained rats with the present experimental design. Further studies are needed to evaluate the relative contribu-
tions of the systemic adaptations (i.e., reduced metabolic perturbations) and the adaptations in RBC population (i.e., reduced sensitivity to these metabolic perturbations).

RBC aggregation in autologous plasma was found to be significantly higher than the control value 24 h after exercise in the trained rats. This higher RBC aggregation can be assumed as the “normal” for these regularly exercising subjects. Comparative hemorheological studies suggested that athletic species have higher RBC aggregation compared with sedentary species (27). The exact structural, genetic, and physiological basis of this suggestion is not clear. However, our results indicate that this higher aggregation tendency might be the result of the “lifestyle.” Further investigations are needed to support this suggestion.

Our results suggest that significant hemorheological alterations accompany the exhaustive exercise episodes and may continue after the cessation of exercise. These alterations may well be expected to contribute to the circulatory problems and related sudden death. It is important to note that RBC deformability and aggregation were both at a level that may have a pathophysiological significant effect on blood flow resistance 24 h after the exercise in untrained animals. During the exercise, there is an important degree of hemodynamic hyperactivity, mainly resulting from the increased cardiac output and elevated driving pressures in the vascular system. This hyperactivity may balance the impact of hemorheological deterioration during the active phase of exercise. However, by the end of the exercise hemodynamic forces return to the resting level in a relatively short time period, whereas it takes longer for hemorheological alterations to be normalized. During this hemodynamic recovery period, it seems to be more likely to encounter perfusion problems related to impaired blood rheology.

Obviously, tissue perfusion is well regulated by local mechanisms, mainly on the basis of the metabolic status of a given tissue reflected by the level of certain metabolites (29). If the tissues have a sufficient auto-regulating capacity (i.e., if the microcirculatory vessels are not fully dilated), any RBC mechanical alteration can be tolerated and an impairment in tissue perfusion does not occur. However, if the autoregulatory reserve has already been used as a result of existing vascular problems, the extra load induced by RBC mechanical alterations may result in insufficient blood flow (4). A hemorheological extra load due to the RBC mechanical alterations related to strenuous exercise is more likely to be effective during the early recovery phase. It has been shown previously that RBC deformability in circulation is a well-controlled parameter and that mechanically altered RBC can be effectively removed from the circulation by the reticuloendothelial system (3).

In conclusion, our data indicated that exhaustive exercise in untrained individuals may result in significant RBC damage that may affect tissue perfusion and play a role in exercise-related morbidity/mortality. Alternatively, exercise training induces adaptive mechanisms that suppress such alterations. These adaptive mechanisms should include the metabolic adaptations that may result in reductions in metabolic perturbations resulting from exercise as well as the adaptations in the RBC as the target cell.

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