

Effect of Inflammation on Amino Acid Profile in Heart Failure Patients*Kalp Yetersizliği Hastalarında İnflamasyonun Amino Asit Profili Üzerine Etkisi*Zulkif Tanriverdi^{1*}, Fatih Gungoren², Mustafa Begenc Tascanov¹, Ibrahim Halil Altıparmak¹, Halil Fedai¹,Kenan Toprak¹, İsmail Koyuncu³¹Department of Cardiology, Faculty of Medicine, Harran University, Sanliurfa/Turkiye²Department of Cardiology, Faculty of Medicine, Aydin University, Istanbul/ Turkiye³Department of Medical Biochemistry, Faculty of Medicine, Harran University, Sanliurfa/ Turkiye**Abstract**

Background: Heart failure (HF) is a complex disease and inflammation play a crucial role in its pathophysiology. The metabolism of energy substrate alters in HF and these changes may lead to the impairment in amino acid (AA) metabolism by increasing the heart's dependence on AAs. Limited studies evaluated the relationship between inflammation and AA profile in patients with HF. In this study, we aimed to evaluate the AA profile in patients with HF and to reveal its relationship with inflammation.

Materials and Methods: Seventy-two patients with HF and 64 healthy controls were included in this study. C-reactive protein/albumin ratio (CAR) was used to assess inflammatory status of the patients. High performance liquid chromatography technique was used to evaluate the AA profile.

Results: We detected that AAs profile was significantly changed in HF patients compared to controls. HF patients had also significantly higher CAR ($p<0.001$) level. The best cut-off value of CAR for predicting HF was 0.91, and patients were divided into 2 groups according to this cut-off value: $CAR\geq 0.91$ (high inflammation group) and $CAR<0.91$ (low inflammation group). When compared to low inflammation, patients with high inflammation had significantly different AAs profile. Correlation analysis showed that CAR was positively correlated with phenylalanine, tyrosine and asparagine whereas negatively correlated with valine, leucine and methionine levels.

Conclusion: We found that AA profile was significantly changed in patients with HF. Also, the impairment in AA metabolism was more pronounced in patients with higher inflammation compared to patients with lower inflammation. We suggest that main mechanism underlying the impaired AA profile in HF may be increased inflammation.

Keywords: Heart failure, inflammation, CRP to albumin ratio, amino acid profile

ÖZ

Amaç: Kalp yetmezliği (KY) kompleks bir hastalıktır ve inflamasyon patofizyolojisinde önemli bir rol oynar. KY'de enerji substratının metabolizması değişir ve bu değişiklikler kalbin amino asitlere (AA) bağımlılığını artırarak AA metabolizmasında bozulmaya yol açabilir. KY hastalarında inflamasyon ve AA profili arasındaki ilişkiyi değerlendiren çalışmalar sınırlıdır. Bu çalışmada, KY hastalarında AA profilini değerlendirmeyi ve inflamasyon ile ilişkisini ortaya koymayı amaçladık.

Gereç ve Yöntem: Yetmiş iki KY hastası ve 64 sağlıklı kontrol çalışmaya dâhil edildi. Hastaların inflamatuvar durumunu değerlendirmek için C-reaktif protein/albumin oranı (CAR) kullanıldı. AA profilini değerlendirmek için yüksek performanslı sıvı kromatografi tekniği kullanıldı.

Bulgular: AA profilinin, KY hastalarında kontrollere kıyasla anlamlı derecede değiştiğini saptadık. KY hastaları ayrıca, anlamlı olarak daha yüksek CAR seviyesine sahipti ($p<0.001$). CAR'ın KY'yi öngörmede en iyi kesim değeri 0.91 idi ve hastalar bu kesim değerine göre 2 gruba ayrıldı: $CAR\geq 0.91$ (yüksek inflamasyon grubu) ve $CAR<0.91$ (düşük inflamasyon grubu). Düşük inflamasyonla karşılaştırıldığında, yüksek inflamasyonlu hastaların AA profili anlamlı derecede farklıydı. Korelasyon analizi CAR'ın fenilalanin, tirozin ve asparajin ile pozitif korelasyon gösterdiğini; aksine valin, lösin ve metiyonin seviyeleri ile negatif korelasyon gösterdiğini ortaya koydu.

Sonuç: KY hastalarında AA profilinin önemli ölçüde değiştiğini bulduk. Ayrıca, AA metabolizmasındaki bozulma, inflamasyonu daha yüksek olan hastalarda, inflamasyonu daha düşük olan hastalara kıyasla daha belirgindi. KY'de bozulmuş AA profilinin altında yatan ana mekanizmanın artmış inflamasyon olabileceğini düşünüyoruz.

Anahtar Kelimeler: Kalp yetmezliği, inflamasyon, CRP/ albumin oranı, amino asit profili

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Highlights

- Altered amino acid (AA) metabolism has been reported in patients with heart failure (HF).
- We also found that AA profile significantly was changed in patients with HF.
- This change in AA metabolism was more pronounced in patients with higher inflammation state.

Introduction

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output. It is a serious public health problem worldwide and has an enormous burden on healthcare systems (1). Its incidence has gradually increased with increasing life expectancy, and this number is expected to more increase in future (2). In these patients, multiple system disorders may occur due to decreased cardiac output. Therefore, HF is known to affect not only the cardiovascular system but also the immune, neuroendocrine, renal and musculoskeletal systems. Despite improved modern treatment approaches, the prognosis of HF patients is still poor (3).

Heart failure has a complex pathophysiology. Inflammation, immune system and neurohormonal activation play critical roles both in the development and progression of HF (2,4,5). To date, many conventional biochemical markers have been studied to evaluate inflammatory status and identify their association with HF (3). Recently, a novel inflammatory marker, C-reactive protein (CRP) to albumin ratio (CAR), has emerged and this ratio reflects the balance of the CRP and albumin (6). Studies reported that CAR may be more sensitive than either CRP or albumin separately for assessing the inflammatory process, and its clinical importance has been well documented in patients with coronary artery disease (6-8). However, limited studies evaluated CAR in patients with HF and showed its association with the prognosis of HF (9,10).

The heart may utilize many substrates to meet its high energy demand, including fatty acids, glucose, ketone bodies and amino acids (AAs). Although AAs are essential nutrient metabolites for normal cellular development in the human body, the heart uses very small amounts of AA for direct energy production. It frequently uses AAs to regulate energy metabolism and myocardial protein turnover (11). However, if HF develops, the metabolism of substrates used by the heart for energy needs is significantly altered. For example, the primary substrate utilized for the energy demand changes from fatty acids to glucose in HF (12). In addition, the heart's dependence on AAs increases during HF because of increased myocardial anabolic activity (13). Therefore, the metabolism of AAs in HF patients is altered compared to healthy individuals.

Studies have demonstrated that the plasma AA profile is altered in HF patients and the evaluation of AA profile may have an important impact on risk stratification and prognosis in these patients (12). However, the mechanism underlying impaired AA metabolism in HF patients has not been fully elucidated yet. Limited studies evaluated the relationship between inflammation, which is a main pathophysiological process in HF, and AA profile in patients with HF. In the present study, it was aimed to evaluate the AA profile in patients with HF and to reveal its relationship with inflammation.

Material and Methods

A total of 72 consecutive patients with compensated HF who were admitted to our cardiology clinic between 01 July 2021 and 01 October 2021 were included in the study as the patient group. Also, age- and gender-matched subjects who applied to our cardiology outpatient clinic with any symptom and were not detected heart failure after the detailed examinations were consecutively included as the control group, between the same dates. The diagnosis of HF was made according to the European Society of Cardiology Heart Failure guidelines (1). Patients with compensated HF, left ventricular ejection fraction (LVEF) <40%, and those patients whose archive data were available were included in the study. Patients with decompensated HF, preserved and mildly reduced EF, active infection, thyroid diseases, inflammatory or hematological diseases, intestinal malabsorption diseases, history of malignancy, steroid use and chronic renal failure were excluded from the study. Approval for the study was obtained from the ethics committee of Harran University Faculty of Medicine (number: HRU/21.11.19, date: 07.06.2021). It was implemented in accordance with the rules of the Declaration of Helsinki and informed consent was obtained from all patients included in the study. Baseline characteristics, clinical features and comorbid

conditions of all participants were recorded.

Blood samples were collected from the participants under appropriate conditions. Baseline hemogram and biochemical parameters were analyzed from the blood samples. An automatic device (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp, Hialeah, Florida) was used for complete blood count. Biochemical parameters were measured by standard techniques. CRP to albumin ratio was calculated by dividing CRP to albumin. In addition, 1 tube of blood was sent to the biochemistry laboratory for examination of the amino acid profile. Plasma and serum obtained by centrifugation at 5000 rpm for 5 minutes were separated into ependorfs and stored at -80°C. High performance liquid chromatography technique was used for AA profile (14).

Echocardiographic evaluation was performed with Vivid S5 (General Electrics, Vivid S5 echocardiography, Milwaukee, WI, USA). Detailed echocardiographic evaluation was performed to all patients and LVEF was calculated with Simpson methods.

Statistical Analysis

Statistical analysis was performed with SPSS 22 (SPSS, Chicago, IL, USA) software program. Kolmogorov-Smirnov test was used to determine the normality of continuous variables. Normally distributed variables were presented as mean \pm SD and compared with Student-t test. Non-normally distributed variables were presented as median (25-75th interquartile range) and were compared with Mann-Whitney U test. Categorical variables presented as number and percentage and compared with chi-square test. Receiver optic characteristics (ROC) curve analysis was performed to determine optimal cut off value of CAR for predicting the presence of HF. Pearson and/or Spearman correlation coefficients were used for correlation analysis. A p value of <0.05 was considered as statistically significant.

Results

Seventy-two patients with HF and 64 healthy subjects were included in this study. Baseline clinical and laboratory variables of the patients and control group are listed in Table 1. Age (p=0.260) and gender (p=0.510) were similar between two groups. However, the frequency of hypertension (p=0.037) was significantly higher and LVEF (p<0.001) was lower in HF patients than in the healthy subjects. Regarding laboratory parameters, it was found that CRP (p<0.001), CAR (p<0.001) and leukocyte (p=0.039) values were significantly higher whereas hemoglobin (p=0.035) was significantly lower in HF patients (Table 1).

Table 1. Comparison of baseline demographic and laboratory characteristics of the heart failure patients and healthy control

Variables	Heart failure group (n = 72)	Control group (n = 64)	P
Age, years	60.03 \pm 8.83	58.30 \pm 8.99	0.260
Gender, male (%)	41 (56.9)	40 (62.5)	0.510
Hypertension (%)	25 (34.7)	12 (18.8)	0.037
Diabetes mellitus (%)	20 (27.8)	14 (21.9)	0.427
Smoking (%)	13 (18.1)	11 (17.2)	0.895
LVEF (%)	32.24 \pm 7.89	56.33 \pm 3.80	<0.001
Creatinine, mg/dl	0.96 \pm 0.22	0.87 \pm 0.22	0.009
Glucose, mg/dl	98.71 \pm 21.10	100.67 \pm 18.70	0.569
Total cholesterol, mg/dl	161.49 \pm 39.64	172.42 \pm 41.34	0.118
LDL- cholesterol, mg/dl	108.58 \pm 25.89	106.54 \pm 19.18	0.605
HDL- cholesterol, mg/dl	40.01 \pm 12.18	40.91 \pm 9.17	0.631
Triglyceride, mg/dl	134.82 \pm 49.73	143.33 \pm 56.12	0.350
CRP, mg/dl	6.80 (2.83-10.0)	2.10 (0.62-5.89)	<0.001
Albumin, g/dl	4.08 \pm 3.49	4.18 \pm 0.59	0.813
CAR	1.87 (0.70-2.80)	0.51 (0.15-1.32)	<0.001
Hemoglobin, g/dl	12.80 \pm 1.89	13.44 \pm 1.58	0.035
Leukocytes, x10 ³ /mL	11.55 \pm 2.47	10.75 \pm 1.86	0.039
Platelets, x10 ³ /mL	260.92 \pm 79.16	273.24 \pm 53.02	0.294

Abbreviations: LVEF: left ventricular ejection fraction, LDL: low density lipoprotein, HDL: high density lipoprotein, CRP: C-reactive protein, CAR: CRP to albumin ratio

Comparison of amino acid profile of the HF patients and healthy control are presented in **Table 2**. When compared to the control group, patients with HF had significantly lower valine ($p=0.040$), leucine ($p<0.001$) and methionine levels ($p=0.001$) whereas significantly higher phenylalanine ($p<0.001$), tyrosine ($p=0.027$), asparagine ($p<0.001$), arginine ($p<0.001$), glycine ($p=0.006$) and ornithine ($p=0.035$). Alanine, cytosine and glutamine levels were similar between two groups.

ROC curve analysis was performed to determine the optimal cut-off value of CAR for predicting the presence of HF (**Figure 1**). $CAR \geq 0.91$ predicted the presence of HF with a sensitivity of %72.2 and specificity of %71.9 ($p<0.001$). Heart failure patients were divided into two groups according to this cut-off value: HF patients with $CAR \geq 0.91$ (high inflammation status group, $n=52$) and $CAR < 0.91$ (low inflammation status group, $n=20$), and comparisons were made. It was detected that patients with high inflammation status had significantly higher phenylalanine ($p<0.001$), tyrosine ($p<0.001$), asparagine ($p<0.001$) and ornithine ($p=0.006$) levels whereas lower valine ($p<0.001$) and leucine levels ($p<0.001$) (**Table 3**).

Table 2. Comparison of amino acid profile of the heart failure patients and healthy controls

Variables	Heart failure group (n = 72)	Control group (n = 64)	P
Valine	124.63 (111.15-150.43)	137.00 (113.45-175.98)	0.040
Leucine	91.88 (79.35-113.26)	108.37 (95.55-128.99)	<0.001
Methionine	9.72 (8.07-12.82)	11.10 (10.23-14.47)	0.001
Phenylalanine	55.25 (45.79-77.71)	40.54 (36.46-42.30)	<0.001
Tyrosine	67.40 (52.31-76.82)	56.24 (50.34-70.14)	0.027
Asparagine	97.05 (88.73-123.86)	62.03 (43.74-76.39)	<0.001
Alanine	164.53 (138.52-204.29)	170.58 (144.76-204.57)	0.585
Arginine	46.96 (39.39-72.33)	36.87 (28.47-43.22)	<0.001
Cytosine	38.63 (28.97-46.55)	37.24 (31.49-41.17)	0.096
Glycine	233.81 (191.14-275.62)	196.82 (172.57-247.30)	0.006
Ornithine	106.16 (90.17-129.62)	88.52 (62.75-133.57)	0.035
Glutamine	194.62 (159.61-222.64)	184.66 (174.33-223.44)	0.780

Table 3. Comparison of amino acid profile of the heart failure patients with high and low inflammation status

Variables	High inflammation group (CAR ≥ 0.91) (n = 52)	Low inflammation group (CAR < 0.91) (n = 20)	P
Valine	116.75 (104.88-131.00)	155.57 (139.22-175.87)	<0.001
Leucine	83.65 (74.90-104.12)	98.66 (95.45-115.31)	<0.001
Methionine	9.56 (8.09-13.18)	9.88 (8.06-11.97)	0.821
Phenylalanine	68.68 (48.88-86.22)	43.77 (40.52-47.76)	<0.001
Tyrosine	69.81 (57.00-81.18)	51.89 (48.78-56.30)	<0.001
Asparagine	105.0 (96.0-132.13)	90.83 (78.98-95.41)	<0.001
Alanine	165.41 (138.52-218.02)	156.01 (135.62-167.60)	0.197
Arginine	46.96 (38.86-81.05)	46.86 (41.64-63.73)	0.715
Cytosine	38.91 (28.48-47.80)	38.19 (29.81-43.38)	0.493
Glycine	238.22 (191.17-274.30)	225.25 (189.20-284.13)	0.841
Ornithine	115.31 (95.11-133.23)	88.40 (82.57-104.07)	0.006
Glutamine	194.30 (159.61-222.64)	206.82 (146.27-221.76)	0.815

Correlation analysis was performed to determine the correlation of amino acids with clinical parameters. We found that CAR was positively correlated with phenylalanine, tyrosine and asparagine levels whereas negatively correlated with valine, leucine and methionine levels. In addition, LVEF was positively correlated with valine, leucine and methionine levels whereas negatively correlated with phenylalanine, tyrosine and asparagine levels (**Table 4**).

Table 4. Correlation analysis of amino acids with clinical parameters

	Valine	Leucine	Methionine	Phenylalanine	Tyrosine	Asparagine
CAR	r = -0.221 p = 0.010	r = -0.402 p < 0.001	r = -0.193 p = 0.025	r = 0.454 p < 0.001	r = 0.202 p = 0.018	r = 0.361 p < 0.001
LVEF	r = 0.110 p = 0.203	r = 0.342 p < 0.001	r = 0.264 p = 0.002	r = -0.543 p < 0.001	r = -0.135 p = 0.118	r = -0.469 p < 0.001

Abbreviations: CRP to albumin ratio, LVEF: left ventricular ejection fraction

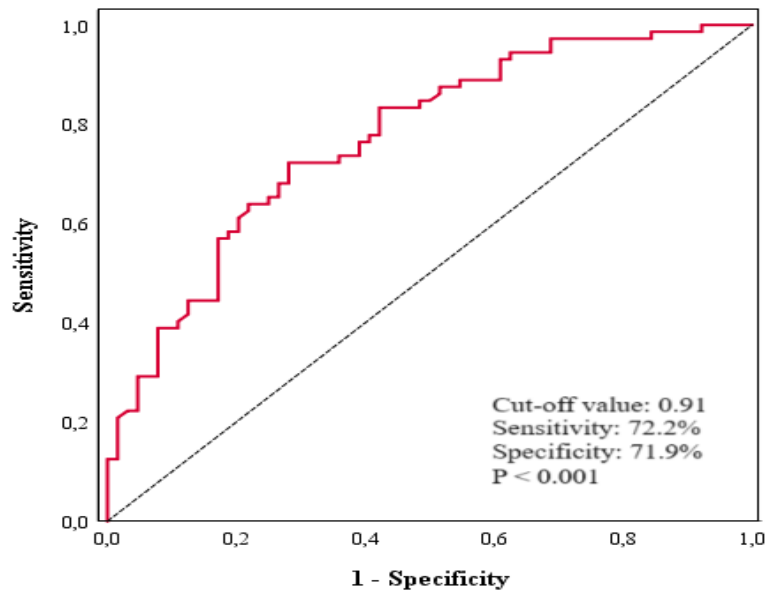


Figure 1. ROC curve analysis to determine the optimal cut-off value of CAR for predicting heart failure

Discussion

In current study, it was aimed to investigate the relationship between inflammation, which is a main pathophysiological process in HF, and AA profile. Main finding of the current study was that the AA profile was impaired in HF patients compared to healthy controls and this impairment was more pronounced in patients with higher inflammation status.

Heart failure is a major public health problem worldwide and its incidence is gradually increasing as life expectancy is prolonged (1,2). Because these patients have poor prognosis, better elucidation of the underlying mechanisms may allow to improve the prognosis in HF. Although there are many factors in the pathophysiology of HF, increased inflammatory response is considered as a major pathophysiological contributor in these patients and has a critical role in the development and progression of heart failure (3-5). CAR has emerged as a novel marker of inflammatory status and its use in daily practice is gradually increased. It reflects the balance between CRP and albumin levels and has found that the combination of these two parameters is more sensitive than CRP and albumin alone (6,7). In this study, we found that HF patients had significantly higher CAR value than healthy controls. This result support the hypothesis of an increased inflammatory response in patients with HF. In addition, recent studies performed in patients with HF have demonstrated that CAR is independently associated with advanced HF, higher hospitalization frequency, severe New York Heart Association (NYHA) classification and may be used to predict mortality in these patients (9,10,15). When all these findings evaluated together, it can be concluded that CAR is an important parameter that can be used in HF patients to predict high risk status.

The heart requires high energy as it pumps blood throughout the body. Fatty acids are the primarily energy sources; however, the metabolism of the substrates' changes dramatically in a failing heart. The primary energy source switches to glucose from fatty acids due to higher anabolic activity and cardiomyocyte energy shortage, and the hearts' dependence on AAs increases during HF (11-13, 16). Because of all these reasons, the metabolism of AAs in patients with HF may be altered. Previous studies showed that AAs profile was significantly changed in patients with HF compared to the controls (13,17,18). In addition, the AAs profile was found to be correlated

with LVEF, HF severity and NYHA classification and a good predictor of prognosis (19,20). Although we could not evaluate the NYHA classification and prognosis, we also found that AAs profile of HF patients was significantly different from the healthy controls and it was showed a significant correlation with LVEF in the current study. Accordingly, it can be concluded that AAs profile is altered in patients with HF and this altered plasma level of AAs are related to the severity of cardiac impairment.

When the change in AA types was analyzed, it was found that valine, leucine and methionine levels decreased, whereas phenylalanine, tyrosine, asparagine, arginine, glycine, ornithine levels increased in patients with HF compared to the healthy controls in our study. Similarly, Liu et al. (21) showed that valine level was lower whereas phenylalanine, tyrosine and ornithine levels were higher in patients with HF compared to the controls. Supporting to these results, it was demonstrated that lower valine, leucine and methionine levels and higher phenylalanine, tyrosine and ornithine levels were associated with poor prognosis in HF patients (22-26). On the other hands, the results obtained in studies evaluating AA levels in patients with HF may differ. Aquilani et al. (13) reported that HF subjects had lower levels of aspartic acid, glutamic acid, cysteine, methionine and taurine compared to healthy subjects whereas did not find significantly increased AAs in HF patients. Saleem et al. (17) found that HF group had significantly higher levels of valine, leucine, isoleucine, tyrosine, phenylalanine, glutamate and asparagine while lower levels of aspartate, methionine, alanine, arginine, lysine, serine, and threonine versus controls. Hakuna et al. (18) observed that HF group had lower amounts of histidine and tryptophan, whereas higher amounts of phenylalanine, tyrosine, asparagine, glycine, ornithine, serine, glutamate, citrulline, cystine and β -alanine compared to controls. The possible reason for these differences in AA levels in the studies may be due to diet and vitamin supplements, because it has been shown that plasma AA concentrations can be affected by these factors (12,27). In our study, we did not investigate these possible confounders. We think that further studies are needed that evaluating the AA profile in HF patients by taking into account diet and vitamin (AAs) supplementation.

Although the AA profile of HF patients has been analyzed in previous studies, the underlying mechanism of impaired AA metabolism has not been investigated in detail. In the present study, the effect of inflammatory response on the impaired AA profile was investigated. Because previous studies showed CAR had a higher accuracy than other conventional parameters (6,7), we used CAR as the inflammatory marker in current study. The optimal cut-off value of CAR for predicting HF was determined by ROC curve analysis, and the study population was divided into two groups according to this cut-off value. Accordingly, HF patients with CAR ≥ 0.91 was defined as the high inflammation group, while patients with CAR < 0.91 was defined as low inflammation group. We observed that AAs profile was significantly altered in high inflammation group compared to low inflammation group, and CAR levels were significantly correlated with the level of these AAs. Supporting to our findings, Chen et al. found that higher phenylalanine levels were correlated with higher C-reactive protein levels and inflammatory cytokines in their recent study (26). According to these results, we speculate that the main mechanism underlying the impaired AA profile in HF may be the increased inflammatory response. Future prospective studies are required to better elucidate the relationship between inflammation and AAs profile in patients with HF.

Study Limitations

The main limitation of our study was the small number of patients. Second, other traditional inflammatory parameters were not analyzed. Third, patients were not followed up for long-term prognosis. Long-term follow-up of the patients and determination of prognosis according to the deterioration in AA profile could have made an additional contribution to our study. Fourth, since some medications, such as statins, are known to have anti-inflammatory properties, they could have had an impact on the study results. However, unfortunately we did not record the medical treatment of the patients. Last, determining the NYHA class and comparing the AAs profile according to this variable could have increased clinical importance of the study.

Conclusion

We found that AAs profile altered significantly in patients with HF compared to healthy controls. In addition, impaired AAs profile was more prominent in HF patients with higher inflammation compared with HF patients with lower inflammation. Therefore, it can be suggested that increased inflammation may be the main mechanism underlying the impaired AA profile in HF patients.

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Ethical Approval: The study was granted permission from the Ethics Committee of Harran University Faculty of Medicine (number: HRU/21.11.19, date: 07.06.2021). Informed consent was obtained from all patients.

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