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Vascular Wall Changes and Arterial Functions in Children with Surgically Repaired Aortic Coarctation

Nilüfer Çetiner[1], Elif Erolu[2], Neslihan Baran Him[3], Berna Şaylan Çevik[4] and Figen Akalın[4]

[1]Department of Pediatric Cardiology, Koç University, Faculty of Medicine, İstanbul, Turkey
[2]Department of Pediatric Cardiology, Koşuyolu Highly Specialized Training and Research Hospital, İstanbul, Turkey
[3]Department of Pediatrics, Marmara University, Faculty of Medicine, İstanbul, Turkey
[4]Department of Pediatric Cardiology, Marmara University, Faculty of Medicine, İstanbul, Turkey

What is already known on this topic?

- *Although coarctation of the aorta is a treatable condition with excellent early surgical results, long-term morbidity may occur despite successful correction.*

What this study adds on this topic?

- *The reasons for the long-term morbidity are multifactorial, including systemic hypertension, increased left ventricle mass index, preoperative pressure gradient, and operation time.*
- *In children and adolescents who have been operated for aortic coarctation, physiological changes in the arteries and structural changes in the arterial wall may lead to the development of atherosclerosis in later ages.*

ABSTRACT

Objective: We investigated arterial functions by measuring carotid–intima–media thickness, flow-mediated dilatation of the brachial artery, and distensibility and stiffness of the abdominal aorta as early indicators of cardiovascular risk in children followed up after coarctation repair.

Materials and Methods: Twenty patients with successful repair of coarctation and 27 healthy children were investigated. Two-dimensional echocardiographic images, and carotid and brachial ultrasound studies were performed.

Results: The ages of the study group ranged from 5.3 to 22 years, and those of the control group from 7 to 17 years. The age at time of surgery was between 0.23 and 257 months. Average follow-up duration after repair was between 11 and 257 months. The stiffness index of the abdominal aorta was significantly higher in patients with coarctation repair than controls (mean = 0.625 ± 0.41, mean = 0.11 ± 0.73; P = .007). Flow-mediated dilatation of the brachial artery in the first minute decreased significantly among the patients (mean = 4.5 ± 2.7, mean = 6.9 ± 4.5; P = .005). Age of the patients had a negative correlation with distensibility of the abdominal aorta (r = −0.572; P = .008) and a positive correlation with stiffness of abdominal aorta (r = 0.566, P = .009).

Conclusion: This study suggested that vascular wall changes in children and adolescents can be seen even after successful coarctation repair and may progress toward overt atherosclerosis at older ages.

Keywords: aortic stiffness index, arterial elasticity, carotid intima–media thickness, coarctation of aorta, flow-mediated dilatation

INTRODUCTION

Coarctation of the aorta (CoA) is a treatable condition with excellent early surgical results. However, previous reports have suggested that long-term morbidity can occur despite successful correction.[1,2] Patients undergoing repair for aortic coarctation are known to be capable of becoming hypertensive at a young age. Systemic hypertension is recognized as a major adverse prognostic factor during rest and exercise.[1,2] Systemic hypertension may develop during long-term follow-up even in the absence of residual or recurrent coarctation. The constancy or repetition of hypertension after correction has been connected to a late operation time, the presence of remaining occlusion, a suboptimal aortic arch form, and ambiguous neuro-humoral mechanisms occurring before correction. In addition, histological abnormalities of the arterial wall, especially cystic medial necrosis, have been

Corresponding author:
Nilüfer Çetiner
✉nilufercetiner@hotmail.com
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demonstrated in patients with coarctation. These arterial wall changes may also cause abnormal hemodynamics and abnormalities of arterial functions even in the peripheral arterial tree, which may lead to early atherosclerosis.[3-8]

Various non-invasive diagnostic methods have been used to evaluate the risk of cardiovascular disease (CVD) in recent years. Adult reports suggest that endothelial dysfunction is one of the earliest indicators of vascular changes at an early stage. Various studies have evaluated endothelial dysfunction by measuring brachial flow-mediated dilatation (FMD).[9,10] Additionally, peripheral arterial elasticity may be a premature marker of atherosclerosis. Aortic distensibility and the stiffness index (SI) have been used in cardiology clinics as a non-invasive method for detecting early atherosclerosis in adults.[11]

Carotid–intima–media thickness (CIMT) has been utilized as a non-invasive procedure for testing premature or subclinical atherosclerotic changes in both children and adults. It has also been utilized as a useful indicator of atherosclerosis for both coronary and peripheral arteries.[12,13]

Despite successful repair at a young age, CoA has been associated with an increased risk of arterial hypertension, early-onset CVD, and premature mortality. Therefore, we aimed to evaluate the arterial functions in children after aortic coarctation repair and determine the risk factors which may be related with impaired arterial functions.

MATERIALS AND METHODS

Patients

This study was conducted in 2014 and 2015 at the Pediatric Cardiology Department outpatient clinics, Turkey. The study group included 20 patients who had undergone successful surgical repair of coarctation between 1993 and 2013 and who were recruited retrospectively. No patients had evidence of re-coarctation at their most recent visit (defined as >20 mmHg pressure gradient by measuring upper and lower limb non-invasive blood pressure). Hypertension was defined as systolic and/or diastolic blood pressure (sBP/dBP) above the 95th percentile of Task Force on Blood Pressure Control in Children reference values. Seven (35%) patients in the study group were hypertensive (6 received antihypertensive drugs). Eleven patients with a bicuspid aortic valve had no important aortic valve stenosis or regurgitation. The control group included 27 gender- and age-matched healthy children consulting the pediatric cardiology outpatient clinics for murmur or atypical chest pain but without any cardiac abnormality found on physical examination or echocardiography. Children with other causes of systemic hypertension, hyperlipidemia, diabetes, obesity, and systemic disease were excluded. Children with more complex congenital heart diseases other than coarctation were also not included. All participants underwent complete physical examination. Physical examination findings, height–weight measures, body mass index (kg/m^2), and SBP–DBP were recorded. Blood pressure was measured with a manual sphygmomanometer by the same physician in all cases. The average of 3 consecutive blood pressure measurements was accepted as the final value. The ethics committee of Marmara University revised and approved this study with the date/decision number of May 02, 2014/09.2014.0061. Patients' legal representatives provided written informed consent for their participation in the study and the usage of their medical records.

Echocardiography

We performed 2D, M-mode, and Doppler studies using a Philips IE33-model echocardiography device (Andover, Md, USA) equipped with a 5-MHz transducer by the same physician in the patients and controls. End-systolic diameter of the left ventricle/end-diastolic diameter of left ventricle (LVEDD), end-diastolic diameter of posterior wall (LVPWDD), left atrial, and aortic root diameters were measured. Systolic functions of LV were computed by the M-mode method. Left ventricular mass (LVM) was computed utilizing the Devereux modified method (LVM ¼ 1.04 [(IVSTd+LVIDd+LVPWTd)^3 – LVIDd^3] – 13.6 g), where IVStd is the interventricular septum end-diastolic thickness, LVIDd is the left ventricular internal dimension at end-diastole, and LVPWTd is the left ventricular posterior wall end-diastolic thickness.[14] The LVM index was calculated by dividing the LVM value from 2.7 degrees by the "height." If the value yielded was greater than 38 g/m$^{2.7}$, this was regarded as left ventricular hypertrophy (LVH). Standard techniques recommended by the American Society of Echocardiography were used for measurements.[15]

Systolic and diastolic diameters of the abdominal aorta at the diaphragm level (in subcostal abdominal long-axis view) were obtained at the peak of the R wave for systolic diameter and end of T wave for diastolic diameter at simultaneously recorded electrocardiograms, and 3 measurements were averaged for each diameter. Abdominal aortic elasticity measures were applied as previously defined by Lacombe et al[16]:

Aortic strain (%) = 100 × (systolic aortic diameter – diastolic aortic diameter)/diastolic aortic diameter;

Aortic distensibility (cm^2 dyn^{-1}) = 2 × (aortic strain)/(aortic pulse pressure).

Aortic SI = ln(systolic pressure/diastolic pressure)/(aortic strain), where systolic and diastolic pressure refer to SBP and DBP of brachial arteries measured in mmHg, respectively.

Brachial Artery Ultrasound Studies

All ultrasound studies were performed with a Philips IE33 echocardiography device equipped with L-11-MHz linear transducer by the same physician in all cases. In order to reduce the effect of external stimuli, all studies were carried out quietly in a temperature-controlled room (24–26°C). The participant laid supine on a couch in that room. Right brachial artery thickness was evaluated from B-mode ultrasound images at rest and during reactive hyperemia. Following 10 minutes' rest, a straight, non-branching segment of the brachial artery above the antecubital fossa was determined and analyzed in longitudinal form. Brachial artery diameter was initially recorded after depth and gain settings were regulated. A pneumatic cuff was then inflated to above 50 mmHg on the upper arm for 5 minutes and then released. After cuff deflation, brachial artery thickness was measured at every 30 seconds for 3 minutes in the end-diastolic phase. Flow-mediated dilatation was calculated as the percentage change in diameter from baseline to the highest value after cuff deflation. The average of 3 sequential measures was adopted as the final measurement.[17]

Carotid Ultrasound Studies

The studies were performed using a Philips IE33 echocardiography machine (Philips Medical Systems) equipped with an L-11-MHz linear transducer by the same physician in all cases as described in the literature.[18] The common carotid artery images used for assessment were obtained while the patient was in a supine position with the head turned to the left. Images were acquired at the end-diastolic phase simultaneously with the tip of R-wave on electrocardiograms. The neck vessel was first shown in a cross-sectional plane, after which the transducer was rotated clockwise to a longitudinal plane. Measurements were obtained when the longitudinal distance of the common carotid artery walls was visible for at least 10 mm on both sides. Measurement of CIMT was performed at the far wall of the common carotid artery. Carotid–intima–media thickness was defined as the distance between 2 bright lines measured edge to edge. An average CIMT value was obtained from 3 separate video-loop measurements.[18,19]

The same echocardiographic measurements were performed in the control group. The difference between the groups for each parameter was subjected to statistical comparisons.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences, version 22.0 software (SPSS Inc.; Chicago,IL, USA). The variables were compared using the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were analyzed with the χ^2 and Fisher's exact tests. Spearman's correlation analysis was used to evaluate the relations between variables. The results were evaluated at a 95% confidence interval, and significance was set at $P \leq .05$.

RESULTS

Patient Characteristics

The study group consisted of 7 (35%) girls and 13 (65%) boys, and the control group of 7 (24%) girls and 23 (76) boys. Patients' ages ranged from 5.3 to 22 years (mean ± SD = 12.6 ± 5) and control group ages ranged from 7 to 17 years (mean ± SD = 12.2 ± 2.5). Operative time ranged from 0.23 months to 257 months (mean ± SD = 62 ± 7, median = 36 months). Mean follow-up time after coarctation repair was between 11 months and 257 months (mean ± SD = 88.92 ± 65.1). End-to-end anastomosis was performed for coarctation repair in 18 patients, the subclavian flap technique was employed in 1 case, and 1 patch aortoplasty in another. The *Z* score for height in the patient group (mean ± SD = −1.19 ± 1.9) was significantly lower than that in the control group (mean ± SD = −0.135 ± 1.3, *P* = .05). Systolic blood pressure in the patient group (mean ± SD = 116.6 ± 18.7 mmHg) was significantly higher than the controls (mean ± SD = 106.7 ± 7.6 mmHg, *P* = .028). Age, height, weight, body mass index (BMI), and diastolic blood pressures did not vary significantly between the 2 groups (Table 1).

Echocardiographic Features

Left ventricular hypertrophy was present in 9 patients (45%) during the postoperative period. Interventricular septal diameter, LVPWDd, and left ventricular mass index (LVMI) were significantly higher in the patient group than in the control group (*P* = .04, *P* = .032, and *P* = .05, respectively). M-mode measurements exhibited no difference in terms of LVEDd, ejection fraction, and shortening fraction between the patient and the control group (Table 2).

Aortic Elasticity Parameters

The *Z* score for the abdominal aorta was higher among the patients than in the controls (*P* = .001). Aortic strain and aortic

Table 1. Clinical Features of the Patients and the Control Group

	Patients (n = 20)	Control (n = 27)	*P*
Female/male	7/13	6/21	.344[a]
Age (years)	12.6 ± 5.0	12.0 ± 2.5	.666[b]
Weight (kg)	39.1 ± 17.95	43.9 ± 1.5	.344[b]
Height (cm)	139.5 ± 19.7	149.0 ± 15.2	.05[b]
Height *Z* score	−1.19 ± 0.9	0.35 ± 1.3	.05[b]
BMI (kg/m^2)	18.8 ± 3.7	19.2 ± 4.2	.79[b]
BMI *Z* score	0.002 ± 1.01	0.0048 ± 0.29	.877[b]
Systolic blood pressure at rest (mmHg)	116.6 ± 18.7	106.7 ± 7.6	.028[b]
Diastolic blood pressure at rest (mmHg)	67.2 ± 7.9	67.3 ± 8.3	.973[b]
Index of systolic blood	0.9 ± 0.11	0.85 ± 0.06	.038[b]
Age of operation (months)	62 ± 7 (0.23–257)		
Follow-up duration (months)	88.92 ± 65.1 (11–254)		
Primary procedure			
End-to-end	18		
Subclavian flap	1		
Patch aortoplasty	1		
Preoperative pressure gradient (mmHg)	67.7 ± 23.2 (30–120)		

SD, standard deviation; F, female; M, male; BMI, body mass index.
[a]Chi-square–Fisher's exact test; [b]Mann–Whitney *U* test.

Table 2. Echocardiographic Characteristics of the Patients and the Control Group

	Patients Group (n = 20)	Control Group (n = 27)	P^a
IVSD (mm)	0.81 ± 0.12	0.72 ± 0.1	.04
LVED (mm)	4.17 ± 0.73	4.08 ± 0.44	.480
LVPWd (mm)	0.82 ± 0.19	0.71 ± 0.14	.032
EF (%)	68.90 ± 6.69	67.8 ± 4.6	.54
SF (%)	38.35 ± 5.07	36,6 ± 3,6	.143
LV mass (g)	91.5 ± 39.4	94.76 ± 22	.830
LVMI (g/cm)	36.5 ± 10.2	32.24 ± 6.2	.05

IVSDd, interventricular septum end-diastolic diameter; LVED, left ventricle end-diastolic diameter; LVPWd, left ventricular posterior wall end-diastolic diameter; EF, ejection fraction; FS, shortening fraction; LV, left ventricle; LVMI, left ventricle mass index.
[a]Mann–Whitney *U* test.

distensibility were lower in the patients, although these differences were not statistically significant ($P = .109$ and $P = .206$, respectively). The aortic SI was higher (mean = 0.625 ± 0.41, mean = 0.11 ± 0.73; $P = .007$) among the patients compared with the healthy children (Table 3).

Carotid Ultrasound Studies

The carotid–intima–media was thicker in the patient group compared to the control group, although this was also not statistically significant ($P = .446$) (Table 3).

Flow-Mediated Dilatation

Flow-mediated dilatation of the brachial artery in the first minute was significantly lower in the patients compared with the healthy children ($P = .05$), but there was no significant difference in terms of dilatation at the third minute ($P = .604$).

Since systemic hypertension is known to occur more frequently in patients operated after 1 year of age, we compared the arterial functions of patients operated before 1 year of age with those operated later. No statistically significant difference was observed between these 2 groups in terms of arterial elasticity, CIMT, or FMD parameters.

We correlated the arterial elasticity parameters, CIMT, and FMD values with age, sex, and follow-up period in the patient group. We discovered a statistically significant correlation of stiffness of abdominal aorta ($r = 0.566$, $P = 0.009$) and distensibility of abdominal aorta with age ($r = -0.572$, $P = .008$) (Figure 1A and B). Arterial elasticity parameters, CIMT, and FMD did not vary significantly between sex and follow-up period.

Table 3. Carotid–Intima–Media Thickness, Abdominal Artery Elasticity Parameters, Flow-Mediated Dilatation of the Brachial Artery, and *Z* Scores of the Abdominal Aorta in the Postoperative Patients and the Control Group

	Patients Group (n = 20)	Control Group (n = 27)	P^a
Z scores (Abd. Aorta)	−0.24 ± 1.12	-1.73 ± 0.63	.001
CIMT	0.58 ± 0.06	0.53 ± 0.06	.446
Aortic strain	10.9 ± 7.4	8.9 ± 8.8	.109
Aortic SI	11.5 ± 8.4	6.2 ± 4.1	.007
Aortic Dis	18.5 ± 6.1	20.9 ± 5.5	.206
FMD (firstmin) (%)	4.5 ± 2.7	6.9 ± 4.5	.005
FMD (thirdmin) (%)	9.2 ± 3.8	9.35 ± 3.9	.604

Abd. Aorta, abdominal aorta; CIMT, carotid–intima–media thickness; SI, stiffness index; Dis, distensibility; FMD, flow-mediated dilatation.
[a]Mann–Whitney *U* test.

DISCUSSION

The present study suggests that postoperative abnormalities in arterial physiology and structural wall changes may be seen even after successful coarctation repair in children and adolescents. The reasons for this can be multifactorial, such as systemic hypertension, increased LVMI, preoperative pressure gradient, operation time, and length of postoperative follow-up.

Previous studies have shown that cardiovascular morbidity and mortality following successful surgical repair of aortic coarctation may occur in the long term after surgery.[1,2] In a study conducted in the early 1990s, the 30-year results after coarctation repair of the patients were examined and revealed that up to 25% of patients could experience death due to complications of hypertensive disease.[20] Left ventricular hypertrophy after correction of coarctation is probably caused by a combination of various factors, such as permanent mild hypertension, increment afterload from small residual gradients, exercise-stimulated gradients or hypertension, bicuspid aortic valve with progressive stenosis, and early coronary disease.[21] Echocardiography in the present study revealed higher diameters of the diastolic interventricular septum, diastolic left ventricular posterior wall, and LVMI values than in the control group. Left ventricular hypertrophy was detected in 45% of the patients. This may be a result of the presence of increased left ventricular afterload in this patient group. The resting arterial blood pressure measurements of patients without re-coarctation showed that 25% had pre-hypertension and 10% had hypertension. The continuity or repetition of hypertension after correction has been associated with the older age at correction, the presence of remaining occlusion, a suboptimal aortic arch shape, ambiguous neuro-humoral mechanisms started before repair, and surgical technique.[22-24] End-to-end anastomosis was performed on 90% of our patients, and patients with re-coarctation were not included. The persistence of arterial hypertension may cause the development of other cardiac complications, such as premature coronary artery disease through intimal proliferation in the coronary arteries and atherosclerosis.[25] In recent years, long observational studies have shown that even after successful CoA repair, patients still suffer from arterial hypertension, atherosclerosis, ischemic heart disease, and chronic heart failure.[7,26,27] Studies in the literature reveal that aortic coarctation is a generalized vascular disease, not a simple mechanical obstruction.[2,27-29]

Aortic stiffness and distensibility have been described as useful parameters for detecting early atherosclerosis in adults using non-invasive methods. The SI of the abdominal aorta increases with hypertension, age, smoking, atherosclerosis, obesity and in patients with β-thalassemia, Marfan syndrome, and Kawasaki disease.[30-32] In the present study, the arterial SI

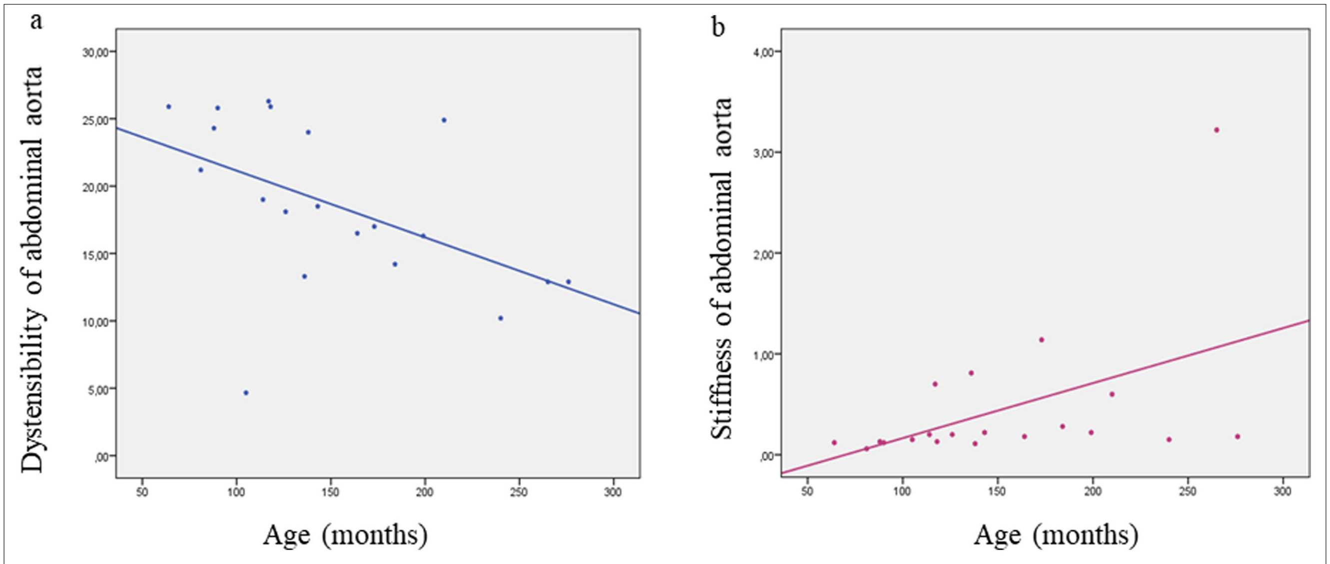

Figure 1. (A,B) Correlations between age and aortic elasticity parameters.

was significantly higher and arterial distensibility was insignificantly lower in the patient group compared to the control group. Another adult study involving 30 postoperative coarctation patients without hypertension and 28 patients with hypertension identified arterial hypertension as a risk factor for increased arterial stiffness.[33] The result from this study may be associated with the patients being younger and the short-term follow-up period. On the other hand, aging is known to have a strong effect on arterial functional properties.[34] Some adult studies reported that the aorta more rapidly stiffens with aging.[35,36] In the present study, similar to some other studies, we found that the distensibility of abdominal aorta was higher and arterial stiffness was lower in the younger group.

Increased CIMT is another marker of atherosclerosis in adults and adolescents. Previous studies have demonstrated that early structural vascular alterations lead to atherosclerosis due to ongoing subclinical inflammation. Most scientists believe that these alterations are outcomes of acute dysfunction of the endothelium and inflammation of the vascular wall.[37-40] Carotid-intima-media thickness has been higher in the patient group compared to the control group in the present study, although the difference was not statistically significant. Previous studies have suggested that CIMT increases with age and the advance of atherosclerosis.[41] However, we could not find a significant correlation between CIMT and age. These results may be associated with the relatively small number of patients and the short-term follow-up period.

Flow-mediated dilatation is an early endothelium-dependent marker of endothelial dysfunction and may be associated with an increased inflammatory process involving the endothelium and a useful indicator of atherosclerosis.[42] Flow-mediated brachial artery dilatation in the first minute decreased significantly in patients with coarctation repair, but FMD decreased insignificantly in the third minute. Cohen et al[2] showed that age at the time of surgical repair was the most significant predictor of hypertension and long-time survival, with the best outcomes analyzed in patients undergoing surgery before the age of 9 years. However, our study showed no relationship between the risk factors such as operation time, age and FMD.

CONCLUSION

This study has certain limitations. The number of children and the postoperative follow-up period were not adequate to evaluate increasing risk of atherosclerotic CVD. Therefore, there is a need for comprehensive studies with larger numbers of patients with longer follow-up periods.

Although successful coarctation repair was efficient in reducing pressure gradient and in controlling systemic arterial hypertension, it may not be able to prevent the structural and functional damage of features of the peripheral arteries, such as arterial stiffness, FMD, and CIMT. This result of arterial elasticity suggested that children exhibit detectable vascular wall changes following coarctation repair, which may start and progress toward overt atherosclerosis at older ages. Close monitoring for systemic hypertension, LVH, and recurrence of coarctation, early medical treatment or timely re-intervention, and elimination of other preventable risk factors for atherosclerotic heart disease will improve long-term results in this patient group.

Ethics Committee Approval: This study was approved by Ethics committee of Marmara University, (Approval No: 09.2014.0061/02.05.2014).

Informed Consent: Informed consent was obtained from the patients' parents who participated in this study.

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