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The association of midlife cardiorespiratory fitness with later life carotid atherosclerosis: Cooper Center Longitudinal Study

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HIGHLIGHTS

- Midlife cardiorespiratory fitness (CRF) is inversely associated with odds of later life carotid artery disease.
- These findings support adherence to physical activity guidelines in middle age.
- Habitual physical activity in middle age may reduce the risk of stroke in later life.

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ABSTRACT

Background and aims: While numerous cross-sectional studies have demonstrated an inverse relationship between cardiorespiratory fitness (CRF) and carotid atherosclerosis in middle age, much less is known about the association of midlife CRF with carotid atherosclerosis in later life.

Methods: We studied 1094 participants, free of cardiovascular disease, who completed a maximal exercise test (GXT) for an objective measure of CRF between ages 40 and 59 and carotid ultrasound after the age of 59, with at least five years between studies. Carotid intima media thickness was measured. Assessments were also made regarding the presence of plaque and percent stenosis in four regions: common carotid, bulb, internal carotid and external carotid arteries. Multivariable logistic regression models were constructed to estimate the association of CRF with carotid artery disease.

Results: At the time of GXT and carotid scan, participants were aged 50.7 ± 5.7 years and 69.3 ± 6.4 years, respectively. Almost half of participants had high midlife CRF (48.6%); 41.3% and 10.1% had moderate and low CRF, respectively. Over a mean follow-up period of 18.6 ± 8.5 years, the odds of having carotid artery disease in later life in the high CRF group was 0.50 (95% CI: 0.29–0.87) compared with the low CRF group. Each 1 MET increase in CRF was associated with 10% lower odds of having carotid artery disease (OR = 0.89, 95% CI: 0.80–0.98).

Conclusions: Midlife CRF was inversely associated with carotid artery disease measured almost two decades later. This may represent a mechanistic link between high midlife CRF and reduced risk of stroke in later life.

Abbreviations: CRF, cardiorespiratory fitness

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1. Introduction

Given that the progression of atherosclerosis occurs over decades, and typically manifests as overt clinical disease in late life, there has been considerable interest in the impact of mid-life risk factors on the development of atherosclerotic CVD later in life. For example, DeFina et al. found that higher midlife CRF (assessed quantitatively with gated treadmill stress testing) was associated with reduced risk of developing dementia later in life (independent of prior stroke history) in more than 19,000 participants followed prospectively in the Cooper Center Longitudinal Study cohort with median follow-up of 25 years [1]. Using the same cohort, Panday et al. demonstrated a strong, inverse association between midlife CRF and stroke risk in later life independent of baseline and antecedent burden of risk factors, such as hypertension, diabetes mellitus, and atrial fibrillation [2]. Hussain et al. evaluated 14,000 local residents referred to a single center with clinical indications for treadmill stress testing and found that higher CRF was associated with a lower risk of incident stroke, and mortality in the presence or absence of atrial fibrillation with median follow-up of 14 years [3].

These studies have demonstrated that the beneficial impact of midlife CRF on stroke in later life is independent of antecedent risk factors such as hypertension, diabetes or atrial fibrillation. Thus benefit of high CRF on later life stroke does not appear to be mediated through its impact on traditional risk factors for stroke. While numerous cross sectional studies have reported significant association between CRF and carotid atherosclerosis among middle-aged adults [4–6], our study is the first to specifically test the hypothesis that midlife CRF is inversely associated with the development of carotid atherosclerosis in later life.

2. Materials and methods

2.1. Study design, setting, and participants

The Cooper Center Longitudinal Study (CCLS) is an observational database of patient visits to the Cooper Clinic in Dallas, Texas, a preventive medicine practice that began in 1970. CCLS participants are community-dwelling, generally healthy persons who are either self-referred or referred by their employers for preventive health examinations. Since 1970, more than 100,000 individuals have been evaluated with extensive medical and lifestyle behavior histories, physical examinations, laboratory studies, treadmill exercise tests, and additional tests depending on the year of examination. Data collected at the Cooper Clinic and captured in the CCLS database are not based on a systematic research protocol but rather on the previously mentioned clinical practices and patient-specific physician recommendations. Beginning in 2011, a screening carotid ultrasound scan was included as a routine part of the preventive medical examination in self-referred patients ages 60–65; this test could also be ordered on younger patients or prior to 2011 at the physicians' discretion. Approximately 3600 participants completed carotid ultrasound screening between 2011 and 2016 (which may have been a first visit or a return visit). Participants provided informed consent for the use of their data for research. The CCLS database is maintained by The Cooper Institute, a nonprofit, independent research institute with the overarching research goal of assessing the effect of lifestyle behaviors on health outcomes. The data collection and informed consent processes are reviewed and approved annually by the Institutional Review Board at The Cooper Institute.

The study cohort was comprised of 1094 participants between the ages of 40–59 years who were free of cardiovascular disease (CVD) and had an examination with a completed a normal graded maximal exercise test (GXT) (baseline visits from 1971 to 2011) and second examination with a carotid screening ultrasound after the age of 60 years with at least five years between these two visits. Participants were excluded if they had a clinically positive GXT (chest pain, EKG abnormalities) or a submaximal GXT (did not reach at least 85% of age-predicted maximal heart rate).

2.2. Data collection

Each participant underwent comprehensive clinical evaluation that included an extensive medical history questionnaire (self-reported but verified by their doctor) with questions about medical diagnoses, health behaviors, family medical history and medication use as well as 12-h fasting blood chemistry assay, body composition assessment, blood pressure measurement, physical examination and graded maximal exercise test for an objective measure of CRF. The screening carotid ultrasound was conducted on the same day as the clinical examination. All examination procedures were administered by physicians or trained technicians following standardized measurement protocols at the Cooper Clinic.

2.2.1. Exposure: cardiorespiratory fitness (CRF)

CRF was assessed by graded maximal exercise treadmill test using a modified Balke protocol. For the first 25 min, the treadmill speed was set at 90 m/min (3.3 mile/hour) and the grade was 0% for the first minute and 2% at the second minute; the treadmill grade increased by 1% each minute thereafter. After 25 min, the grade remained unchanged while the speed increased by 5.4 m/min (approximately 0.2 mile/hour) each minute until participants are completely exhausted.

Age and sex specific distributions of maximal treadmill test duration were used in analysis, where each individual's treadmill time was classified into an age- and sex-specific quintile of fitness. These quintiles of fitness measures were then combined into 3 mutually exclusive fitness groups: low (quintile 1), moderate (quintile 2 and 3), and high (quintile 4 and 5), which are consistent with previous CCLS research [7].

2.2.2. Outcome: atherosclerotic carotid artery disease

A carotid ultrasound was performed using the General Electric LOGIQ E9 (LE9) scanner. The vascular ultrasound technician then obtained bilateral gray scale and color images of the common carotid artery (CCA) and carotid bulb. Ultrasound recordings were stored to a picture archiving and communication system (PACS). Patients were scanned at a standard depth of 3.6 cm with typical pixel size of 0.10 mm. Measurement of the carotid IMT was performed using semi-automated edge-detection algorithms with B mode measurements averaged over at least 1 cm segments in the posterior wall of the CCA within 1–2 cm of the carotid bulb in anterior, lateral and posterior probe orientation angles. For CIMT measurement, mean carotid IMT across all measured segments for right and left sides was reported. The presence of plaque was defined as protrusion into the lumen, loss of alignment with adjacent arterial wall boundary, and brighter echoes than adjacent boundaries. Clinically, peak systolic velocity measurements were reported only in cases of 50% stenosis or greater and are not included in this study. The validity of carotid IMT measurement of the posterior wall is deemed to be closely related to the true biological thickness of the wall of the carotid artery [8–10]. Additionally, intraclass coefficient (ICC) of carotid IMT measurement between studies showed that the ICC ranges between 0.80 and 0.95 indicating high reliability of carotid IMT measurement [11–13]. Carotid Artery Disease was defined as carotid IMT greater than 1.2 mm or greater than 30% blockage of any measured sites of carotid artery including CCA, carotid bulb, internal carotid artery (ICA), and external carotid artery (ECA) and further dichotomized into absence or presence [6].

2.2.3. Covariates

Age, sex, and reported physical activity were obtained through the standardized medical history questionnaire. While the use of these medications was used to define the presence of hypertension or abnormal cholesterol level, adjustment for the presence or absence of these medications could not be performed in the various models because information on the use of statin and/or anti-hypertensive medications was available in 53% of the study group and the baseline visit on some participants pre-dated the FDA approval of many of these drugs (1987 for the first stain drug, 1981 for the first ACE-inhibitor). Height and weight were measured using a stadiometer and a calibrated scale, respectively, by trained staff at the Cooper Clinic. Blood pressure was measured with a mercury sphygmomanometer according to standard clinic procedures. Following a 12-h fast, venous blood samples were obtained for plasma levels of total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-c), and glucose at the Cooper Clinic laboratory. Low density lipoprotein cholesterol (LDL-c) was estimated using the Friedewald equation [14]. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of any antihypertensive medication. BMI was calculated from height and weight measured during the clinic visit. BMI was calculated by dividing body weight in kg by height in meters squared and participants were categorized as normal weight (< 25 kg/m^2), overweight (≥25 to < 30 kg/m^2), and obese (≥30 kg/m^2).

Diabetes status was classified as normal if 12-h fasting glucose level < 100 mg/dL, impaired if 12-h fasting glucose level ≥100 mg/dL or < 126 mg/dL, and diabetes if 12-h fasting glucose level ≥126 mg/dL. Total cholesterol:HDL-c ratio was categorized into normal if Total cholesterol:HDL-c < 4.5 (men) or < 4.0 (women) and no reported use of statin therapy.

Physical activity is estimated based on the frequency, duration and intensity for various activities listed in the medical history questionnaire. These activities include walking, jogging or running, treadmill, bicycling, stationary cycle, swimming, aerobic dance or floor exercise and vigorous activity (e.g., racquetball, singles tennis, skating, basketball, soccer). Frequency and duration information was converted to minutes of activity per week which is then weighted per activity by multiplying by an estimated MET value derived from the Compendium of Physical Activities and then summed across all activities allowing each participant to be categorized according to their MET-minutes of physical activity per week (MET-minutes/week) [15].

2.3. Statistical analysis

SAS 9.4 statistical software (SAS Institute Inc., Cary, NC) was used to conduct the data management and analysis to address the study hypotheses. The Kolmogorov-Smirnov test was used to check the assumption of normality. Categorical variables were reported as frequencies and proportions and continuous variables were reported as means ± (SD). Characteristics of participants overall and by CRF groups were examined using Mann-Whitney *U* test for non-normally distributed continuous variables, and chi-square test for categorical variables.

To assess the association between midlife CRF and carotid artery disease in later life, univariate and multivariate logistic regression models were constructed as follows: 1) model 1, unadjusted model, 2) model 2, model 1 plus age and sex, 3) model 3, model 2 plus physical activity, 4) model 3 plus CVD risk factors including BMI, hypertension, total cholesterol:HDL-c ratio, diabetes, and follow-up time. Covariates were selected from the literature based on observed associations with the exposure and/or outcome variables [16]. For each regression model, the odds ratio (OR) with 95% confidence interval (CI) was reported.

3. Results

3.1. Participant characteristics by CRF groups

The baseline characteristics of participants overall and by CRF groups (low *vs.* moderate *vs.* high) are shown in Table 1. Among 1094 participants included in the analytic sample, 110 participants (10.1%) had low midlife CRF, 452 participants (41.3%) had moderate CRF, and the remaining 532 participants (48.6%) had high CRF. Overall, the average age of the analytic sample at the time of CRF assessment was 50.7 ± 5.7 years and the majority were male (74.5%). The mean follow-up period between exposure and outcome assessment was 18.6 ± 8.5 years. When examining differences in characteristics by CRF groups, statistically significant differences were noted. Compared to the moderate and high fit groups, those classified as low CRF were older, had a higher BMI, were more likely to be hypertensive, or diabetic, and had lower reported physical activity categories. The low CRF group also showed unfavorable metabolic profile including HDL-c, triglycerides, and percentage of normal total cholesterol:HDL ratio and impaired fasting glucose level. No other statistically significant differences by midlife CRF groups were noted.

3.2. Carotid ultrasound measures by CRF groups

The carotid scan measures by CRF groups are shown in Table 2. Participants with moderate or high CRF had significantly lower mean carotid IMT when compared to individuals classified as low CRF. However, no other statistically significant differences were found.

3.3. The association of CRF with carotid atherosclerosis

Overall, statistically significant inverse associations between midlife CRF and later life carotid artery disease were noted (Table 3). After adjustment for age and sex (model 2), participants with high CRF had 40% lower odds of having atherosclerotic carotid artery disease compared with those with low CRF. The association remained statistically significant after further adjustment for physical activity and in fully adjusted model after additional adjustment of BMI, hypertension, total cholesterol:HDL-c ratio, diabetes, and follow-up time. Similar to the observed associations shown with the categorical CRF, significant associations between continuous CRF, expressed per 1 MET increase in CRF and carotid artery disease were observed (Table 3, $p < 0.05$). Specifically, per 1 MET increase in CRF was associated with the 10% lower odds of having carotid artery disease after adjustment for age, sex, and physical activity. The association remained significant after further adjustment for CVD risk factors including BMI, hypertension, and total cholesterol:HDL-c ratio, diabetes, and follow-up. We also examined the association between CRF and carotid IMT as a continuous variable. CRF was log-transformed before analysis because it was skewed and not normally distributed. Multivariable linear regression models were used to adjust for same covariates as we did in logistic regression. In all models, log-transformed CRF was inversely associated with carotid IMT expressed as continuous variable (Supplementary Table 1).

4. Discussion

Atherosclerotic CVD is still the leading cause of death in the U.S. despite considerable improvement in treatment and preventive strategies [17]. Cardiorespiratory fitness, determined in large measure by physical activity, has been shown to be inversely associated with cardiovascular disease events including fatal and non-fatal myocardial infarction and fatal and non-fatal stroke [18]. Participation in a consistent exercise program is a critical component of lifestyle modification for primary and secondary prevent of atherosclerotic CVD.

4.1. The association between midlife CRF and carotid artery disease in later life

Numerous cross sectional studies have reported significant association between CRF and carotid atherosclerosis among children [19,20], middle-aged adults [4–6], and middle-aged men with hypertension [21]. Lakka et al. assessed progression of carotid IMT over a four year period in 854 Finnish men with an objective measure of CRF and found that low CRF was associated with greater increase in carotid IMT [22]. To our knowledge, ours is the first study to specifically

Table 1
Baseline characteristics (between age 40 and 59 years) overall and by CRF groups for this study cohort of 1094 participants from the Cooper Center Longitudinal Study (CCLS).

Participant characteristic	CRF levels				
	Total (n = 1094)	Low (n = 110)	Moderate (n = 452)	High (n = 532)	*p* value
Age[a]	50.7 ± 5.7	53.3 ± 5.6	51.7 ± 5.3	49.4 ± 5.6	< 0.001
Sex, n (Male %)	815 (74.5)	79 (71.8)	346 (76.6)	390 (73.3)	0.404
Race/ethnicity (White), n (%)	1027 (96.5)	100 (93.5)	425 (96.4)	502 (97.3)	0.141
BMI (kg/m^2)[a]	25.8 ± 3.7	28.8 ± 4.9	26.7 ± 3.4	24.4 ± 2.8	< 0.001
Hypertension, n (%)	313 (28.7)	50 (45.5)	151 (33.4)	112 (21.1)	< 0.001
Diabetes, n (%)	26 (2.4)	9 (8.2)	13 (2.9)	4 (0.8)	< 0.001
HDL-c (mg/dL)[a]	53.7 ± 16.0	51.5 ± 16.7	50.5 ± 15.6	56.9 ± 15.7	< 0.001
LDL-c (mg/dL)[a]	127.1 ± 34.6	128.8 ± 30.1	126.8 ± 36.4	127.1 ± 34.0	0.629
Triglycerides (mg/dL)[a]	119.5 ± 77.2	149.3 ± 100.8	135.7 ± 86.0	99.6 ± 55.7	< 0.001
Total cholesterol (mg/dL)[a]	204.8 ± 38.0	210.8 ± 35.8	204.8 ± 40.1	203.7 ± 36.5	0.096
TC:HDL-c (normal), n (%)	651 (59.5)	47 (42.7)	228 (50.4)	376 (70.7)	< 0.001
Fasting glucose, (mg/dL)[a]	99.4 ± 16.2	106.3 ± 21.7	100.5 ± 19.0	97.0 ± 10.9	< 0.001
Physical activity (MET·min/week)[a]	809.5 ± 1004.4	276.0 ± 501.2	604.5 ± 841.5	1093.9 ± 1117.1	< 0.001
VO_2max (ml/kg/min)[a]	36.6 ± 9.9	26.0 ± 7.3	33.5 ± 7.6	41.5 ± 9.3	< 0.001
Average follow-up	18.6 ± 8.5	15.8 ± 8.7	17.0 ± 8.4	20.4 ± 8.3	< 0.001

CRF, cardiorespiratory fitness; BMI, body mass index; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein; TC, total cholesterol; MET, metabolic equivalent of task.
[a] Mean ± standard deviation.
[b]Race/ethnicity was categorized into White and Other.
[c]Normal total cholesterol:HDL ratio is defined as < 4.5 mg/dL for men and < 4.0 mg/dL for women.
Re: Mann-Whitney *U* test was used for non-normally distributed continuous variables and chi-square test was used for all other categorical variables.

Table 2
Carotid ultrasound measures by CRF groups for this study cohort of 1094 participants from the Cooper Center Longitudinal Study (CCLS).

	Total (n = 1094)	Low (n = 110)	Moderate (n = 452)	High (n = 532)	*p* value
Plaque (n, %)[a]					
CCA	67 (5.9)	10 (9.1)	23 (5.1)	31 (5.8)	0.276
Bulb	521 (47.6)	55 (50.0)	213 (47.1)	253 (47.6)	0.863
ICA	218 (19.9)	22 (20.0)	88 (19.5)	108 (20.3)	0.948
ECA	66 (6.0)	5 (4.6)	24 (5.3)	37 (7.0)	0.440
Stenosis (n, %)[b]					
0–29%	510 (65.4)	49 (59.0)	221 (64.7)	250 (67.4)	
≥30%	270 (34.6)	34 (41.0)	115 (35.3)	121 (32.6)	0.333
Mean carotid IMT, mm	0.78 ± 0.16	0.83 ± 0.19	0.77 ± 0.16	0.77 ± 0.16	0.007
Carotid artery disease (n, %)[c]	280 (25.4)	35 (31.8)	119 (26.3)	126 (23.7)	0.184

CRF, estimated cardiorespiratory fitness; CCLS, Cooper Center Longitudinal Study; CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery; IMT, intima media thickness.
[a] Plaque was defined as any type of plaque in each measurement site on both sides.
[b] Higher percent of blockage was taken from both anatomical sides and stenosis was defined as ≥30% or < 30%.
[c] Carotid artery disease was defined as carotid IMT greater than 1.2 mm or greater than 30% blockage of any measured sites of carotid artery.

examine the association between midlife CRF and carotid atherosclerosis in later life.

We report several important findings. First, in an analysis of CRF as a categorical variable, participants with high CRF during midlife had 50% lower odds of having carotid artery disease in later life after adjustment for age, sex, physical activity, BMI, hypertension, total

Table 3
The independent association of midlife CRF with later-life carotid artery disease for this study cohort of 1094 participants from the Cooper Center Longitudinal Study (CCLS).

	Cases (%)	Model 1	Model 2	Model 3	Model 4
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Continuous CRF					
Per 1 MET increase in CRF	280 (25.6)	1.03 (0.98–1.08)	0.93 (0.86–1.01)	0.90 (0.82–0.98)	0.89 (0.80–0.98)
CRF categories					
Low	35 (31.8)	Reference	Reference	Reference	Reference
Moderate	119 (26.3)	0.77 (0.49–1.20)	0.76 (0.48–1.22)	0.72 (0.45–1.15)	0.70 (0.43–1.15)
High	126 (23.7)	0.67 (0.43–1.04)	0.60 (0.38–0.96)	0.52 (0.32–0.85)	0.50 (0.29–0.87)

CRF, cardiorespiratory fitness; OR, odds ratio; CI, confidence interval; MET, metabolic equivalent of tasks.
CRF was classified as low (quintile 1), moderate (quintile 2 and 3), and high (quintile 4 and 5) based on maximal test duration.
Model 1, unadjusted model; Model 2, model 1 plus age, sex; Model 3, Model 2 plus physical activity; Model 4, Model 3 plus BMI, hypertension, total cholesterol:HDL-c ratio, diabetes, and follow-up time. Carotid artery disease was defined as carotid IMT greater than 1.2 mm or greater than 30% blockage of any measured sites of carotid artery.

cholesterol:HDL-c ratio, diabetes, and follow-up time. Second, in an analysis of CRF as a continuous variable, we found that each 1 MET increase in midlife CRF was associated with 11% lower odds of having carotid artery disease after full adjustments for covariates. Finally, midlife CRF was inversely associated with CIMT analyzed as a continuous variable.

The protective association between high CRF and carotid atherosclerosis could be explained by improvement in CVD risk factors. CRF has also been shown to be inversely related to development of individual and clustered cardiovascular risk factors; these associations have been demonstrated in young and old, healthy and unhealthy, men and women and in different racial/ethnic groups. In our study, the inverse association of CRF with carotid artery disease persisted after adjustment for age, sex, physical activity, BMI, hypertension, total cholesterol:HDL-c ratio, and diabetes.

4.2. Study limitations

There are limitations that should be considered when interpreting the findings from the current study. CRF was measured by estimated treadmill test, not by directly measured peak oxygen uptake, which is the most widely accepted index of CRF. However, the previous study demonstrated high correlation with directly measured peak oxygen uptake ($r = 0.92$) [23]. All known risk factors for the development for carotid atherosclerosis not measured in our study cohort such as insulin resistance [24], systemic inflammation [25] or visceral fat [26] and thus could not be adjusted for. Lastly, the majority of CCLS participants are highly educated (Some college or more: 89.4%) and non-Hispanic White male (White: 97.4% and Male: 72.5%, respectively) in middle or upper socioeconomic levels, which may influence generalizability. These findings need to be confirmed in longitudinal cohorts of men and women and in different racial/ethnic groups.

4.3. CRF as a tool for prevention

In the current study, midlife CRF, assessed categorically and continuously, was inversely associated with later life atherosclerotic carotid artery disease in a well-characterized study cohort with objective measure of fitness. This study has important implications in terms of disease prevention in older age. First, these findings serve to reinforce recent American Heart Association scientific statements have vigorously promoted the concept of CRF as a vital sign to be included in routine clinical practice [27]. Because treadmill stress testing in the primary care setting is resource prohibitive, national experts must develop a surrogate tool for assessing CRF so that primary care providers can measure and follow CRF in their individual patients. Second, given that CRF is determined in large part by habitual physical activity, these findings should motivate middle age adults to initiate or continue a program of regular exercise. Ideally, they should adhere to the 2018 Physical Activity Guidelines for Americans adults should do at least 150–300 min per week of moderate intensity physical activity, or 75–150 min per week of vigorous intensity physical activity, or an equivalent combination of moderate or vigorous intensity physical activity. Also, aerobic activity should be spread throughout the week [28]. These findings are in important reminder that CVD prevention is still an achievable goal in middle age.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

JL analyzed and interpreted the data and drafted the manuscript; BC contributed to the data analysis; KPG conceived, designed and supervised the research; CEB, NBR, and LFD acquired the data; BC, HWK III, CEB, CL, NBR, LFD, and KPG provided critical revision of the manuscript; All authors reviewed and approved the final manuscript as submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.009.

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