Original Article

Measuring Procedure and Maximal Hyperemia in the Assessment of Fractional Flow Reserve for Superficial Femoral Artery Disease

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Aim: The optimal fractional flow reserve (FFR) measurement method for superficial femoral artery (SFA) lesions remains to be established. We clarified the optimal measuring procedure for FFR for SFA lesions and investigated the necessary dose of papaverine for inducing maximal hyperemia in SFA lesions.

Methods: Forty-eight patients with SFA lesions who underwent measurement of peripheral FFR (pFFR: distal mean pressure divided by proximal mean pressure) after endovascular treatment by the contralateral femoral crossover approach were prospectively enrolled. In the pFFR measurement, a guide sheath was placed on top of the common iliac bifurcation and pressure equalization was performed. After advancing the pressure wire distal to the SFA lesion, sequential papaverine administration selectively to the affected common iliac artery was performed.

Results: There were no symptoms, electrocardiogram changes, and significant pressure drops at the guide sheath tip with increasing papaverine dose. pFFR changes following 20, 30, and 40 mg of papaverine were 0.87 ± 0.10 , 0.84 ± 0.10 , and 0.84 ± 0.10 , respectively ($P < 0.001$). Although not significantly different, pFFR decreased more in several patients at 30 mg of papaverine than at 20 mg. The pFFR at 40 mg of papaverine was almost similar to that at 30 mg of papaverine. The necessary papaverine dose was not changed according to sex and number of run-off vessels.

Conclusions: The contralateral femoral crossover approach is useful in FFR measurement for SFA lesions, and maximal hyperemia is induced by 30 mg of papaverine.

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Key words: Fractional flow reserve, Peripheral arterial disease, Superficial femoral artery

Introduction

The efficacy of endovascular treatment (EVT) using a self-expandable nitinol stent for superficial femoral artery (SFA) lesions compared with balloon angioplasty has been widely supported by clinical data¹⁻³). However, restenosis still remains as a major problem in the chronic phase⁴), and drug-eluting stents

or drug-coated balloons have been developed to resolve this issue^{5, 6}). We gauged that the stages of advances in the treatment strategy have been similar between SFA lesions and coronary artery disease (CAD), which initially started with the use of balloon dilatation, followed by bare-metal stents, and then drug-eluting stents. Thereafter, fractional flow reserve (FFR) emerged as an important alternative treatment strategy. FFR may subsequently become a useful tool for the treatment of peripheral artery disease (PAD) as FFR is useful for the treatment of CAD. For CAD treatment, measurement of FFR to assess the functional severity of the stenosis has well been established⁷⁻¹⁰). In CAD treatment, FFR-guided percutaneous coronary intervention (PCI) was found to be superior to angi-

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ography-guided PCI in terms of mortality and myocardial infarction at 2 years¹¹). Moreover, post-stenting FFR was an independent predictor of repeat target vessel revascularization at 6 months¹²). However, despite the fact that FFR measurement for CAD treatment is useful for indicating coronary stenting and evaluating whether the stenting is optimal, there are very few studies elucidating the efficacy and clinical application of FFR measurement for the treatment of SFA lesions. The FFR measuring procedure for CAD in terms of the necessary dose, drug type, and administration method to induce maximal hyperemia has been well investigated^{13, 14}). However, the optimal measuring procedure and the maximum vasodilator dose needed to induce maximal hyperemia remain unknown in the case of FFR evaluation for SFA lesions. The main aim of this study was to preliminarily clarify the optimal FFR measuring procedure for SFA lesions and identify the needed papaverine dose that induces maximal hyperemia in SFA lesions.

Materials and Methods

Study Population and Study Design

This research was a single-center, prospective, non-randomized study. The study population consisted of 45 patients who underwent FFR measurement for 48 SFA lesions after EVT. They were enrolled in this study from February 2013 to September 2014. The exclusion criteria were as follows: 1) patients with aneurysm or stenosis in the aorta or iliac artery; 2) patients with congestive heart failure (New York Heart Association functional class III-IV); 3) patients with severe pulmonary hypertension as shown by ultrasound cardiography; 4) patients with no run-off vessel. Patients who were previously treated by stent implantation for iliac artery disease with no restenosis were included in this study. All patients had a baseline physical evaluation, ankle-brachial index measurement, duplex ultrasound, and angiography before the EVT. The severity of SFA lesions were assessed using the TransAtlantic InterSociety Consensus (TASC) II classification¹⁵). The indication for EVT was decided after consulting with vascular surgeons, particularly for TASC II type C and D lesions. The general indication of EVT for SFA lesions was >70% diameter stenosis as demonstrated by angiography in patients with claudication or critical limb ischemia which affected the quality of life despite exercise and medication. All patients provided informed consent for the procedure and subsequent data collection. The study protocol was in accordance with the Declaration of Helsinki and approved by our institu-

tional review board.

Endovascular Intervention

Determination of the EVT strategy was left to each operator's discretion. EVT was performed under local anesthesia, and all cases were treated using an antegrade approach through the contralateral common femoral artery. A 6-Fr guide sheath (6-Fr Sheath Less PV: Asahi Intecc, Tokyo, Japan; or 6-Fr Destination: Terumo, Tokyo, Japan) was used and a bolus of 5000 U of heparin was administered intravenously after sheath insertion. A 0.014-inch wire was advanced into the SFA lesion. Balloon angioplasty using a balloon with a diameter 1–2 mm less than the reference diameter as assessed by intravascular ultrasound (IVUS) was performed for 120–180 s. If the patients had a residual diameter stenosis of >30%, and/or flow-limiting dissection after balloon angioplasty, a self-expandable stent was implanted. Dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was started at least 1 week before the intervention and continued for ≥ 1 month thereafter.

FFR Measurement

After the EVT, FFR was measured using the contralateral antegrade approach in 48 lesions (45 patients). No slow flow phenomenon was observed after EVT in this study. Of these lesions, FFR was successfully measured in 44 SFA lesions (41 patients) (91.7%). Measurement failure was caused by the inability to advance the pressure wire distal to the SFA lesion because of the severe angulation of the common iliac bifurcation and the severe tortuosity of the iliac artery. Pressure measurement did not induce any complications in all the patients.

The problem with FFR measurement using the contralateral antegrade approach was that the pressure at the tip of the guide sheath could decrease because the 6-Fr guide sheath occupied some part of the lumen of the iliac artery and decreased the blood flow and arterial pressure in 5 cases. **Fig. 1** shows a representative case of this problem. Angiography showed no stenosis in the common and external iliac artery; however, systolic blood pressure at the tip of the guide sheath increased from 178 mmHg to 198 mmHg when the tip of guide sheath was pulled back from the external iliac artery to the proximal common iliac artery. FFR measurement using a complete crossover guide sheath was therefore thought to be an incorrect method, thus FFR measurement was performed using a different original method. **Fig. 2** shows a summary of our original method for measuring FFR. This case was treated for a right SFA lesion using the contralat-

Fig. 1. Changes in pressure at the tip of the guide sheath when it is pulled back to the proximal common iliac artery.

A: The arrow shows the tip of the guide sheath located at the external iliac artery.

B: After pulling back the guide sheath, the arrow shows the tip of guide sheath located at the proximal common iliac artery.

C: The pressure at the tip of the guide sheath is gradually increased when the guide sheath is pulled back.

eral crossover approach. A 6-Fr guide sheath was inserted via the left common femoral artery and the tip of the crossover guide sheath was located at the right common femoral artery. EVT was administered for the right SFA lesion under this guide sheath position. After the treatment, the 6-Fr guide sheath was pulled back to the terminal aorta immediately above the iliac bifurcation. Then, a 0.014-inch pressure wire (Aeris G8 300 cm, St. Jude Medical Inc., St. Paul, MN, USA) was advanced to the tip of the guide sheath and pressure was equalized at the descending aorta immediately above the iliac bifurcation (**Fig. 2A**). Thereafter, the pressure wire was advanced distal to the SFA lesion, if needed with guidance of a 4-Fr microcatheter which has a small curve on the tip (4-Fr Fransac®, Terumo Clinical Supply Co., Ltd., Gifu, Japan; or 4-Fr Seiha, Medikit, Tokyo, Japan) (**Fig. 2B, 2C**). A 4-Fr catheter was then inserted into the 6-Fr

guide sheath and the tip was turned to the affected common iliac artery, and 20 mg of papaverine was selectively injected from the ostium of the common iliac artery (**Fig. 2D**). After confirmation of the return of pressure to the baseline value, we additionally injected papaverine at 30 mg and then at 40 mg. A previous study administered 20 mg to induce maximal hyperemia for iliac lesion; however, incremental dose administration of papaverine was not performed¹⁶⁾. Therefore, we performed incremental administration of papaverine (20 mg, 30 mg, and 40 mg) in the present study to determine the optimal dose. After the injection of 40 mg of papaverine, the pressure wire was withdrawn to the proximal site of the treated SFA lesion and then to the tip of the guide sheath and pressure equalization was reconfirmed. The pressures at the tip of guide sheath and pressure wire were continuously recorded and digitally stored.

Fig. 2. Original measuring procedure for peripheral FFR for SFA lesions using the crossover approach.

A: Equalization of pressure at the tip of the guide sheath at the descending aorta immediately above the iliac bifurcation.

B, C: Advancement of the pressure wire to the distal SFA lesion.

D: Selective injection of papaverine via a 4-Fr catheter which has a small curve on the tip. The arrow shows the tip of the 4-Fr catheter turning to the affected common iliac artery.

Definitions

We measured peripheral FFR (pFFR) defined as the distal mean pressure divided by the proximal mean pressure. Procedural success was defined as a residual stenosis of $<30\%$ and the absence of a flow-limiting dissection on angiography. The number of run-off vessels was assessed on angiography after the EVT. Non-ambulatory status was defined as bed-ridden or wheelchair use as the patients cannot walk by themselves even with the aid of a cane or a circular walker. Patients who used a wheelchair because of wound pain were not considered to have a non-ambulatory status. Hypertension was defined as a casual blood pressure $\geq 140/90$ mmHg or the current use of antihypertensive drugs. Diabetes mellitus indicated treatment with insulin or oral hypoglycemic drugs, or a casual plasma glucose level >200 mg/dL or HbA1c $>6.5\%$. Dyslip-

idemia was defined as a fasting serum low-density cholesterol level ≥ 140 mg/dL, a high-density cholesterol level <40 mg/dL, a triglyceride level ≥ 150 mg/dL, or the use of cholesterol-lowering agents.

Statistical Analysis

Categorical variables were expressed as percentage and continuous variables were expressed as mean $\pm$ standard deviation. Comparisons of the pFFR values, and changes in systolic and diastolic pressure at the tip of the guide sheath according to the different papaverine doses were tested by one-way analysis of variance. Multiple comparisons were performed using Tukey's honest significant difference test. A two-sided P -value of <0.05 was considered to indicate a statistically significant difference. All analyses were performed using SPSS software (version 19; IBM Corporation, Somers,

Table 1. Patient characteristics (44 lesions and 41 patients)

Variable	
Age, years	74 ± 10
Sex, male (%)	24 (58.5)
BMI, kg/m ²	22.9 ± 3.2
Hypertension (%)	37 (90.2)
Diabetes mellitus (%)	22 (53.7)
Insulin use (%)	10 (24.4)
Dyslipidemia (%)	17 (41.5)
Hemodialysis (%)	11 (26.8)
Current smoker (%)	9 (22.0)
Clinical presentation	
Claudication (%)	41 (93.2)
Critical limb ischemia (%)	3 (6.8)
Rutherford category	
1 (%)	1 (2.3)
2 (%)	9 (20.5)
3 (%)	31 (70.4)
4 (%)	0 (0)
5 (%)	3 (6.8)
6 (%)	0 (0)
Non-ambulatory status (%)	3 (6.8)
Medications	
Aspirin (%)	41 (100)
Tienopyridin (%)	33 (80.5)
Cilostazole (%)	11 (26.8)
ACE-I/ARB (%)	24 (58.5)
β-blocker (%)	12 (29.3)
Statin (%)	22 (53.7)

ACE-I, Angiotensin converting enzyme inhibitor

ARB, Angiotensin II receptor blocker

NY, USA).

Results

Baseline Characteristics

Table 1 shows a summary of the baseline characteristics of the patients who successfully underwent FFR measurement (44 lesions and 41 patients). The mean patient age was 74 ± 10 years and the percentage of male patients was 58.5%. The prevalence rates of diabetes mellitus and hemodialysis were 53.7% and 26.8%, respectively. There were 41 patients (93.2%) who presented with claudication and the remaining 3 patients (6.8%) presented with critical limb ischemia. **Table 2** shows a summary of the lesion and procedure characteristics. Fifteen lesions (34.1%) were classified as TASC II type C or D lesions. The mean lesion length was 93.6 ± 73.7 mm and the rates according to the level of lesions, namely, proximal, mid, and distal

Table 2. Lesion and procedure characteristics (44 lesions)

Variable	
Lesion characteristics	
TASC classification	
A (%)	15 (34.1)
B (%)	14 (31.8)
C (%)	6 (13.6)
D (%)	9 (20.5)
Mean lesion length (mm)	93.6 ± 73.7
Level of SFA lesion	
Proximal (%)	15 (34.1)
Mid (%)	21 (47.7)
Distal (%)	8 (18.2)
Chronic total occlusion (%)	12 (27.3)
Restenosis (%)	10 (22.7)
Vessel calcification (%)	12 (27.3)
Interventional results	
POBA (%)	14 (31.8)
STENT (%)	30 (68.2)
No. of stents	1.6 ± 0.89
Total stent length (mm)	142 ± 106
Mean stent diameter (mm)	7.0 ± 0.79
No. of run-off vessels	
1 (%)	7 (15.9)
2 (%)	21 (47.7)
3 (%)	16 (36.4)

TASC, TransAtlantic InterSociety Consensus

SFA, Superficial femoral artery

POBA, Plain old balloon angioplasty

were 34.1%, 47.7%, and 18.2%, respectively. Chronic total occlusion was included in 27.3% of the lesions and restenosis was included in 22.7% of the lesions. Stent implantation was performed in 30 lesions (68.2%) and only balloon angioplasty in 14 lesions (31.8%). The percentages of 1, 2, and 3 run-off vessels after EVT were 15.9%, 47.7%, and 36.4%, respectively.

Effects of Different Papaverine Doses

Table 3 shows the effects of different doses of papaverine. After the incremental dose administration of papaverine, the drop in pressure at the tip of guide sheath which was located on top of the common iliac bifurcation was very little and there were no significant differences (Δ systolic pressure 20 mg: -6.3 ± 9.8 mmHg, 30 mg: -4.6 ± 10.3 mmHg, and 40 mg: -7.5 ± 11.6 mmHg, $P=0.445$; Δ diastolic pressure 20 mg: -5.4 ± 10.5 mmHg, 30 mg: -3.4 ± 6.0 mmHg, and

Table 3. Effects of different doses of papaverine

	SBP (mmHg)	ΔSBP (mmHg)	DBP (mmHg)	ΔDBP (mmHg)	pFFR	ECG change	Symptom
Baseline	158.4 ± 25.9	–	57.4 ± 11.1	–	0.97 ± 0.04	–	–
Papaverine 20 mg	152.6 ± 27.6	– 6.3 ± 9.8	56.4 ± 11.0	– 5.4 ± 10.5	0.87 ± 0.10	None	None
Papaverine 30 mg	155.2 ± 26.3	– 4.6 ± 10.3	57.0 ± 11.0	– 3.4 ± 6.0	0.84 ± 0.10	None	None
Papaverine 40 mg	152.8 ± 26.2	– 7.5 ± 11.6	55.4 ± 10.9	– 5.0 ± 8.0	0.84 ± 0.10	None	None

SBP, Systolic blood pressure

DBP, Diastolic blood pressure

pFFR, peripheral fractional flow reserve

ECG, electro cardiography

40 mg; -5.0 ± 8.0 mmHg, $P=0.60$). There were no abnormal electrocardiogram changes including QT prolongation, ST change, or any arrhythmia with increasing papaverine dose. All patients had no symptoms during the FFR measurement.

Fig. 3 shows the changes in pFFR according to the serial administration of papaverine. After the administration of 20 mg of papaverine, the pFFR significantly decreased from the baseline value (baseline: 0.97 ± 0.04 vs 20 mg: 0.87 ± 0.10 , $P<0.001$). pFFR decreased more in several cases after the administration of 30 mg of papaverine than after the administration of 20 mg of papaverine, but the decrease was not significantly different (20 mg: 0.87 ± 0.10 vs 30 mg: 0.84 ± 0.10 , $P=0.602$). After the administration of 40 mg of papaverine, the pFFR changes showed a plateau (30 mg: 0.84 ± 0.10 vs 40 mg: 0.84 ± 0.10 , $P=1.000$).

Fig. 4 and **5** show the changes in pFFR according to gender difference and the number of run-off vessels. After the administration of 20 mg of papaverine, pFFR significantly decreased from the baseline value in both male and female patients (male patient baseline: 0.98 ± 0.02 vs 20 mg: 0.86 ± 0.11 , $P<0.001$; female patient baseline: 0.97 ± 0.06 vs 20 mg: 0.87 ± 0.08 , $P<0.001$) and in both 3 run-off vessels and 1 or 2 run-off vessels (3 run-off vessels baseline: 0.99 ± 0.02 vs 20 mg: 0.86 ± 0.08 , $P<0.001$; 1 or 2 run-off vessels baseline: 0.97 ± 0.05 vs 20 mg: 0.87 ± 0.11 , $P=0.002$). The drop in pFFR was more in several cases after the administration of 30 mg of papaverine than after the administration of 20 mg of papaverine; however, the pFFR between 30 mg and 40 mg of papaverine was nearly similar in both male and female patients, and in both 3 run-off vessels and 1 or 2 run-off vessels.

Discussion

The main findings of this study were as follows:

1) an increase in the dose of papaverine (20, 30, and

40 mg) did not induce any side effects and the pressure drop at the tip of the guide sheath was extremely low; 2) 30 mg of papaverine is sufficient to induce maximal hyperemia of SFA lesions; 3) the necessary dose of papaverine did not change according to the gender difference and the different number of run-off vessels; 4) the contralateral femoral crossover approach is useful in FFR measurement for SFA lesions.

Little is known about the optimal stenting for SFA lesions. A recent report revealed that stent implantation in a tiny vessel, stent edge dissection, and total stent length were independent predictors of target lesion revascularization after implantation of a self-expandable nitinol stent for SFA lesions¹⁷. These findings closely resemble the results of previous IVUS studies for CAD. Poststenting FFR in CAD is reportedly associated with adverse events in the chronic phase¹². However, the usefulness of physiological assessment for SFA lesions after EVT remains unclear. The present study was a preliminary investigation to evaluate a measuring procedure for FFR and the papaverine dose necessary to achieve maximal hyperemia for SFA lesions.

Only few studies have performed FFR measurement for SFA lesions^{18, 19}. To our knowledge, this is the first study to identify problems regarding the measuring procedure for FFR in SFA lesions and to clarify the necessary dose of papaverine during serial administration to achieve maximal hyperemia. One of the problems regarding the measuring procedure for FFR for SFA lesions was the position of the guide sheath where pressure equalization was performed. We considered the level below the common iliac artery as one component as well as the level below the left main coronary artery for measuring FFR in CAD. One of the pitfalls of measuring FFR in CAD is that the guide catheter can limit coronary blood flow particularly if a stenosis is present at the left main ostium or if a large French size catheter is used^{20, 21}. If a large

Fig. 3. Changes in peripheral FFR values according to the different injection doses papaverine.

guide sheath is located at the iliac artery, the guide sheath may act as an artificial stenosis proximal to the SFA lesion. As a result, the severity of the SFA lesion may be underestimated by FFR measurement. In fact, we encountered a case in which the pressure dropped at the tip of guide sheath when the guide sheath was located deeply at the iliac artery using the crossover approach. Therefore, the ideal measuring procedure for FFR for SFA lesions as well as for CAD is that a catheter must not be present in the iliac artery but only a pressure wire. We believe that our method is ideal because only a 0.014-inch pressure wire was present in the iliac artery, and thus blood flow was not interrupted. However, the problem with our method was our failure to successfully measure FFR in several patients (our success rate was 91.7%) who mainly had a severe angulation of the common iliac bifurcation and severe tortuosity of the iliac artery. An ideal method is of course theoretically necessary, but a simple and useful measuring procedure is highly favorable in daily practice. The problem of limiting the blood flow with the use of a crossover 6-Fr guide sheath scarcely occurred; therefore, further research is needed to investigate which cases require the guide sheath to be pulled back to the iliac bifurcation to avoid limiting the blood inflow. We usually perform EVT for SFA lesions using the crossover approach, thus we

could not evaluate whether the antegrade ipsilateral approach was suitable for FFR measurement for SFA lesions. However, limiting the blood flow may also occur because of the presence of the sheath in the ipsilateral common femoral artery. Therefore, we consider the ipsilateral antegrade approach theoretically as not an ideal method for measuring FFR for SFA lesions.

The present results showed that the necessary papaverine dose for inducing maximal hyperemia in SFA lesions is between 20 mg and 30 mg. Maximal hyperemia in all SFA lesions can therefore be induced with 30 mg of papaverine. The distal vascular bed plays an important role in the interpretation of FFR. As male patients have a larger volume of lower extremity muscle than female patients, we evaluated the necessary papaverine dose for inducing maximal hyperemia between male and female patients. Moreover, downstream stenosis has been reported to affect the FFR of the proximal lesion in CAD^{22, 23}. The presence of severe infrapopliteal stenosis may cause the underestimation of SFA lesion severity by FFR measurement. We also evaluated the necessary papaverine dose for inducing hyperemia according to the number of run-off vessels. There was no significant difference in the necessary papaverine dose according to gender difference and the amount of infrapopliteal vessels. These factors affect the changes in FFR and are

Fig. 4. Changes in peripheral FFR values according to gender differences.

A: Changes in peripheral FFR values in male patients.

B: Changes in peripheral FFR values in female patients.

important for assessing FFR which require further research.

Study Limitations

This research has some limitations. *First*, this

Fig. 5. Changes in peripheral FFR values according to the number of run-off vessels.

A: Changes in peripheral FFR values in patients with 3 run-off vessels.

B: Changes in peripheral FFR values in patients with 1 or 2 run-off vessels.

prospective study had a small sample size. *Second*, FFR measurement was performed only after EVT but not before EVT. In CAD patients, exercise test, thallium scintigraphy, and dobutamine stress echocardiography

are appropriately performed according to the patient status to decide the intervention indication. In contrast, only exercise ankle-brachial indices (ABIs) are available as functional assessment modality in PAD

patients^{24, 25)}. However, it is occasionally difficult to obtain these indices in older patients who cannot sufficiently perform exercise. In this case, FFR measurement is an easy and rapid method. Thus a comparison of the abilities of FFR and exercise ABIs in predicting PAD patients requiring EVT is meaningful. In this study, we focused on the ability of FFR to identify the optimal endpoint of EVT and to predict future adverse clinical outcomes but not to assess the candidates for EVT. Therefore, we performed FFR measurement after EVT and not before EVT to investigate the effects of post-EVT FFR on the chronic phase results. *Third*, only papaverine was used in this study to induce maximal hyperemia as this is the only drug currently utilized for such purpose in our hospital. Other vasodilators such as adenosine, adenosine 5-triphosphate, nicorandil, and sodium nitroprusside were previously used to induce hyperemia in CAD, with the benefit of each drug investigated^{13, 26-29)}. We intend to perform future studies to clarify the differences in the ability of each of these drugs to induce maximal hyperemia in SFA lesions. *Finally*, no data was obtained regarding the relationship between post-EVT FFR for SFA lesions and future clinical outcomes. Additional investigations are warranted to determine whether post-EVT FFR for SFA lesions affects restenosis or re-occlusion of the target lesion site in the chronic phase.

Conclusions

We identified an optimal procedure for measuring FFR for SFA lesions using the contralateral crossover approach. We also suggest that the administration of 30 mg of papaverine is sufficient to induce maximal hyperemia of SFA lesions. The application of physiological assessment using FFR for SFA lesions remains unclear. This necessitates further research aiming to clarify whether FFR measurement is useful for SFA lesions as well as for CAD and RAS in terms of deciding the optimal SFA stenting.

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Disclosure

The authors declare that they have no financial relationships or conflicts of interest relevant to the contents of this paper.

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